National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Cell Transplantation (HCT)

Version 2.2024 — August 30, 2024

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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Hematopoietic Cell Transplantation

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Φ Infectious disease
Þ Internal medicine
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¥ Patient advocacy
∑ Pharmacology
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NCCN Guidelines Panel Disclosures

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 2.2024 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 1.2024 include:

GVHD-E 1 of 3

- Suggested Systemic Agents for Steroid-Refractory GVHD
  - Table header revised: Suggested Systemic Agents for Steroid-Refractory GVHD ~~(listed in alphabetical order, except for category 1 and FDA-approved agents)~~
  - Table sub-headers added for Acute GVHD: Category 1 agents, and Alternative agents (listed in alphabetical order)
  - Table sub-headers added for Chronic GVHD: Category 1 agents, FDA-approved agents (listed in order by FDA approval date), and Alternative agents (listed in alphabetical order)
    - ◊ FDA-approved agents:
      - Axatilimab-csfr has been added as a category 2A recommendation
      - Footnote added: Axatilimab-csfr is FDA approved for the treatment of adult and pediatric patients weighing ≥40 kg with chronic GVHD after failure of at least two prior lines of systemic therapy.

GVHD-E 3 of 3

- Reference added: Wolff D, Cutler C, Lee SJ, et al. Safety and efficacy of axatilimab at 3 different doses in patients with chronic graft-versus-host disease (AGAVE-201). Blood 2023;142:(Supplement 1):1.

MS-1

- The Discussion section has been updated to reflect the changes in the algorithm.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 3.2023 include:

Global

• References have been updated throughout.

HCT-2

• Laboratory Tests
  ▸ Sub-bullet 3, text modified: *estimated* glomerular filtration rate
  ▸ Sub-bullet 6, Infectious disease testing: syphilis added
• Footnote a modified: ...It also generates information that may inform *other transplant-related decisions* ~~the choice of the preparative regimen (drug choice, dose intensity, and immunosuppressive regimen)~~. (Also for HCT-3)
• Reference added to footnote e: Coffey DG, et al. Bone Marrow Transplant 2013;48:1253-1256.
• Footnote h modified: Assess medication adherence, high-risk behavior, *mood disorders,* and caregiver availability to ensure patient ~~compliance~~ *adherence* to treatment. *If needs are identified, ensure referral to psycho-oncology, social work, mental health provider, or addiction psychiatry as appropriate.*
• Footnote i revised: The HCT-CI predicts the risk of NRM after transplant more accurately than age and performance status; however, it does not predict the risk of relapse. Detailed explanation of the HCT-CI has been published [Sorror ML. Blood 2013;121:2854-2863]. ~~Allogeneic HCT: Increased HCT-CI scores were predictive for increased risks of NRM and overall mortality. Autologous HCT: Scores ≥3 were predictive for increased risks of NRM and overall mortality.~~ See HCT-CI score calculator: http://hctci.org. (Also for HCT-A 2 OF 10)

HCT-3

• Additional Clinical Assessment
  ▸ Bullet 1, sub-bullet 2 revised: Discuss fertility preservation~~/sperm banking~~
• Additional Laboratory Tests
  ▸ Sub-bullet 4 revised: Urine toxicology screen if history of ~~illicit drug use~~ *substance use disorder*

HCT-4

• Hematopoietic Cell Mobilization
  ▸ Footnote m modified: For donor evaluation and follow-up recommendations, refer to ~~Eighth Edition FACT-JACIE International Standards, available at: http://www.factwebsite.org/ctstandards/ (Accessed 08/03/21).~~ *: Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee - ISCT and EBMT. FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration (8th edition); 2021.*
  ▸ Footnotes removed and information added to the manuscript:
    ◊ G-CSF + plerixafor is superior to single-agent G-CSF in heavily pre-treated multiple myeloma and non-Hodgkin lymphoma (NHL).
    ◊ G-CSF + cyclophosphamide may be superior to single-agent G-CSF in heavily pre-treated multiple myeloma and NHL.
    ◊ No difference was observed between G-CSF/cyclophosphamide and Granulocyte-macrophage colony-stimulating factor/cyclophosphamide (Gazitt Y, et al. J Hematother Stem Cell Res 2000;9:737-748).
    ◊ Motixafortide is indicated in combination with filgrastim (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma. Crees ZD, et al. Nat Med 2023;29:869-879. (Also for HCT-4A)

HCT-4A

• Autologous Donors
  ▸ Regimen language revised for Filgrastim + Cyclophosphamide ± Plerixafor and Sargramostim + Cyclophosphamide ± Plerixafor: ~~Start on day 1–5 after cyclophosphamide and continue daily until apheresis starts and collection goal is met~~ *Daily starting 24 hours after cyclophoshamide and continuing until collection goal is met. Begin apheresis at least 4-5 days after cyclophoshamide administration.*

Continued

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Hematopoietic Cell Transplantation

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Updates in Version 1.2024 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 3.2023 include:

HCT-4A (continued)
- Footnote t added: Consider checking circulating CD34+ cells and initiating apheresis based on institutional guidelines.

HCT-5
- Post-Transplant Follow-Up
  - Text modified: *Intensive supportive care is required for all post-transplant recipients until engraftment occurs.* ~~Additional recommendations for post-HCT follow-up will be addressed in subsequent versions of the NCCN Guidelines for Hematopoietic Cell Transplantation.~~

HCT-A 1 of 10
- Definitions of Conditioning Regimen Intensity
  - Bullet 2 modified: Non-myeloablative (NMA) conditioning regimen: One that will produce minimal cytopenia, and there is no *absolute* need for hematopoietic cell support.
  - Bullet 3 modified: Reduced-intensity conditioning (RIC) regimen: One that does not fulfill *criteria for* MA or NMA.

HCT-A 2 of 10
- Allogeneic Conditioning Regimen Selection
  - Bullet 1 modified: The choice among an MA, NMA, or RIC regimen is a nuanced decision that should be made by the transplant team at the time of patient evaluation *or upon review of pre-transplant organ testing, frailty/geriatric assessment, or other evaluation.*
- Special Situations
  - Bullet 2, sub-bullet 2 modified: *Dual* alkylator-based regimens...
  - Bullet 4 modified: ...with *immune* checkpoint inhibitors...

HCT-A 3 of 10
- MA Regimens: Allogeneic Transplant
  - Fludarabine + Busulfan
    - ◊ Fludarabine regimen modified: ...for *4*–5 days
- Footnote c added: If using post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis, carefully evaluate cyclophosphamide doses used for conditioning.
- Footnote e added: If an MA conditioning regimen is planned for a recipient of UCB, omidubicel-onlv has been shown to shorten the time to engraftment and reduce the risk of some infections. Horwitz ME, et al. Blood 2021;138:1429-1440.
- Footnote f added: These recommendations are for IV busulfan, which is the preferred route of administration due to more favorable pharmacokinetic and toxicity profiles. Oral busulfan may be considered in select cases but tends to exhibit more pharmacokinetic variability and requires different dosing.

HCT-A 4 of 10
- RIC Regimens: Allogeneic Transplant
  - Fludarabine + Melphalan
    - ◊ Fludarabine regimen modified: ...for *4*–5 days
  - Fludarabine + Busulfan
    - ◊ Regimen and dosing modified: Fludarabine 30 mg/m^2/day for ~~5–6~~ *4–5* days, Busulfan 3.2 mg/kg/day IV for 2–3 days *OR 1.6 mg/kg/day IV for 4 days*
      - – Reference added: Chen YB, Coughlin E, Kennedy KF, et al. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. Biol Blood Marrow Transplant 2013;19:981-987.
  - Header removed from right column: Commonly Used with PTCy
- Footnote i added: If using PTCy for GVHD prophylaxis, carefully evaluate melphalan and TBI doses. Gaballa S, et al. Cancer 2016;122:3316-3326.

HCT-A 5 of 10
- Conditioning Regimens Without Fludarabine
  - Text modified: ...given the ~~ongoing~~ *intermittent* drug shortage in the United States.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 3.2023 include:

HCT-A 5 of 10 (continued)
- Regimen revised: Cladribine + busulfan ~~2~~ + TBI 2 Gy
  - Footnote l revised: The use of ~~BU2~~ *busulfan* ± TBI 2 Gy may be associated with risk of engraftment failure.
- Footnote k modified: ~~Cytokine release syndrome~~ *A systemic inflammatory syndrome* has been reported with clofarabine use. Concomitant steroid use may mitigate this risk.
- Footnotes removed:
  - Reported with primary immunodeficiency disorders using post-transplant cyclophosphamide.
  - This regimen was reported for salvage second transplant after engraftment failure.

HCT-A 6 of 10
- Germ Cell Tumors
  - Regimen removed: Paclitaxel + ifosfamide + carboplatin + etoposide
    - Reference combined and added to carboplatin + etoposide: Feldman DR, Sheinfeld J, Bajorin DF, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol 2010;28:1706-1713.

HCT-A 8 of 10
- All references listed throughout HCT-A have been moved to the references section (HCT-A 8 of 10 through HCT-A 10 of 10).

GVHD-1
- Acute GVHD suspected
  - Workup
    - Bullet 2, sub-bullet 1 modified: Skin rash: *consider* biopsy of suspicious skin sites
    - Bullet 3 modified: ~~LFT~~ *Liver abnormalities*: Consider liver biopsy if elevated *liver-associated* enzymes *or total/direct bilirubin* and no evidence of acute GVHD elsewhere
- Grade
  - Grade removed: Grade 0 (No acute GVHD)

GVHD-2
- Acute GVHD Grade 1; First-Line Therapy
  - Topical steroids modified: Topical steroids ~~(skin-directed)~~ until resolution of rash
- Response
  - No response, text modified: Continue topical steroids ~~(skin-directed)~~
  - Progression, text modified: Progression ~~toward grade II~~ and/or Symptomatic (ie, pruritus*, pain, sloughing, increasing BSA involvement*)

GVHD-3
- Footnote l modified: ...in conjunction with GI topical steroids (beclomethasone dipropionate *[available as a compounded agent]* ± budesonide) was safe and effective for upper GI symptoms...*Of note, budesonide is less effective at treating the upper GI tract.*

GVHD-4
- Chronic GVHD; First-Line Therapy
  - Treatment option added: Inhaled steroid ± azithromycin ± *montelukast* for lung involvement
- Footnote u revised: ~~Due to recent data suggesting an increased risk for cancer relapse azithromycin should be used only for the treatment of bronchiolitis obliterans syndrome (BOS) and not for lung GVHD prophylaxis.~~ *Azithromycin should only be used for treatment of bronchiolitis obliterans syndrome (BOS), not for prophylaxis, due to a suggestion of an increased risk of leukemic relapse or secondary neoplasms in recent clinical trials. Bergeron A, et al. JAMA 2017;318:557-566. Cheng GS, et al. Biol Blood Marrow Transplant 2020;26:392-400.*

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 3.2023 include:

GVHD-E 1 of 3

- Suggested Systemic Agents for Steroid-Refractory GVHD
  - Table header modified: (listed in alphabetical order, except for category 1 *and FDA-approved agents)*
    - Acute GVHD
      - Drug added: Vedolizumab
    - Chronic GVHD
      - Text revised: While the following systemic agents may be used ~~in any site~~ *to treat cGVHD in any organ*, some agents are used more commonly ~~in~~ *for* certain sites *involved with cGVHD* based on available data (see Discussion).
      - Order of listed agents revised based on FDA approvals: belumosudil and ibrutinib have been moved up after ruxolitinib

GVHD-F 1 of 2

- GVHD Supportive Care
  - All Patients
    - Bullet 2, sub-bullet 2 modified: Surveillance for CMV reactivation *is recommended in appropriate patients.*
    - Sub-bullet 5, sub-sub-bullet 1 revised: Vitamin D and calcium supplementation ~~are often required~~ *should be considered* for patients on HD steroid.
    - Sub-bullet 6 revised: DEXA scan (in particular *for patients with either current or past exposure to* ~~with~~ HD steroids) ~~with repeat imaging as appropriate based on findings/results with appropriate management if osteoporosis~~ *with treatment and repeat imaging as indicated based on results.*
    - Sub-bullet 7 revised: ~~Baseline and every 6 months exam for dermatology, dental, and ophthalmology~~ *Dermatologic, dental, and ophthalmologic evaluation at appropriate intervals beginning 6–12 months post-transplant.*
  - Acute GVHD
    - Skin
      - Sub-bullet 2 revised: Dermatologic assessment is recommended for advanced disease. ~~(may benefit from steroid wet wraps).~~
    - Gut changed to 'GI Tract' (Also for Chronic GVHD)
      - Sub-bullet 3 modified: Prolonged oral beclomethasone *or budesonide* may cause adrenal insufficiency.
    - Sub-bullet title added: Nutrition
      - Sub-bullet 2 modified: Total parenteral nutrition *and bowel rest* should be considered in patients with voluminous diarrhea...
  - Chronic GVHD
    - Oral
      - Sub-bullet 2 modified: Dental/oral surgery assessment is recommended for suspicious oral ~~ulceration~~ *lesions* (risk of malignancy).
      - Sub-bullets added:
        - Consider dexamethasone mouth rinses (swish and spit).
        - Monitor for oral thrush and use appropriate antifungal topical therapy as indicated.
    - Genital Tract
      - Sub-bullets revised: ~~Gynecologic assessment is recommended for patients with genital symptoms. Concerns around genitourinary symptoms (e.g. urinary issues or erectile dysfunction) in males should be addressed with referrals as appropriate (dermatology, urology).~~ *Concerns around genitourinary symptoms (eg, urinary issues, erectile dysfunction, vulvovaginal symptoms) should be addressed with referrals as appropriate (dermatology, urology, gynecology).*

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 3.2023 include:

GVHD-F 2 of 2
- References and footnotes have been combined on one page.
- Footnote added: Oral beclomethasone is available as a compounded agent.

MS-1
- The Discussion section has been updated to reflect the changes in the algorithm.

INTRODUCTION

The NCCN Guidelines for Hematopoietic Cell Transplantation (HCT) pertain to the care of adult patients undergoing HCT for malignant diseases.

Note: All recommendations are category 2A unless otherwise indicated.

INDICATIONS FOR TRANSPLANTATION

Indications for HCT vary by disease.
Indications for HCT can be found in the following NCCN Guidelines:

- NCCN Guidelines for Acute Lymphoblastic Leukemia
- NCCN Guidelines for Acute Myeloid Leukemia
- NCCN Guidelines for B-Cell Lymphomas
- NCCN Guidelines for Central Nervous System Cancers
- NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- NCCN Guidelines for Chronic Myeloid Leukemia
- NCCN Guidelines for Gestational Trophoblastic Neoplasia
- NCCN Guidelines for Hodgkin Lymphoma
- NCCN Guidelines for Multiple Myeloma
- NCCN Guidelines for Myelodysplastic Syndromes
- NCCN Guidelines for Myeloproliferative Neoplasms (MPN)
- NCCN Guidelines for Primary Cutaneous Lymphomas
- NCCN Guidelines for Systemic Light Chain Amyloidosis
- NCCN Guidelines for Systemic Mastocytosis (SM)
- NCCN Guidelines for T-Cell Lymphomas
- NCCN Guidelines for Testicular Cancer
- NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma

→ Pre-Transplant Recipient Evaluation (HCT-2)
and
Hematopoietic Cell Mobilization (HCT-4)

Note: All recommendations are category 2A unless otherwise indicated.

PRE-TRANSPLANT RECIPIENT EVALUATION[a,b]

- **Clinical Assessment:**
  - Confirm histologic diagnosis
  - History & physical exam, including evaluation of performance status (Eastern Cooperative Oncology Group [ECOG] or Karnofsky Performance Scale [KPS]) and body mass index
  - Assess disease status[c] (including cytogenetic/molecular testing for risk stratification and assessment of minimal residual disease, if applicable)
  - Bone marrow aspiration & biopsy[d] to confirm remission status (as indicated by underlying disease: pathology, flow cytometry, cytogenetics, molecular studies) and rule out other diseases
  - Pulmonary function tests (PFTs) including spirometry, lung volumes, and diffusing capacity of the lungs for carbon monoxide (DLCO)[e,f]
  - Electrocardiogram (with QTc interval assessment)
  - Measure left ventricular ejection fraction (LVEF)[g] with echocardiogram (if valvular assessment required) or multigated acquisition scan
  - Psychosocial evaluation[h]
  - HCT Comorbidity Index (HCT-CI)[i] score (for allogeneic HCT)
- **Imaging:**
  - Disease-specific restaging studies (NCCN Guidelines for Treatment by Cancer Type)
  - Chest x-ray (if no other chest imaging done)
- **Laboratory Tests:**
  - Complete blood count with differential
  - ABO/Rh typing
  - Chemistry profile (including blood glucose, creatinine/estimated glomerular filtration rate[j], electrolytes, and liver function tests [LFTs] [transaminases and bilirubin])[k,l]
  - Prothrombin time/partial thromboplastin time
  - Urinalysis
  - Infectious disease testing for cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis
  - Human leukocyte antigen (HLA) typing per FACT-JACIE International Standards[b]
  - Toxoplasma serology (for allogeneic HCT)
  - Donor and recipient short tandem repeat (STR) genotyping to inform post-transplant chimerism analysis (for allogeneic HCT)

→ Additional Evaluation as Clinically Indicated (HCT-3)

[a] The pre-transplant recipient evaluation generates data to estimate risks of post-transplant complications including non-relapse mortality (NRM). It also generates information that may inform other transplant-related decisions.

[b] For pre-transplant donor evaluation and HLA typing, refer to: Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee- ISCT and EBMT. FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration (8th edition); 2021.

[c] Disease risk index may be used to predict overall survival based on only disease-related risk factors: http://www.cibmtr.org/ReferenceCenter/Statistical/Tools/Pages/DRI.aspx.

[d] For acute leukemia, bone marrow biopsy is ideally performed within 4 weeks of starting a conditioning regimen.

[e] DLCO should be corrected for hemoglobin concentration using the Dinakara method. In patients with significantly reduced DLCO, caution should be exercised when using busulfan or carmustine-based regimens. Coffey DG, et al. Bone Marrow Transplant 2013;48:1253-1256.

[f] Consider pulmonary consultation and/or arterial blood gas analysis if DLCO <60%.

[g] Consider cardiac consultation in patients with compromised LVEF.

[h] Assess medication adherence, high-risk behavior, mood disorders, and caregiver availability to ensure patient adherence to treatment. If needs are identified, ensure referral to psycho-oncology, social work, mental health provider, or addiction psychiatry as appropriate.

[i] The HCT-CI predicts the risk of NRM after transplant more accurately than age and performance status; however, it does not predict the risk of relapse. Detailed explanation of the HCT-CI has been published (Sorror ML. Blood 2013;121:2854-2863). See HCT-CI score calculator: http://hctci.org.

[j] Calcineurin inhibitors (CNIs) are associated with increased risk of renal failure after HCT.

[k] Cirrhosis (in particular with portal hypertension) is generally considered a contraindication for allogeneic HCT.

[l] Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) risk calculator may be used to predict risk of VOD/SOS: http://www.cibmtr.org/ReferenceCenter/Statistical/Tools/Pages/VOD.aspx.

Note: All recommendations are category 2A unless otherwise indicated.

PRE-TRANSPLANT RECIPIENT EVALUATION[a,b]
ADDITIONAL EVALUATION AS CLINICALLY INDICATED

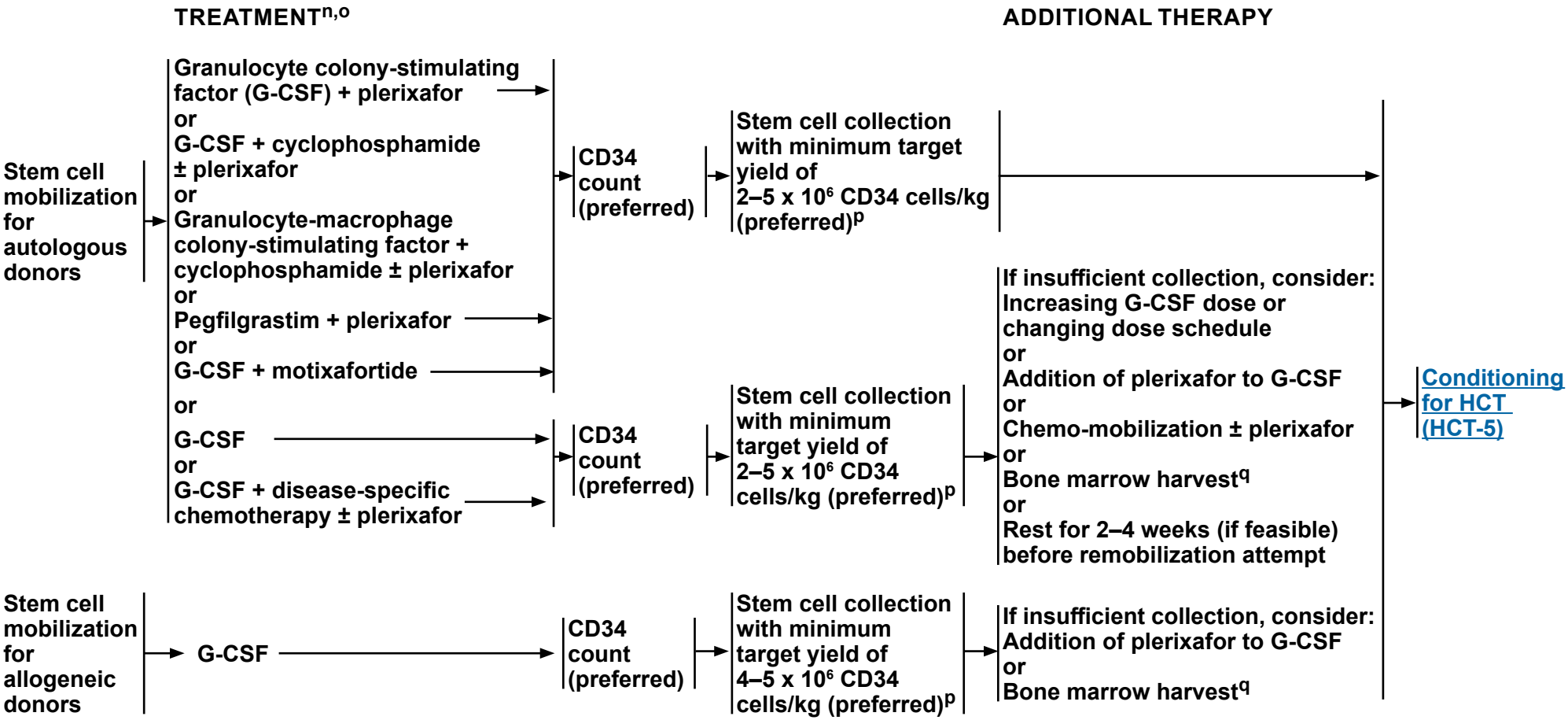
As clinically indicated:

- **Additional Clinical Assessment**
  - **Lumbar puncture for cerebrospinal fluid analysis**
  - **Discuss fertility preservation**
  - **Pregnancy test for individuals of childbearing potential**
  - **Physical therapy evaluation (strength, flexibility, function)**
  - **Nutritional evaluation**
  - **Consider geriatric assessment for select patients (category 2B) (NCCN Guidelines for Older Adult Oncology)**
  - **Dental evaluation (for allogeneic HCT)**
- **Additional Imaging**
  - **CT (chest and/or sinuses)**
- **Additional Laboratory Tests**
  - **Epstein-Barr virus testing or other infectious disease testing (if high risk) (eg, tuberculosis, strongyloides, human T-cell lymphotropic virus types I and II [for allogeneic HCT])**
  - **HLA antibody assessment if using HLA-mismatched donor**
  - **24-hour urine creatinine clearance (for borderline renal dysfunction or low muscle mass)**
  - **Urine toxicology screen if history of substance use disorder**
  - **Thyroid-stimulating hormone level**
  - **Iron profile (including ferritin level)**
  - **Blood lipid panel**
  - **Vitamin D level**

[a] The pre-transplant recipient evaluation generates data to estimate risks of post-transplant complications including NRM. It also generates information that may inform other transplant-related decisions.
[b] For pre-transplant donor evaluation and HLA typing, refer to: Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee- ISCT and EBMT. FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration (8th edition); 2021.

Note: All recommendations are category 2A unless otherwise indicated.

HEMATOPOIETIC CELL MOBILIZATION[m]



[m] For donor evaluation and follow-up recommendations, refer to: Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee - ISCT and EBMT. FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration (8th edition); 2021.
[n] Hematopoietic Cell Mobilization Regimens (HCT-4A).
[o] Alternative chemo-mobilization regimens with disease-specific activity are also appropriate.
[p] Adequate stem cell collection depends on individual patient- and disease-related factors. Lower yields may be adequate, but >2 x 10^6 CD34 cells/kg is strongly preferred, with a target of 4–5 x 10^6 CD34 cells/kg. Stem cell yields <2 x 10^6 CD34 cells/kg may result in delayed engraftment, while larger cell doses have been associated with a more rapid time to platelet and neutrophil recovery.
[q] For bone marrow harvest recommendations, refer to the National Marrow Donor Program/Be the Match (https://bethematch.org).

Note: All recommendations are category 2A unless otherwise indicated.

HEMATOPOIETIC CELL MOBILIZATION REGIMENS

Autologous Donors

Filgrastim[r] ± Plerixafor
- Filgrastim: 10 mcg/kg weight SC for 4–5 days
  - Continued daily until collection goal is met
- Plerixafor: 0.24 mg/kg actual body weight SC (max 40 mg/day) on the day before apheresis[s]

Filgrastim[r] + Cyclophosphamide ± Plerixafor
- Cyclophosphamide: 1500–3000 mg/m^2 IV for 1 dose
- Filgrastim: 10 mcg/kg SC
  - Daily starting 24 hours after cyclophoshamide and continuing until collection goal is met. Begin apheresis at least 4-5 days after cyclophoshamide administration.[t]
- Plerixafor: 0.24 mg/kg actual body weight SC (max 40 mg/day) on the day before apheresis[s]

Sargramostim + Cyclophosphamide ± Plerixafor
- Cyclophosphamide: 1500–3000 mg/m^2 IV for one dose
- Sargramostim: 250 mcg/m^2/day SC
  - IV over 24 hours or SC once daily
  - Daily starting 24 hours after cyclophoshamide and continuing until collection goal is met. Begin apheresis at least 4-5 days after cyclophoshamide administration.[t]
- Plerixafor: 0.24 mg/kg actual body weight SC (max 40 mg/day) on the day before apheresis[s]

Pegfilgrastim[u] + Plerixafor
- Pegfilgrastim: 6 mg SC on day 1
- Upfront plerixafor 0.24 mg/kg actual body weight SC (max 40 mg/day) on day 3 followed by apheresis on day 4

Filgrastim[r] + Motixafortide
- Filgrastim: 10 mcg/kg SC daily x 4 days prior to first dose of motixafortide
- Motixafortide: 1.25 mg/kg actual body weight SC 10–14 hours prior to initiation of apheresis

Allogeneic Donors

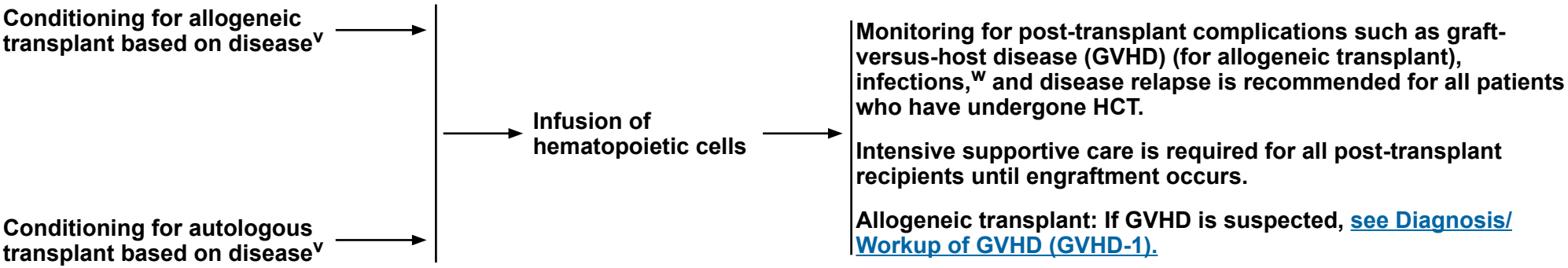
Filgrastim[r]
- 10 mcg/kg donor weight SC (or split twice daily)
- Daily for 4–5 days
- Collect on day 4 or 5

[r] Tbo-filgrastim or an FDA-approved biosimilar is an appropriate substitute for filgrastim.
[s] Plerixafor is generally administered 11 hours prior to stem cell collection.
[t] Consider checking circulating CD34+ cells and initiating apheresis based on institutional guidelines.
[u] An FDA-approved biosimilar is an appropriate substitute for pegfilgrastim.

Note: All recommendations are category 2A unless otherwise indicated.

CONDITIONING FOR HCT

POST-TRANSPLANT FOLLOW-UP



[v] Principles of Conditioning for Hematopoietic Cell Transplant (HCT-A).
[w] NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

- **Indications for HCT vary by disease. Refer to applicable NCCN Guidelines for Treatment by Cancer Type.**

Definitions of Conditioning Regimen Intensity[1]

- **Myeloablative (MA) conditioning regimen: One that will cause irreversible (or close to irreversible) pancytopenia. Hematopoietic cell support is required to rescue marrow function and prevent aplasia-related death. Examples include:**
  - **Total body irradiation (TBI) ≥5 Gy single dose or ≥8 Gy fractionated**
  - **Busulfan >8 mg/kg orally (>6.4 mg/kg IV) or busulfan plasma exposure unit equivalent[a]**
- **Non-myeloablative (NMA) conditioning regimen: One that will produce minimal cytopenia, and there is no absolute need for hematopoietic cell support. Examples include:**
  - **TBI ≤2 Gy ± purine analog**
  - **Fludarabine + cyclophosphamide ± antithymocyte globulin (ATG)**
  - **Fludarabine + cytarabine + idarubicin**
  - **Cladribine + cytarabine**
  - **Total lymphoid irradiation + ATG**
- **Reduced-intensity conditioning (RIC) regimen: One that does not fulfill criteria for MA or NMA.**

[a] Busulfan plasma exposure unit should be reported as area under the curve (AUC) in mg x h/L. For example, AUC 5000 µM x min is equivalent to 20.5 mg x h/L (McCune JS, et al. Biol Blood Marrow Transplant 2019;25:1890-1897).

Note: All recommendations are category 2A unless otherwise indicated.

References Continued

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Allogeneic Conditioning Regimen Selection

- The choice among an MA, NMA, or RIC regimen is a nuanced decision that should be made by the transplant team at the time of patient evaluation or upon review of pre-transplant organ testing, frailty/geriatric assessment, or other evaluation.
- Conditioning regimen intensity depends on:
  - Patient age (chronologic and physiologic)
  - Performance status
  - HCT-CI and other pertinent comorbidities[b]
  - Disease type
  - Remission status (including measurable residual disease)
  - History of prior HCT
- MA regimens may be preferred for the following disease types, if the patient is young and fit[b,2]:
  - Acute lymphocytic leukemia (TBI-based regimens preferred)
  - Acute myeloid leukemia
  - Chronic myeloid leukemia
  - Myelodysplastic syndromes
- RIC/NMA regimens may be preferred for:
  - Lymphoma (non-Hodgkin lymphoma [NHL] or Hodgkin lymphoma [HL])
  - Chronic lymphocytic leukemia
  - Plasma cell disorders (eg, multiple myeloma, plasma cell leukemia)
  - Patients who have received a prior autologous HCT
  - Patients who are older or unfit[b]

Special Situations

- For patients with significant pulmonary dysfunction, caution is recommended if using high-dose (HD) busulfan, carmustine, and HD TBI.
- Increased risk of SOS has been associated with the use of:
  - HD busulfan and HD TBI in patients with significant liver dysfunction.
  - Dual alkylator-based regimens with pre-transplant inotuzumab or gemtuzumab.
- The combination of sirolimus[3,4] and tacrolimus may be associated with higher risk of SOS and thrombotic microangiopathy, especially if used with MA regimens.[5-10]
- Increased risk of GVHD has been associated with patients treated with immune checkpoint inhibitors (pre- or post-HCT) and mogamulizumab.
  - Consider a minimum 8- to 12-week window between these treatments and the start of transplant conditioning if clinically feasible.[7-10]
- Thiotepa can be excreted through the skin and requires special skin care. Refer to the package insert.

[b] The HCT-CI predicts the risk of NRM after transplant more accurately than age and performance status; however, it does not predict the risk of relapse. Detailed explanation of the HCT-CI has been published (Sorror ML. Blood 2013;121:2854-2863). See HCT-CI score calculator: http://hctci.org.

References Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Examples of Commonly Used Conditioning Regimens
- **This list is not comprehensive. Other options can be considered.**
- **See Suggested Doses/Modifications by Weight (HCT-A 7 of 10)**

MA Regimens		
Allogeneic Transplant	**TBI-Based** **Cyclophosphamide + TBI[11]** • Cyclophosphamide 60 mg/kg/day for 2 days[c] • TBI 12–13.2 Gy fractionated **Fludarabine + TBI[12]** • Fludarabine 30 mg/m²/day for 4 days • TBI 12–13.2 Gy fractionated **Etoposide + TBI[13]** • Etoposide 60 mg/kg in 1 dose • TBI 12–13.2 Gy fractionated	**Busulfan-Based[f]** **Busulfan + Cyclophosphamide[g,14]** • Busulfan 3.2 mg/kg/day for 4 days • Cyclophosphamide 60 mg/kg/day for 2 days[c] **Fludarabine + Busulfan[15]** • Busulfan 3.2 mg/kg/day (12.8 mg/kg total) for 4 days • Fludarabine 30–32 mg/m²/day for 4–5 days **Fludarabine + Busulfan + Thiotepa[16,17]** • Fludarabine 30-40 mg/m²/day for 4 days OR 50 mg/m²/day for 3 days • Busulfan 3.2 mg/kg/day total for 3–4 days; • Thiotepa 5 mg/kg/day for 1–2 days **Clofarabine + Busulfan[18,19]** • Clofarabine 20–40 mg/m²/day for 4–5 days • Busulfan AUC 4000–5500 (or 3.2 mg/kg/day) for 4 days
Umbilical Cord Blood (UCB)[d,e]	**TBI-Based** **Fludarabine + Cyclophosphamide + TBI[12]** • Fludarabine 30–45 mg/m²/day for 4 days; • Cyclophosphamide 60 mg/kg/day for 2 days • TBI 13.2 Gy fractionated **Fludarabine + Thiotepa + TBI[20,21]** • Fludarabine 40 mg/m²/day for 4 days; • Thiotepa 5 mg/kg/day for 2 days; • TBI 13.2 Gy fractionated	**Busulfan-Based[f]** **Fludarabine + Busulfan + Thiotepa[22]** • Thiotepa 5 mg/kg/day for 2 days • Busulfan 3.2 mg/kg/day for 3 days • Fludarabine 50 mg/m²/day for 3 days
NMA Regimens		
Allogeneic Transplant	**TBI-Based** **Fludarabine + TBI[23]** • Fludarabine 30 mg/m²/day for 3 days • TBI 2 Gy	**Other** **Fludarabine + Cyclophosphamide ± Rituximab[24]** Fludarabine 30 mg/m²/day for 3 days • Cyclophosphamide 750 mg/m²/day for 3 days • Rituximab ▸ 375 mg/m² IV for 1 day before transplant; and ▸ 1000 mg/m² IV on days 1, 8, and 15 after transplant

[c] If using post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis, carefully evaluate cyclophosphamide doses used for conditioning.

[d] Referral to a center with experience in UCB transplants is strongly recommended.

[e] If an MA conditioning regimen is planned for a recipient of UCB, omidubicel-onlv has been shown to shorten the time to engraftment and reduce the risk of some infections. Horwitz ME, et al. Blood 2021;138:1429-1440.

[f] These recommendations are for IV busulfan, which is the preferred route of administration due to more favorable pharmacokinetic and toxicity profiles. Oral busulfan may be considered in select cases but tends to exhibit more pharmacokinetic variability and requires different dosing.

[g] Cyclophosphamide/busulfan is different than busulfan/cyclophosphamide (Rezvani AR, et al. Biol Blood Marrow Transplant 2013;19:1033-1039).

References Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Examples of Commonly Used Conditioning Regimens
- **This list is not comprehensive. Other options can be considered.**
- **See Suggested Doses/Modifications by Weight (HCT-A 7 of 10)**

RIC Regimens[h]		
Allogeneic Transplant	**Fludarabine + Melphalan[25]** • Fludarabine 20–36 mg/m^2/day for 4–5 days • Melphalan 100–140 mg/m^2 over 1–2 days[i] **Fludarabine + Busulfan[26]** • Fludarabine 30 mg/m^2/day for 4–5 days • Busulfan 3.2 mg/kg/day IV for 2–3 days OR 1.6 mg/kg/day IV for 4 days[27]	**Fludarabine + Cyclophosphamide + TBI[28]** • Fludarabine 30 mg/m^2/day for 5 days OR 25 mg/m^2/day for 6 days • Cyclophosphamide 14.5 mg/kg/day for 2 days • TBI 2–4 Gy **Fludarabine + Melphalan + TBI[i,29]** • Fludarabine 30 mg/m^2/day for 5 days OR 25 mg/m^2/day for 6 days • Melphalan 100–140 mg/m^2 over 1–2 days • TBI 2–4 Gy **Fludarabine + Melphalan + Thiotepa[30,31]** • Fludarabine 40 mg/m^2/day for 4 days • Melphalan 140 mg/m^2 for 1 day • Thiotepa 10 mg/m^2 for 1 day **Fludarabine + Busulfan + Thiotepa[16]** • Thiotepa 5 mg/kg/day for 1 day • Busulfan 130 mg/m^2/day IV for 2 days[j] • Fludarabine 30–40 mg/m^2/day for 4 days
UCB[d]	**Fludarabine + Cyclophosphamide + Thiotepa + TBI[32]** • Fludarabine 150 mg/m^2 • Cyclophosphamide 50 mg/kg • Thiotepa 10 mg/kg/day • TBI 4 Gy **Fludarabine + Cyclophosphamide + TBI[33]** • Fludarabine 200 mg/m^2 • Cyclophosphamide 50 mg/kg • TBI 2 Gy	

[d] Referral to a center with experience in UCB transplants is strongly recommended.
[h] See RIC regimens without fludarabine (HCT-A 5 of 10).
[i] If using PTCy for GVHD prophylaxis, carefully evaluate melphalan and TBI doses. Gaballa S, et al. Cancer 2016;122:3316-3326.
[j] Typically, this is equivalent to 3.2 mg/kg/day.

Note: All recommendations are category 2A unless otherwise indicated.

References Continued

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Conditioning Regimens Without Fludarabine

- **The following is a non-inclusive list of non-fludarabine RIC regimens given the intermittent drug shortage in the United States. However, because of lack of comparative data with fludarabine-based regimens, choice of regimen should be based on institutional preference and experience. See *Update on FDA Drug Shortages***
- **See Suggested Doses/Modifications by Weight (HCT-A 7 of 10)**
- **Please refer to corresponding published data for GVHD prophylaxis.**

RIC Regimens Without Fludarabine	
Pentostatin-based	• Pentostatin + busulfan[34] • Pentostatin + busulfan + cyclophosphamide[35] • Pentostatin + TBI 4 Gy[36]
Clofarabine-based[k]	• Clofarabine + busulfan[37,38] • Clofarabine + melphalan[39] ± thiotepa[40] • Clofarabine + TBI 2 Gy[41] • Clofarabine + cyclophosphamide + TBI 2 Gy[42] (with PTCy)
Cladribine-based[l]	• Cladribine + busulfan + ATG[43,44] • Cladribine + busulfan + TBI 2 Gy[45]
Cyclophosphamide-based	• Cyclophosphamide + TBI 5.5 Gy[46]

[k] A systemic inflammatory syndrome has been reported with clofarabine use. Concomitant steroid use may mitigate this risk.
[l] The use of busulfan ± TBI 2 Gy may be associated with risk of engraftment failure.

References Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Examples of Commonly Used Conditioning Regimens

- **This list is not comprehensive. Other options can be considered.**
- **See Suggested Doses/Modifications by Weight (HCT-A 7 of 10)**

Autologous Regimens by Disease Type	
NHL (without central nervous system disease) or HL	• BEAM (carmustine + etoposide + cytarabine + melphalan)[47] • BEAC (carmustine + etoposide + cytarabine + cyclophosphamide)[48-50] • Carmustine + thiotepa[51] • Busulfan + cyclophosphamide + etoposide[52] • TEAM (thiotepa + etoposide + cytarabine + melphalan)[53] • Bendamustine + etoposide + cytarabine + melphalan[54]
Primary Central Nervous System Lymphoma or NHL (with central nervous system disease)	• Thiotepa + busulfan + cyclophosphamide[51] • Carmustine + thiotepa[51]
Multiple Myeloma/Plasma Cell Leukemia	• Melphalan (200 mg/m^2)[55] • Melphalan (70–140 mg/m^2 for select patients)[m,56-58] • Melphalan + busulfan (high risk)[59]
Germ Cell Tumors	• Carboplatin + etoposide[60,61]
Acute Promyelocytic Leukemia	• Busulfan + melphalan[62-64] • Cyclophosphamide + TBI[64] • Busulfan + cyclophosphamide[64]

[m] Lower dose melphalan can be considered for amyloidosis, older age, high HCT-CI, low KPS, and chronic kidney disease.

Note: All recommendations are category 2A unless otherwise indicated.

References
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PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Suggested Doses/Modifications by Weight	
Busulfan	• Adults: mg/kg dosing: dose based on 25% adjusted body weight ▸ Body surface area (BSA) dosing: dose based on total body weight • Pediatrics: dose based on total body weight • Risk of SOS/VOD is correlated with higher busulfan exposure (higher AUC)
Carmustine	• Dose adults on BSA • Total body weight ≤120% ideal body weight: dose based on total body weight • Total body weight >120% ideal body weight: dose based on 25% adjusted body weight • Pulmonary toxicity >50% at 600 mg/m^2 with multiple agent regimens. Maximum tolerated dose of 1200 mg/m^2 as single agent with 9.5% pulmonary toxicity
Cyclophosphamide	• Cy200 regimen: dose based on the lesser of total body weight or ideal body weight • Cy120 regimen: dosing can be either ideal body weight or total body weight until >120% ideal body weight, then dose based on 25% adjusted body weight[n]
Cytarabine	Dose adults and children on BSA based on total body weight
Etoposide	• Mg/kg dosing: dose based on 25% adjusted body weight[n] • BSA dosing: dose based on total body weight
Fludarabine	Dose adults on BSA based on total body weight
Melphalan	• Dose adults on BSA based on total body weight • Adjustments for age and renal function are not standardized
Thiotepa	• Dose adults on BSA if total body weight ≤120% • Total body weight ≤120% ideal body weight dose on BSA based on total body weight • Total body weight >120% ideal body weight dose on BSA based on 40% adjusted body weight[n]

Adapted from: Bubalo J, Carpenter PA, Majhail N, et al. Conditioning chemotherapy dose adjustment in obese patients: a review and position statement by the American Society for Blood and Marrow Transplantation practice guideline committee. Biol Blood Marrow Transplant 2014;20:600-616.

[n] 25% adjusted body weight indicates ideal body weight + 0.25 (total body weight - ideal body weight); 40% adjusted body weight indicates ideal body weight + 0.4 (total body weight - ideal body weight).

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Note: All recommendations are category 2A unless otherwise indicated.

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Note: All recommendations are category 2A unless otherwise indicated.

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Note: All recommendations are category 2A unless otherwise indicated.

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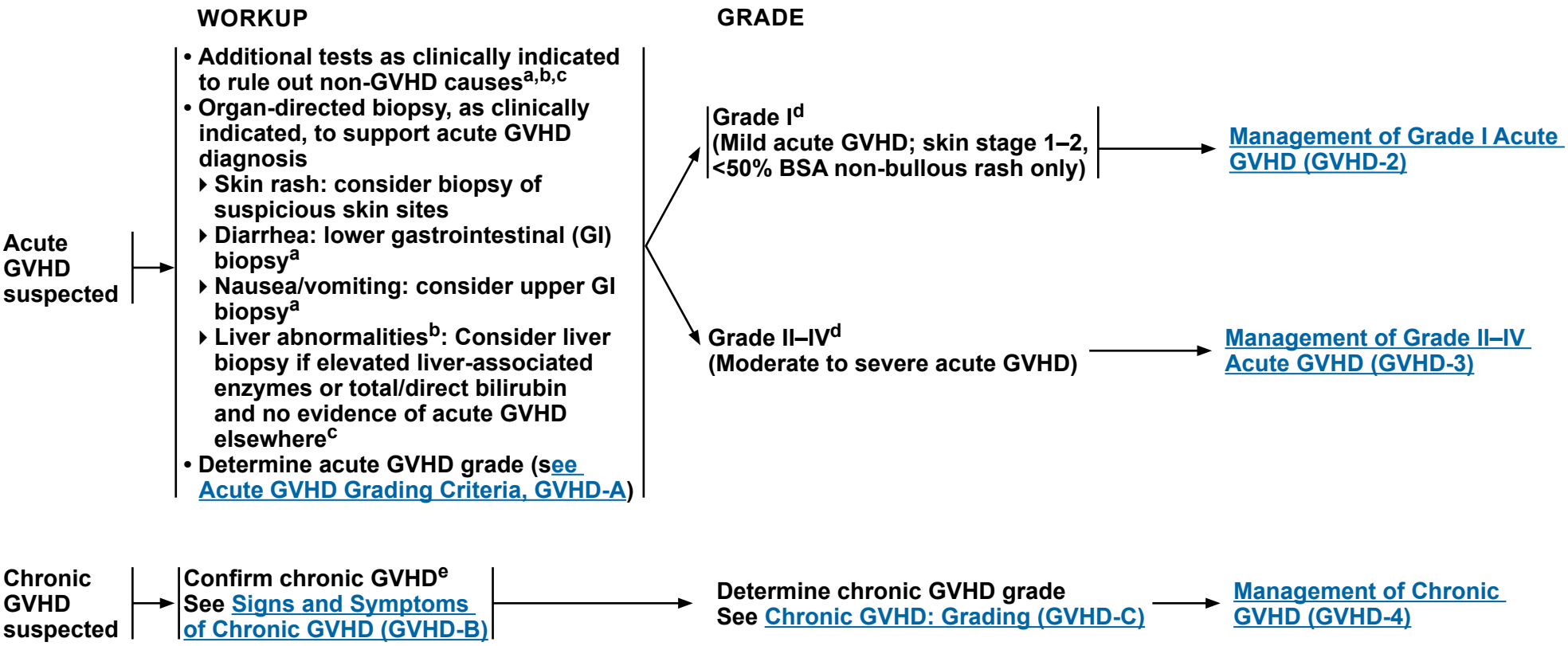
Note: All recommendations are category 2A unless otherwise indicated.

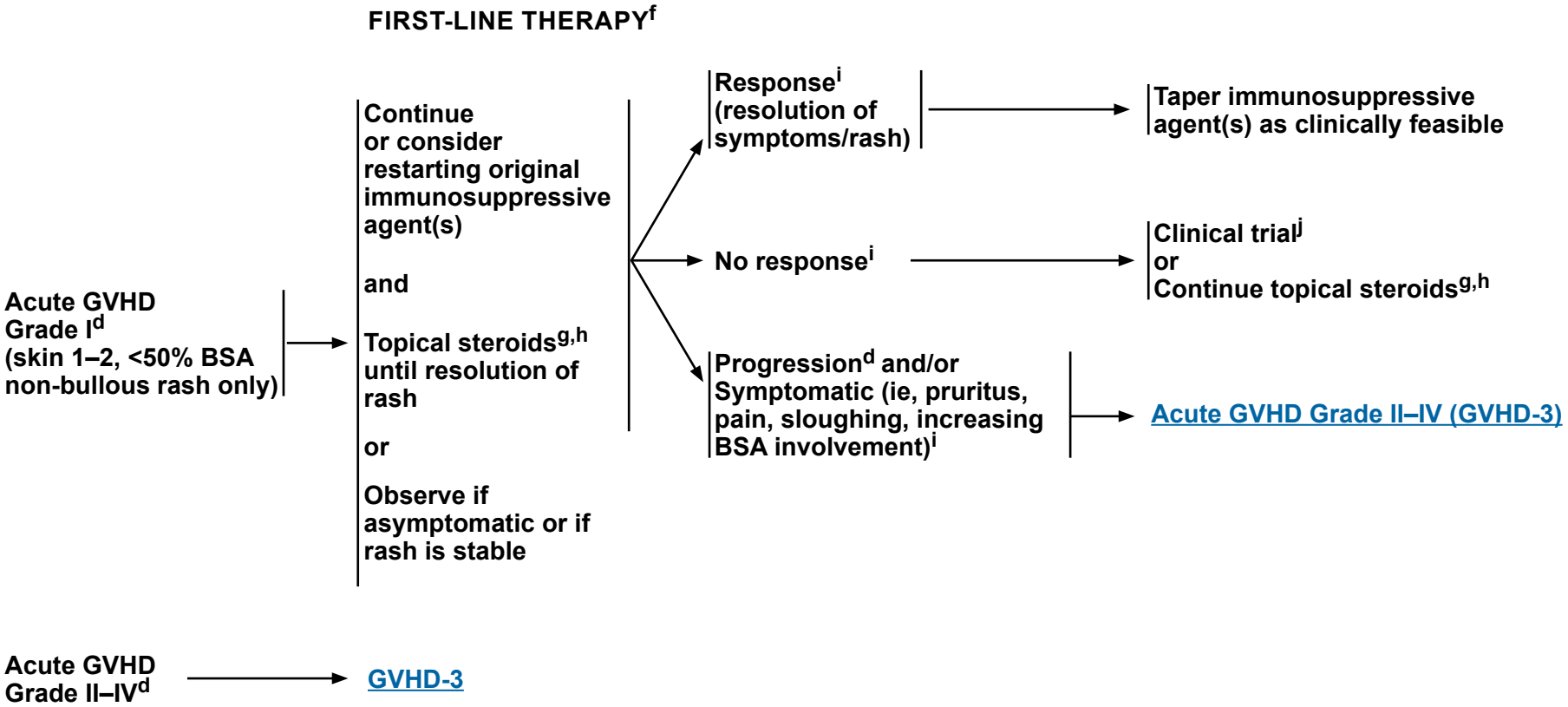
DIAGNOSIS/WORKUP OF GVHD



[a] GI biopsy (esophagogastroduodenoscopy, colonoscopy, and/or flexible sigmoidoscopy) as clinically indicated to support the diagnosis of GI acute GVHD. Stool testing may be used to rule out infectious etiology of diarrhea.
[b] Consider imaging as clinically indicated to evaluate the etiology of LFT abnormalities (eg, ultrasound and/or CT scan of the abdomen).
[c] Liver biopsy and/or viral reactivation testing may be used to rule out non-GVHD causes of liver dysfunction (ie, VOD/SOS, infection, effects of preparatory regimen, drug toxicity). Transjugular approach may be preferred, especially if thrombocytopenia or coagulopathy is present.
[d] Acute GVHD Grading Criteria (GVHD-A).
[e] While a biopsy may be done to confirm chronic GVHD, a biopsy is not always feasible and is not mandatory if the patient has at least one of the diagnostic findings of chronic GVHD (Jagasia MH, et al. Biol Blood Marrow Transplant 2015;21:389-401).

Note: All recommendations are category 2A unless otherwise indicated.

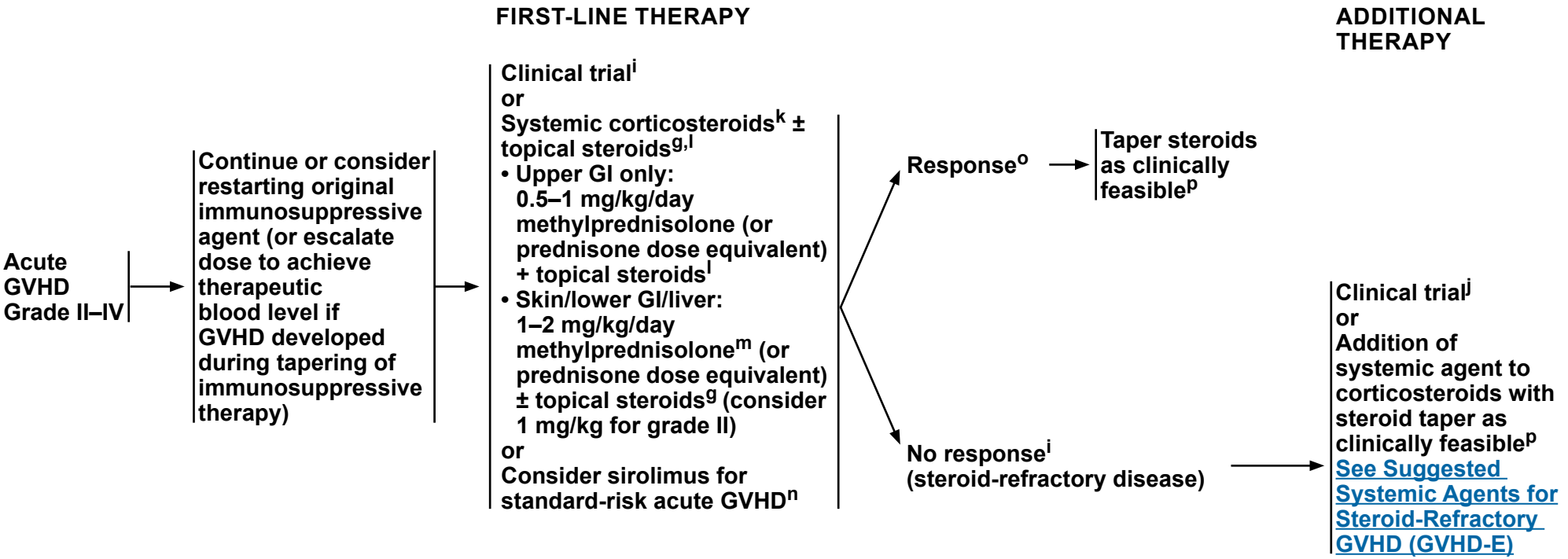
MANAGEMENT OF ACUTE GVHD



[d] Acute GVHD Grading Criteria (GVHD-A).
[f] For recommendations on antibiotic prophylaxis during immunosuppressive therapy, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[g] Topical steroids (eg, triamcinolone, clobetasol) and/or topical tacrolimus. Medium to high potency formulations are recommended except on the face or intertriginous areas where low potency hydrocortisone can be used.
[h] Antihistamines may be used for symptoms (eg, itching), as needed.
[i] GVHD Steroid Response Definitions/Criteria (GVHD-D).
[j] Enrollment in well-designed clinical trials should be encouraged, since no standard, effective therapy for steroid-refractory GVHD has been identified. The selection of therapy for steroid-refractory GVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF ACUTE GVHD



[g] Topical steroids (eg, triamcinolone, clobetasol) and/or topical tacrolimus. Medium to high potency formulations are recommended except on the face or intertriginous areas where low potency hydrocortisone can be used.

[i] GVHD Steroid Response Definitions/Criteria (GVHD-D).

[j] Enrollment in well-designed clinical trials should be encouraged, since no standard, effective therapy for steroid-refractory GVHD has been identified. The selection of therapy for steroid-refractory GVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

[k] Addition of other systemic agents in conjunction with systemic steroids as initial therapy for acute GVHD should not be done outside the context of a well-designed clinical trial.

[l] In a phase III randomized controlled trial, initial treatment with systemic prednisone at 0.5 mg/kg/day in conjunction with GI topical steroids (beclomethasone dipropionate [available as a compounded agent] ± budesonide) was safe and effective for upper GI symptoms (ie, nausea, vomiting, anorexia), with or without skin involvement (<50% BSA), in patients with diarrhea volumes of <1000 mL/day (Mielcarek M, et al. Haematologica 2015;100:842-848). Of note, budesonide is less effective at treating the upper GI tract.

[m] There is no role for escalation of methylprednisolone dose beyond 2 mg/kg/day.

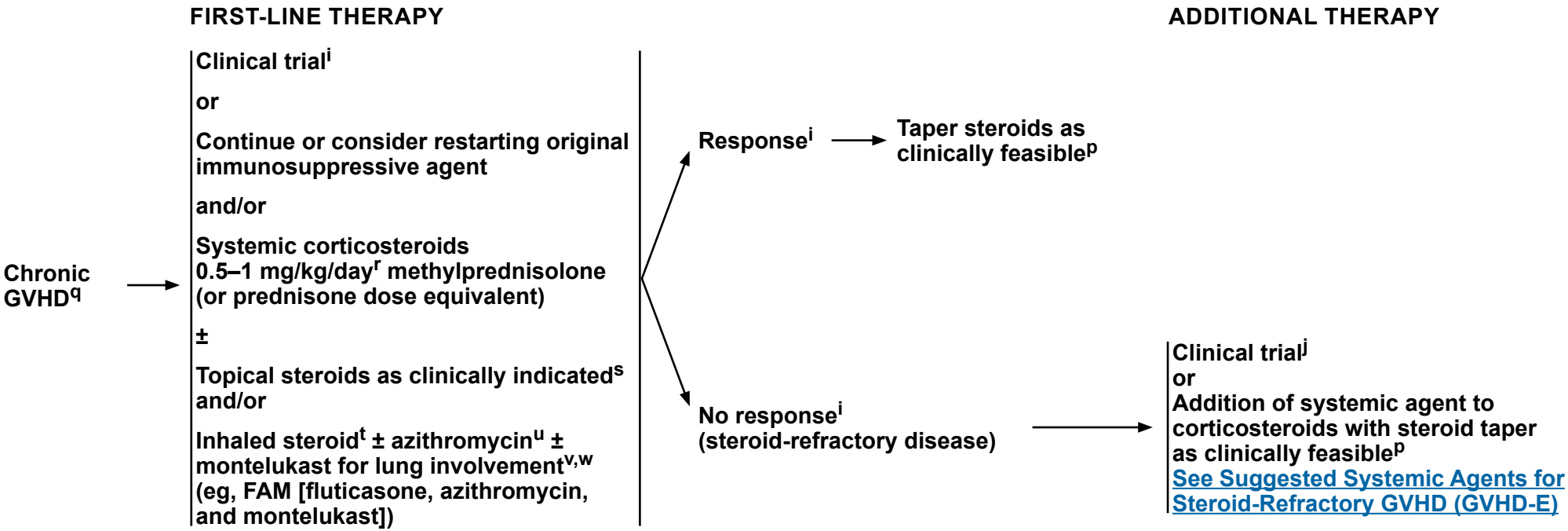
[n] Standard-risk acute GVHD as defined by clinical risk score and biomarker status. (CTN1501 trial: Pidala J, et al. Blood 2020;135:97-107.)

[o] Complete resolution of GVHD or improvement in at least one organ without any progression in any other organs.

[p] If response, taper systemic steroids to mitigate long-term steroid side effects and risk of infection, as clinically feasible.

Note: All recommendations are category 2A unless otherwise indicated.

MANAGEMENT OF CHRONIC GVHD



[i] GVHD Steroid Response Definitions/Criteria (GVHD-D).

[j] Enrollment in well-designed clinical trials should be encouraged, since no standard, effective therapy for steroid-refractory GVHD has been identified. The selection of therapy for steroid-refractory GVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

[p] If response, taper systemic steroids to mitigate long-term steroid side effects and risk of infection, as clinically feasible.

[q] Multidisciplinary care aimed at avoiding organ damage and preserving function is recommended.

[r] Initial dose may vary depending on organs involved, GVHD severity, patient comorbidities, and overlapping syndromes.

[s] Topical steroids (eg, triamcinolone, clobetasol), topical estrogen (vulvovaginal GVHD), topical tacrolimus, or dexamethasone oral rinse (oral GVHD). Medium- to high-potency formulations are recommended except on the face or intertriginous areas where low-potency hydrocortisone can be used.

[t] Examples of acceptable inhaled steroids include budesonide or fluticasone.

[u] Azithromycin should only be used for treatment of bronchiolitis obliterans syndrome (BOS), not for prophylaxis, due to a suggestion of an increased risk of leukemic relapse or secondary neoplasms in recent clinical trials. Bergeron A, et al. JAMA 2017;318:557-566. Cheng GS, et al. Biol Blood Marrow Transplant 2020;26:392-400.

[v] Patients with progression/worsening of lung chronic GVHD following 2–3 lines of therapy may be evaluated for lung transplant.

[w] PFT at onset of chronic GVHD and subsequently as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.

ACUTE GVHD: STAGING AND GRADING

Commonly used criteria for the staging/grading of adults with acute GVHD include:
- **Keystone (modified Glucksberg) criteria (see below)**
- **MAGIC criteria (GVHD-A, 2 of 2)**
- **Minnesota criteria (MacMillan ML, et al. Biol Blood Marrow Transplant 2015;21:761-767; https://z.umn.edu/MNAcuteGVHDRiskScore)**

Modified Glucksberg Criteria: Staging and Grading of Acute GVHD*

	Extent of Organ Involvement		
	Skin	**Liver**	**Gut**
Stage			
1	Rash on <25% of skin[a]	Bilirubin 2–3 mg/dl[b]	Diarrhea >500 ml/day[c] or persistent nausea[d]
2	Rash on 25–50% of skin	Bilirubin 3–6 mg/dl	Diarrhea >1000 ml/day
3	Rash on >50% of skin	Bilirubin 6–15 mg/dl	Diarrhea >1500 ml/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1–2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2–3	Stage 2–4
IV[f]	Stage 4	Stage 4	—

*Used with permission: Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995;15:825-828.

[a] Use 'Rule of Nines' or burn chart to determine extent of rash.
[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.
[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on BSA. Gut staging criteria for pediatric patients was not discussed at the consensus conference. Downgrade one stage if an additional cause of diarrhea has been documented.
[d] Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.
[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.
[f] Grade IV may also include lesser organ involvement but with extreme decrease in performance status.

Note: All recommendations are category 2A unless otherwise indicated.

ACUTE GVHD: STAGING AND GRADING

MAGIC Criteria: Acute GVHD Target Organ Staging & Overall Clinical Grade[g]

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500–999 mL/day or 3–4 episodes/day Child: 10–19.9 mL/kg/day or 4–6 episodes/day
2	Maculopapular rash 25%–50% BSA	3.1–6 mg/dL		Adult: 1000–1500 mL/day or 5–7 episodes/day Child: 20–30 mL/kg/day or 7–10 episodes/day
3	Maculopapular rash >50% BSA	6.1–15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Grade (based on most severe target organ involvement)	
0	No stage 1–4 of any organ.
I	Stage 1–2 skin without liver, upper GI, or lower GI involvement.
II	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
III	Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI.
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0–1 upper GI

[g] Reproduced with permission from Elsevier: Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant 2016;22(1):4-10. DOI: 10.1016/j.bbmt.2015.09.001. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: DIAGNOSIS

Signs and Symptoms of Chronic GVHD[a]				
Organ Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GVHD)	**Distinctive**[b] (seen in chronic GVHD, but insufficient to establish a diagnosis)	**Other features for unclassified entities**[c]	**Common**[d] (seen with both acute and chronic GVHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) • Premature gray hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.

[b] In all cases, infection, drug effect, malignancy, or other causes must be excluded.
[c] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.
[d] Common refers to shared features by both acute and chronic GVHD.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: DIAGNOSIS

Signs and Symptoms of Chronic GVHD[a]				
Organ Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GVHD)	**Distinctive**[b] (seen in chronic GVHD, but insufficient to establish a diagnosis)	**Other features for unclassified entities**[c]	**Common**[d] (seen with both acute and chronic GVHD)
Genitalia	• Lichen planus-like features • Lichen sclerosus-like features • Vaginal scarring or clitoral/labial agglutination • Phimosis or urethral/meatus scarring or stenosis	• Erosions • Fissures • Ulcers		
GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children)
Liver				• Total bilirubin, alkaline phosphatase (AP) > 2 × upper limit of normal (ULN) • Alanine transaminase (ALT) > 2× ULN
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • BOS[e]	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia (COP)[f] • Restrictive lung disease[f]	

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.

[b] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[c] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

[d] Common refers to shared features by both acute and chronic GVHD.

[e] BOS can be diagnostic for lung chronic GVHD only if distinctive signs or symptoms of chronic GVHD are present in another organ. BOS diagnosis requires the following criteria:

1. Forced expiratory volume in the first second (FEV1)/vital capacity (VC) ratio <0.7 or the fifth percentile predicted.
2. FEV1 <75% of predicted with ≥10% decline within 2 years. FEV1 should not be corrected to >75% of predicted after albuterol inhalation, and the absolute decline for the corrected values should still remain at ≥10% over 2 years.
3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as chest radiographs, CT scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).
4. One of the 2 supporting features of BOS: Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest CT; or evidence of air trapping by PFT: residual volume >120% of predicted or residual volume/total lung capacity elevated outside the 90% confidence interval.

If a patient already carries the diagnosis of chronic GVHD by virtue of organ involvement elsewhere, then only the first 3 criteria above are necessary to document chronic GVHD lung involvement.

[f] Pulmonary entities under investigation or unclassified.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: DIAGNOSIS

Signs and Symptoms of Chronic GVHD[a]				
Organ Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GVHD)	**Distinctive**[b] (seen in chronic GVHD, but insufficient to establish a diagnosis)	**Other features for unclassified entities**[c]	**Common**[d] (seen with both acute and chronic GVHD)
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis[g]	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (autoimmune hemolytic anemia [AIHA], immune thrombocytopenia [ITP]) • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.
[b] In all cases, infection, drug effect, malignancy, or other causes must be excluded.
[c] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.
[d] Common refers to shared features by both acute and chronic GVHD.
[g] Diagnosis of chronic GVHD requires biopsy.

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]	Score 0	Score 1	Score 2	Score 3
Performance Score: _____ KPS ECOG (circle one)	Asymptomatic and fully active (ECOG 0; KPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS 80–90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS 60–70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3–4, KPS <60%)
Skin[b]				
Score % BSA: _____ GVHD features to be scored by BSA (check all that apply): ○ Maculopapular rash/erythema ○ Lichen planus-like features ○ Sclerotic features ○ Papulosquamous lesions or ichthyosis ○ Keratosis pilaris-like GVHD	No BSA involved	1–18% BSA	19–50% BSA	>50% BSA
Skin Features Score:_____	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	Check all that apply: ○ Deep sclerotic features ○ "Hidebound" (unable to pinch) ○ Impaired mobility ○ Ulceration

Other skin GVHD features, NOT scored by BSA (check all that apply):
○ Hyperpigmentation
○ Hypopigmentation
○ Poikiloderma
○ Severe or generalized pruritis
○ Hair involvement
○ Nail involvement
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.

[b] Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of BSA score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]				
	Score 0	**Score 1**	**Score 2**	**Score 3**
Mouth				
Lichen planus-like features present: ○ Yes ○ No	No symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs with partial limitation of oral intake	Severe symptoms with disease signs on examination with major limitation of oral intake
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
Eyes				
Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist ○ Yes ○ No ○ Not examined	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
GI Tract				
Check all that apply: ○ Esophageal web/proximal stricture or ring ○ Dysphagia ○ Anorexia ○ Nausea ○ Vomiting ○ Diarrhea ○ Weight loss ≥5%[c] ○ Failure to thrive	No symptoms	Symptoms without significant weight loss[c] (<5%)	Symptoms associated with mild to moderate weight loss[c] (5–15%) OR moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss[c] >15%, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.
[c] Weight loss within 3 months.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]	Score 0	Score 1	Score 2	Score 3
Liver				
	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤3 mg/dL or ALT > 5 x ULN	Elevated total bilirubin >3 mg/dL
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
Lungs[d]				
Symptom score: _____	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O_2)
Lung score: _____% FEV1 Pulmonary function tests: Not performed	FEV1 ≥80%	FEV1 60–79%	FEV1 40–59%	FEV1 ≤39%
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
Joints and Fascia				
P-ROM score (see GVHD-C, 5 of 5) Shoulder (1-7): ___ Elbow (1-7): ___ Wrist/finger (1-7): ___ Ankle (1-4): ___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM *AND* significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
Genital Tract[e]				
○ Not examined Currently sexually active: ○ Yes ○ No	No signs	Mild signs[e] and females with or without discomfort on exam	Moderate signs[e] and may have symptoms with discomfort on exam	Severe signs[e] with or without symptoms
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.

[d] Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

[e] Referral and close surveillance by a specialist is recommended for early detection of chronic GVHD and full assessment of disease.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0, mild – 1, moderate – 2, severe – 3)

- ○ Ascites (serositis) _____
- ○ Pericardial effusion _____
- ○ Pleural effusion(s) _____
- ○ Nephrotic syndrome _____
- ○ Myasthenia gravis _____
- ○ Peripheral neuropathy _____
- ○ Polymyositis _____
- ○ Weight loss >5% without GI symptoms _____
- ○ Eosinophilia >500/µl _____
- ○ Platelets <100,000/µl _____
- ○ Others (specify): _____

Overall GVHD Severity

Opinion of the evaluator: ○ No GVHD ○ Mild ○ Moderate ○ Severe

NIH Global Severity of Chronic GVHD[a]

Mild chronic GVHD	Moderate chronic GVHD	Severe chronic GVHD
1 or 2 organs involved with no more than score 1 *plus* Lung score 0	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Key points:

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

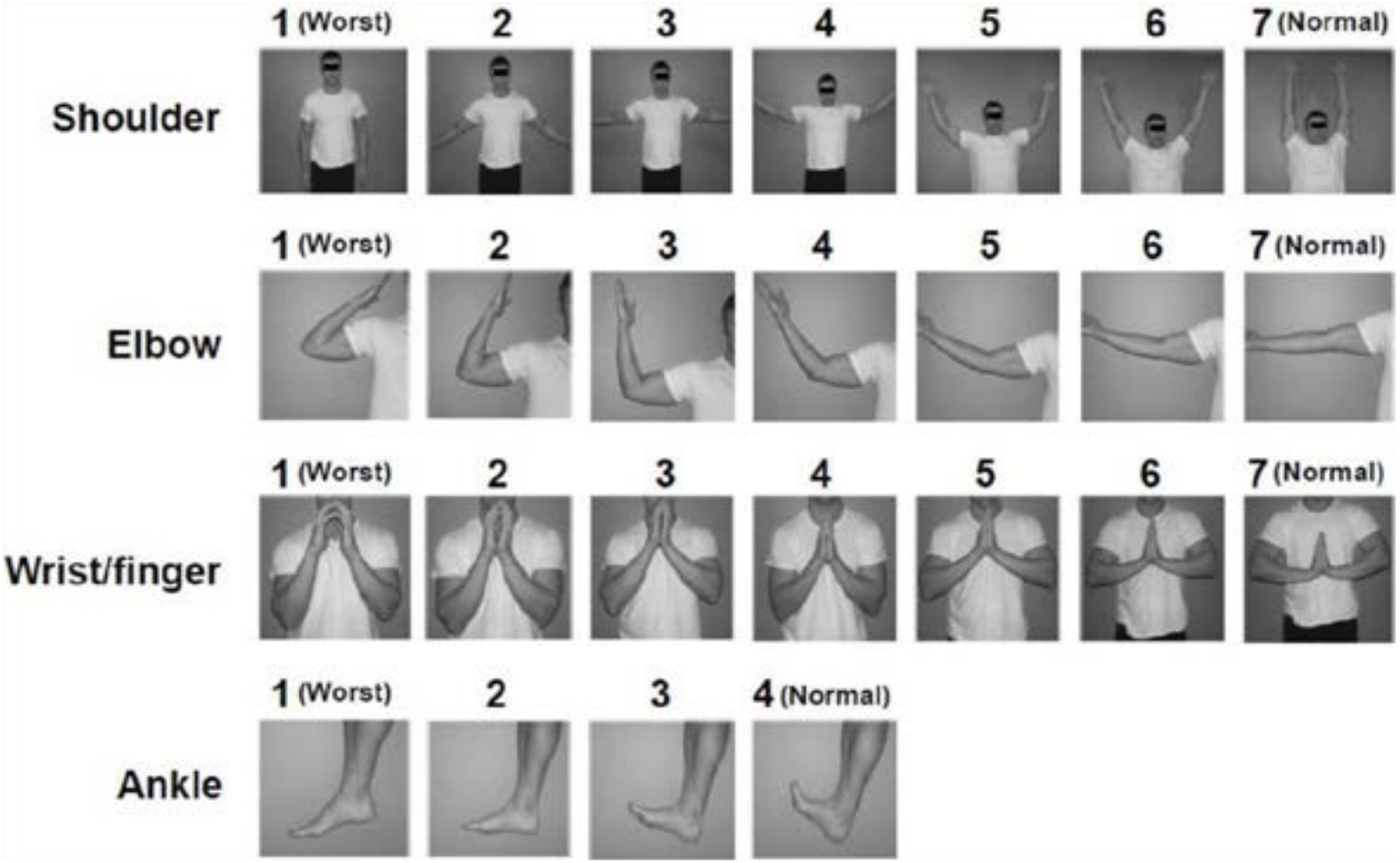
[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

CHRONIC GVHD: GRADING

Photographic Range of Motion (P-ROM)[a]



[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant 2015;21:389-401.

Note: All recommendations are category 2A unless otherwise indicated.

GVHD STEROID RESPONSE DEFINITIONS/CRITERIA

Response Criteria for GVHD Clinical Trials[a]

	Acute GVHD Steroid Response	Chronic GVHD Steroid Response
Steroid Refractoriness or Resistance	Progression of acute GVHD within 3–5 days of therapy onset with ≥2 mg/kg/day of prednisone OR Failure to improve within 5–7 days of treatment initiation OR Incomplete response after more than 28 days of immunosuppressive treatment including steroids	Chronic GVHD progression while on prednisone at ≥1 mg/kg/day for 1–2 weeks OR Stable GVHD disease while on ≥0.5 mg/kg/day (or 1 mg/kg every other day) of prednisone for 1–2 months
Steroid Dependence	Inability to taper prednisone below 2 mg/kg/day OR A recurrence of acute GVHD activity during steroid taper	Inability to taper prednisone below 0.25 mg/kg/day (or >0.5 mg/kg every other day) in at least two unsuccessful attempts separated by at least 8 weeks
Steroid Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

Chronic GVHD Response Criteria (GVHD-D, 2 of 2)

[a] Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT−NIH−CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant 2018;53:1401-1415.

Note: All recommendations are category 2A unless otherwise indicated.

GVHD STEROID RESPONSE DEFINITIONS/CRITERIA

Chronic GVHD Response Criteria[b]

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified Oral Mucosa Rating Score 0 after previous involvement	Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points	Increase in NIH Modified Oral Mucosa Rating Score of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and total bilirubin after previous elevation of one or more	Decrease by 50%	Increase by 2x ULN
Lungs	-Normal %FEV1 after previous involvement -If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	-Increase by 10% predicted absolute value of %FEV1 -If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	-Decrease by 10% predicted absolute value of %FEV1 -If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and Fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least one measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0–10 scale	Clinician overall severity score increases by 2 or more points on a 0–10 scale

[b] Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant 2015;21:984-999.

Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD

- **Participation in clinical trials is encouraged.**
- **The following systemic agents are used in conjunction with corticosteroids for steroid-refractory GVHD. There is insufficient evidence to recommend one systemic agent as preferred over another. However, these are the most commonly used agents among the NCCN Member Institutions.**
- **The selection of systemic agent should be based on institutional preferences, physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.**

Suggested Systemic Agents for Steroid-Refractory GVHD[a]

Acute GVHD[1]	Chronic GVHD
The following agents are often used in conjunction with the original immunosuppressive agent.	*While the following systemic agents may be used to treat chronic GVHD in any organ, some agents are used more commonly for certain sites involved with chronic GVHD based on available data (see Discussion).*
Category 1 agents • Ruxolitinib (category 1)[b,2]	**Category 1 agents** • Ruxolitinib (category 1)[b,23-25]
Alternative agents (listed in alphabetical order) • Alemtuzumab[3,4] • Alpha-1 antitrypsin[5] • ATG[6] • Basiliximab[7] • CNIs (eg, tacrolimus, cyclosporine) • Etanercept[8] • Extracorporeal photopheresis (ECP)[c,9] • Infliximab[10] • mTOR inhibitors (eg, sirolimus)[11,12] • Mycophenolate mofetil[13,14] • Pentostatin[15-17] • Tocilizumab[d,18-21] • Vedolizumab[22]	**FDA-approved agents (listed in order by FDA approval date)** • Ibrutinib[e,26] • Belumosudil[f,27] • Axatilimab-csfr[g,28] **Alternative agents (listed in alphabetical order)** • Abatacept[29] • Alemtuzumab[30,31] • CNIs (eg, tacrolimus, cyclosporine) • Etanercept[32] • ECP[c,9] • Hydroxychloroquine[33] • Imatinib[34,35] • Interleukin-2 (IL-2)[36] • Low-dose methotrexate[37-39] • mTOR inhibitors (eg, sirolimus)[40-42] • Mycophenolate mofetil[43] • Pentostatin[44-46] • Rituximab[d,47]

[a] For patients receiving immunosuppressive agents for GVHD, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[b] Ruxolitinib is FDA approved for the treatment of adult and pediatric patients (age ≥12 years) with either steroid-refractory acute GVHD, or chronic GVHD after failure of one or two lines of systemic therapy.

[c] Psoralen and ultraviolet A irradiation (PUVA) may be used for sclerotic or cutaneous GVHD if ECP is not available or feasible.

[d] An FDA-approved biosimilar is an appropriate substitute.

[e] Ibrutinib is FDA approved for the treatment of adult and pediatric patients ≥1 year and older with chronic GVHD after failure of one or more lines of systemic therapy. Ibrutinib should be used with caution in patients with a history of heart arrhythmias or heightened risk of bleeding.

[f] Belumosudil is FDA approved for the treatment of adult and pediatric patients (age ≥12 years) with chronic GVHD after failure of two or more prior lines of systemic therapy.

[g] Axatilimab-csfr is FDA approved for the treatment of adult and pediatric patients weighing ≥40 kg with chronic GVHD after failure of at least two prior lines of systemic therapy.

Note: All recommendations are category 2A unless otherwise indicated.

References

SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD
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Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD
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Note: All recommendations are category 2A unless otherwise indicated.

GVHD SUPPORTIVE CARE

All Patients

- Supportive care is essential for patients with GVHD.[1]
- Special attention is required for the following issues:
  - Appropriate antimicrobial prophylaxis should be used with escalating immunosuppressive therapy. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
  - Surveillance for CMV reactivation is recommended in appropriate patients. Additional viral surveillance may be considered.
  - Vaccination:
    - ◊ Avoid live vaccines if patient is on immunosuppressive therapy or has active GVHD.
    - ◊ COVID-19 re-vaccination is recommended in all patients 3 months post-transplant. See the CDC for Use of COVID-19 Vaccines in the US.
  - IV immunoglobulin (IVIG) replacement: There may be subsets of patients where prophylactic immunoglobulin replacement after bone marrow transplant may be considered, such as in recipients of a UCB transplant, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in patients with chronic GVHD with recurrent sinopulmonary infections.[2]
  - HD steroid therapy may be associated with glucose intolerance, hypertension, adrenal insufficiency, poor wound healing, myopathy, osteoporosis, vitamin D deficiency, and mood swings.
    - ◊ Vitamin D and calcium supplementation should be considered for patients on HD steroid. Monitoring of vitamin D level is recommended.
  - DEXA scan (in particular for patients with either current or past exposure to HD steroids) with treatment and repeat imaging as indicated based on results.
  - Dermatologic, dental, and ophthalmologic evaluation at appropriate intervals beginning 6–12 months post-transplant.
  - Ursodiol for patients with liver GVHD may be considered.[3,4]

Acute GVHD

- Skin
  - Avoid direct sunlight, use sunscreen, and avoid photosensitizing agents.
  - Dermatologic assessment is recommended for advanced disease.
- GI Tract
  - Cautious use of opioid medications is recommended for severe abdominal pain (risk of ileus).
- GI Tract (continued)
  - Cautious use of octreotide is recommended for diarrhea control. It should be stopped once diarrhea resolves, or after 7 days of treatment (risk of ileus).
  - Prolonged oral beclomethasone[a] or budesonide may cause adrenal insufficiency. Monitor for symptoms and evaluate as clinically necessary.
- Nutrition
  - Patients may suffer from malnutrition and protein-losing enteropathy with deficiency of trace elements (eg, magnesium, zinc) and vitamins (eg, thiamine, vitamins B12 and D).
  - Total parenteral nutrition and bowel rest should be considered in patients with voluminous diarrhea or poor tolerance to oral intake.
  - Monitoring for thiamine deficiency should be considered for patients with altered mental status.

Chronic GVHD

- Oral
  - Sialagogues (eg, cevimeline) may be considered with severe xerostomia.
  - Dental/oral surgery assessment is recommended for suspicious oral lesions (risk of malignancy).
  - Consider dexamethasone mouth rinses (swish and spit).
  - Monitor for oral thrush and use appropriate antifungal topical therapy as indicated.
- Eyes
  - Ophthalmologic assessment is recommended.
  - Patients may benefit from artificial tears, autologous serum drops, punctal plugs, or gas-permeable scleral lenses.
  - Patients with severe ocular sicca may benefit from cholinergic agents (cevimeline or pilocarpine).
- GI Tract
  - GI consultation is recommended for patients with esophageal stricture (may benefit from periodic dilatation).
  - Workup is recommended for malabsorption from prolonged diarrhea (patients with pancreatic atrophy may benefit from oral pancreatic enzymes).
- Genital Tract
  - Concerns around genitourinary symptoms (eg, urinary issues, erectile dysfunction, vulvovaginal symptoms) should be addressed with referrals as appropriate (ie, dermatology, urology, gynecology).
- Physical therapy may help patients with musculoskeletal, sclerotic, or neuromuscular disease.

Note: All recommendations are category 2A unless otherwise indicated.

Footnotes and References

GVHD SUPPORTIVE CARE
FOOTNOTES AND REFERENCES

Footnotes

[a] Oral beclomethasone is available as a compounded agent.

References

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Note: All recommendations are category 2A unless otherwise indicated.

ABBREVIATIONS

ADL	activities of daily living
AIHA	autoimmune hemolytic anemia
ALT	alanine transaminase
AP	alkaline phosphatase
ATG	antithymocyte globulin
AUC	area under the curve
BOS	bronchiolitis obliterans syndrome
BSA	body surface area
CMV	cytomegalovirus
CNI	calcineurin inhibitor
COP	cryptogenic organizing pneumonia
DEXA	dual-energy x-ray absorptiometry
DLCO	diffusing capacity of the lungs for carbon monoxide
ECOG	Eastern Cooperative Oncology Group
ECP	extracorporeal photopheresis
FEV1	forced expiratory volume in the first second
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCT	hematopoietic cell transplant
HCT-CI	HCT Comorbidity Index
HCV	hepatitis C virus
HD	high-dose
HL	Hodgkin lymphoma
HLA	human leukocyte antigen
HSV	herpes simplex virus
ITP	immune thrombocytopenia
IVIG	intravenous immunoglobulin
KCS	keratoconjunctivitis sicca
KPS	Karnofsky Performance Status
LFT	liver function test
LVEF	left ventricular ejection fraction
MA	myeloablative
NHL	non-Hodgkin lymphoma
NMA	non-myeloablative
NRM	non-relapse mortality
PFT	pulmonary function test
P-ROM	photographic range of motion
PTCy	post-transplant cyclophosphamide
PUVA	psoralen and ultraviolet A irradiation
RIC	reduced-intensity conditioning
ROM	range of motion
STR	short tandem repeat
TBI	total body irradiation
UCB	umbilical cord blood
ULN	upper limit of normal
VC	vital capacity
VOD/SOS	veno-occlusive disease/ sinusoidal obstruction syndrome
VZV	varicella zoster virus

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2024
Hematopoietic Cell Transplantation (HCT)

Discussion

This discussion corresponds to the NCCN Guidelines for Hematopoietic Cell Transplantation. Last updated August 30, 2024.

Table of Contents

Overview

Hematopoietic cell transplantation (HCT) involves the infusion of hematopoietic cells after preparation with cytotoxic conditioning regimens in order to eradicate disease and establish adequate hematopoietic and immune function.[1] HCT is potentially curative for patients with certain types of hematologic malignancies and is also used to support patients undergoing high-dose chemotherapy for the treatment of certain solid tumors. HCT is classified as autologous or allogeneic based on the origin of hematopoietic cells. An autologous HCT uses the patient's own cells while an allogeneic HCT uses hematopoietic cells from a human leukocyte antigen (HLA)-compatible related or unrelated donor. Prior to HCT, most patients receive chemotherapy, immunotherapy, and/or radiation therapy for pre-transplant conditioning (conditioning regimen). In allogeneic HCT, conditioning regimens are administered in order to eradicate malignant cells in the bone marrow (if using a myeloablative [MA] regimen) and to immunosuppress the recipient so that engraftment of healthy donor cells can occur.[1] In autologous HCT, MA conditioning regimens are used to treat the malignancy. This is followed by rescue infusion of the patient's own cells, which are collected and stored before high-dose therapy, in order to restore hematopoiesis and reconstitute the immune system.[1]

The Center for International Blood and Marrow Transplant Research (CIBMTR) estimates that 8295 allogeneic transplants and 11,434 autologous transplants were performed in the United States in 2021.[2] Acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndromes (MDS), and myeloproliferative neoplasms (MPN) were the most common malignancies treated with allogeneic HCT, while autologous HCT was used most frequently in multiple myeloma (MM)/plasma cell disorders, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL).[2] Difficult logistics and high costs create significant barriers to access for many patients. A systematic review found older age, lower socioeconomic status, and non-white race to be associated with reduced access to HCT.[3]

Outcomes of HCT vary according to the type and stage of the disease being treated, the overall health and comorbidities of the patient, and for allogeneic HCT, the degree of HLA-mismatch between donor and recipient, the source of the hematopoietic cells, and the immunosuppressive regimen given post-transplant to prevent graft-versus-host disease (GVHD), a common complication of allogeneic HCT.[1,4] Hematopoietic cells can be obtained from peripheral blood, bone marrow, or umbilical cord blood (UCB). Several clinical factors should be considered when determining the optimal graft source for an individual patient, including disease type, disease stage, patient comorbidities, and the urgency for transplantation.[5] The use of peripheral blood progenitor cells (PBPCs) has largely replaced the use of bone marrow grafts (in particular for autologous HCT) due to the ease of collection, avoidance of general anesthesia, more rapid engraftment rates and reduced risk of graft failure.[6-8] However, allogeneic PBPC transplants are associated with an increased risk of chronic graft-versus-host disease (cGVHD) compared to bone marrow transplants.[8-10]

Advantages of using UCB grafts include rapid cell procurement, lower incidence of cGVHD, and less stringent HLA-matching requirements; however, use of UCB is limited by the cell doses that can be achieved in recipients with high body weight and is also associated with delayed engraftment, higher risk for graft failure, higher rates of infectious complications, and higher costs for procurement.[11] Therefore, UCB transplantation is typically reserved for patients without an HLA-matched donor and should be performed in centers with expertise in this procedure. Patients without an HLA-matched donor may also be candidates for HCT from a haploidentical, or half HLA-matched, related donor. Advantages of haploidentical HCT include lower costs for procurement and rapid

availability of the cell products, while disadvantages include increased risk of graft failure and GVHD as compared to HLA-matched HCT.[12] The use of post-transplant cyclophosphamide has been shown to reduce the incidence of GVHD in haploidentical HCT recipients.[13] Several investigators have also advocated for the use of bone marrow grafts for haploidentical HCT and HLA-mismatched unrelated donor HCT to reduce the risk of GVHD.[9,10,14]

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Cell Transplantation, an electronic search of the PubMed database was performed to obtain key literature in hematopoietic cell transplantation published since the previous Guidelines update, using the following search terms: hematopoietic stem cell transplant; allogeneic cell transplant; autologous cell transplant; and graft-versus-host disease. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[15]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Autologous Hematopoietic Cell Transplant

Autologous HCT is performed to replace or "rescue" hematopoietic cells damaged by the high-dose chemotherapy used to treat certain advanced or high-risk hematologic malignancies and solid tumors. Hematopoietic cells collected from the patient prior to receipt of high-dose chemotherapy are infused back into the patient after administration of the preparative regimen.[1] High-dose chemotherapy with autologous HCT is an effective

treatment for several hematologic malignancies, including MM,[16-20] relapsed/refractory HL,[21,22] and relapsed/refractory NHL.[23-25] However, while autologous HCT may prolong PFS and OS for patients with MM, it is not curative.[26] Autologous HCT is also used in patients receiving high-dose chemotherapy for the treatment of certain solid tumors, including testicular germ cell tumors[27-30] and some central nervous system tumors,[31-35] for whom hematologic toxicity would otherwise limit chemotherapy administration. Additionally, autologous HCT is sometimes used as consolidation therapy for certain patients with AML.[36]

Since autologous HCT uses the patient's own cells, these patients do not typically develop GVHD. Additionally, these patients often have a lower risk of infectious complications since they do not receive post-transplant immunosuppression. While autologous HCT is associated with less morbidity and mortality than allogeneic HCT, risk of disease relapse is often higher with autologous HCT when compared to allogeneic HCT.[1] There is no benefit of graft purging (ex vivo manipulation to eliminate residual neoplastic cells) prior to autologous HCT. [37,38]

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is performed to replace malignant (or defective) hematopoietic cells using those from a healthy donor. A preparative regimen consisting of chemotherapy (often high-dose), immunotherapy, and/or total body (or lymphoid) irradiation is given prior to allogeneic HCT to eliminate residual malignant cells and to suppress the recipient's immune system, which is necessary to allow for engraftment of the donor-derived cells and to prevent graft rejection. There are three potential donor sources for hematopoietic cells: related donor (family members), unrelated volunteers (from donor registries), and UCB units.[1] HLA matching is the most imperative factor when choosing a donor. An HLA-matched sibling remains the preferred donor source, although post-transplant survival is comparable among patients receiving hematopoietic cells from HLA-matched unrelated donors for several diseases.[39,40] When a patient has no HLA-matched related or unrelated donors, a haploidentical donor or UCB may be used. A haploidentical donor is a first-degree relative who matches at half of the HLA loci of the patient. Emerging data suggest that haploidentical HCT with post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis may yield comparable outcomes to HLA-matched HCT.[41,42] Of note, a retrospective multi-center analysis found that use of haploidentical donors beyond first-degree relatives may negatively affect survival.[43] UCB transplant was first reported to cure a child with Fanconi anemia,[44] and has been subsequently used successfully in patients with hematologic malignancies.[45,46] Although the outcomes of UCB transplants have been comparable to HLA-matched transplants in some reports,[39,47-50] delayed engraftment and delayed immune reconstitution often result in increased risks of infectious complications. Additionally, the high degree of HLA disparity that typically occurs with haploidentical or UCB donors has been associated with an increased risk of graft failure.[39,47-51]

Allogeneic HCT improves outcomes in patients with many subtypes of AML[52] and ALL,[53] patients with MDS,[54] patients with relapsed and/or refractory HL[55] and NHL,[56] and certain patients with chronic myeloid leukemia (CML),[57] such as those with advanced phase disease and those whose disease is refractory to tyrosine kinase inhibitor therapy, including patients with certain high risk *ABL* kinase mutations. Allogeneic HCT has also been offered to some patients with chronic lymphocytic leukemia (CLL),[58] MM,[59] and primary and secondary myelofibrosis,[60] although benefits for these patients are less clear and toxicity may be higher. Decisions regarding allogeneic HCT are always complex and should be carefully weighed as part of shared decision-making between the transplant team and patient. Donor-derived immune cells often exert an immune-mediated cytotoxic effect against the recipient's neoplastic cells (ie, graft-versus-tumor effect). This phenomenon was described several decades ago and its clinical impact was demonstrated in a seminal

CIBMTR study of more than 2000 patients that showed a reduced relapse risk among patients with GVHD.[61] The graft-versus-tumor effect is considered a major mechanism for sustained response following allogeneic HCT, in particular with reduced intensity or non-MA (NMA) HCT.[62,63]

Indications for Transplantation

Indications for HCT (allogeneic or autologous) vary by disease type and remission status. Information on indications for HCT can be found in disease-specific NCCN Guidelines, available at www.NCCN.org. The American Society for Transplantation and Cellular Therapy (ASTCT) has also published clinical practice guidelines on indications for autologous and allogeneic HCT.[5]

Pre-Transplant Recipient Evaluation

The pre-transplant recipient evaluation generates data to estimate the risks of relapse, non-relapse mortality (NRM), and overall survival. It also generates information that may inform other transplant related decisions. Physiological age, as measured by performance/functional status and use of geriatric assessments, rather than chronological age, should be used to determine eligibility for HCT.[5,64] Selected patients who are older with limited comorbidities and good functional status can safely receive HCT with a relatively low risk of NRM.[65-68] Studies such as the recently completed BMT CTN 1704, are assessing the utility of geriatric assessment tools in predicting outcome of HCT in patients who are older (Clinical Trial ID: NCT03992352). Determining functional status (Karnofsky's or ECOG performance status) and HCT-Comorbidity Index (HCT-CI) score[69] are essential to determine candidacy for HCT (in particular for allogeneic HCT). HCT-CI score has been validated to predict the risk of NRM and estimated survival after allogeneic transplant.[70,71] HCT-CI has also been shown to predict survival after autologous transplant.[72,73] Furthermore, an updated composite-age HCT-CI has also been shown to have the same utility.[74] Detailed clinical assessment of HCT-CI has been published.[75] For specific information on pre-transplant donor evaluation and HLA typing, refer to Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee- International Society for Cell and Gene Therapy (ISCT) and European Society for Blood and Marrow Transplantation (EBMT) (JACIE) International Standards, 8th edition.[76] For more information regarding pre-transplant recipient evaluation, see *Pre-Transplant Recipient Evaluation* in the algorithm.

Hematopoietic Cell Mobilization

Granulocyte-colony stimulating factors (G-CSF), including filgrastim, tbo-filgrastim, pegfilgrastim, and filgrastim/pegfilgrastim biosimilars, are commonly administered in the HCT setting for mobilization of PBPCs. Mobilization of PBPCs by G-CSF has largely replaced use of bone marrow grafts due to the ease of collection, avoidance of general anesthesia, more rapid engraftment rates, and lower transplant-related mortality (TRM).[6-8] For donor evaluation and follow-up recommendations, refer to the FACT-JACIE International Standards, 8th edition (https://www.factglobal.org/ctstandards/).[76]

Hematopoietic Cell Mobilization for Autologous Donors

Effective mobilization regimens for autologous donors include G-CSF plus plerixafor, G-CSF plus cyclophosphamide with or without plerixafor, granulocyte-macrophage colony-stimulating factor (GM-CSF) plus cyclophosphamide with or without plerixafor, pegfilgrastim plus plerixafor, G-CSF alone, G-CSF plus disease-specific chemotherapy with or without plerixafor, and G-CSF plus motixafortide (for patients with MM). Adequate PBPC collection depends on individual patient- and disease-related factors. The minimum target yield for PBPC collection is 2 to 5 x 10^6 CD34+ cells/kg, with a target of 4 to 5 x 10^6 CD34+ cells/kg.[77] Yields <2 x

10^6 CD34+ cells/kg may result in delayed engraftment, while larger cell doses have been associated with a more rapid time to platelet and neutrophil recovery.[77]

Single-agent G-CSF (filgrastim, tbo-filgrastim, or filgrastim biosimilars) is effective in mobilizing PBPCs in the autologous setting.[78-82] The addition of the CXCR4 inhibitor plerixafor to G-CSF mobilization accelerates the rise in PBPC count.[83-91] In a phase III trial, the addition of plerixafor to G-CSF improved PBPC collection yields and reduced mobilization failure rates in patients with heavily pre-treated NHL, with 59% of patients in the G-CSF plus plerixafor group collecting ≥5 × 10^6 CD34+ cells/kg in ≤4 apheresis days compared to 20% of patients in the G-CSF alone group (P < .001).[89] Another phase III trial found similar results in patients with multiple myeloma, with 71.6% of patients in the plerixafor plus G-CSF group collecting ≥6 × 10^6 CD34+ cells/kg in ≤2 apheresis days compared to 34.4% of patients in the G-CSF alone group (P < .001).[90] Therefore, G-CSF plus plerixafor as well as single-agent G-CSF are recommended for PBPC mobilization in the autologous setting. The addition of a novel cyclic-peptide CXCR4 inhibitor, motixafortide, to G-CSF may also improve PBPC collection yields in patients with MM, with 92.5% of patients in the motixafortide plus G-CSF group collecting ≥6 × 10^6 CD34+ cells/kg in ≤2 apheresis days compared to 26.2% of patients in the G-CSF alone group (P < .0001).[92] Therefore, G-CSF plus motixafortide is a recommended PBPC mobilization option for patients with MM in the autologous setting.

The addition of chemotherapy agents such as cyclophosphamide to G-CSF may also result in higher PBPC collection yields with fewer days of apheresis compared to G-CSF alone and may reduce the burden of residual tumor.[93,94] In a trial comparing chemotherapy + G-CSF to G-CSF alone, the addition of chemotherapy resulted in higher total cells collected (18.6 × 10^6/kg vs. 7.0 × 10^6/kg, P < .001), fewer days of apheresis (2.0 vs. 2.9; P < .001), and fewer re-mobilizations (1.06 vs. 1.2; P = .01) but also required substantially more apheresis days (12.5 vs. 4.2 days; P < .001), with higher total cost ($19,614 vs. $16,852; P = .003).[94] In a study of patients with MM comparing cyclophosphamide plus G-CSF to plerixafor plus G-CSF, the cyclophosphamide group had significantly lower total CD34+ collection yields (median 7 × 10^6/kg vs. 11.6 × 10^6/kg; P = .001) and higher mobilization failure rates (8.1% vs. 0), but significantly lower costs ($19,626.5 vs. $28,980; P < .0001).[83] Another study showed no difference in mobilization efficacy between G-CSF plus cyclophosphamide and GM-CSF (sargramostim) plus cyclophosphamide in patients with NHL.[95] Therefore, G-CSF or GM-CSF plus cyclophosphamide with or without plerixafor are recommended regimens for PBPC mobilization in the autologous setting. Chemomobilization regimens using other chemotherapy agents with disease-specific activity are also appropriate.

Although there are limited high-quality data supporting the use of pegfilgrastim in this setting, some small studies suggest that pegfilgrastim may have similar efficacy to filgrastim for mobilization.[96-101] Therefore, pegfilgrastim or pegfilgrastim biosimilars plus plerixafor are also appropriate options for mobilization in the autologous setting.

Dosing and Administration

The NCCN Panel recommends administration of filgrastim, tbo-filgrastim, or a filgrastim biosimilar as single agents, or as part of a chemomobilization regimen for 4 to 5 days after the completion of cyclophosphamide (or other disease-directed therapy), at a dose of 10 mcg/kg body weight per day in daily or twice daily (split) dosing by subcutaneous injection. Sargramostim should be administered at a dose of 250 mcg/m^2 per day either by intravenous infusion over 24 hours or by subcutaneous injection once daily for 4 to 5 days. Pegfilgrastim is given as a single dose of 6 mg by subcutaneous injection on day 1. Apheresis usually commences on the fourth or fifth day following initiation of growth factor. Plerixafor is generally administered by subcutaneous injection 11

hours prior to hematopoietic cell collection. Plerixafor dosing is based on patient body weight and estimated creatinine clearance. Clinical judgment should be used when the white blood cell count is >50,000; these patients should be monitored carefully for splenic pain due to rare cases of splenomegaly or splenic rupture.

Additional Therapy

If CD34+ cell yield is inadequate (<2 x 10^6 CD34+ cells/kg), consider increasing G-CSF dose or changing dose schedule. If not administered prior to cell collection, the addition of plerixafor to G-CSF or chemotherapy plus G-CSF is also recommended. The addition of plerixafor as a preemptive ("just in time") strategy in patients with poor mobilization after administration of G-CSF with or without chemotherapy has been highly successful.[85,86,102-104] Risk factors associated with poor mobilization include older age, extensive prior therapy, prior radiation to marrow-containing regions, low white blood cell count (<4000), or multiple cycles of certain agents such as fludarabine or lenalidomide.[87,105-114] Additional studies have suggested there may also be genetic parameters that contribute to mobilization outcome.[115] However, predicting mobilization failure based on baseline patient characteristics or risk factors has historically been highly inaccurate.[87] Bone marrow harvest can also be considered in the setting of poor mobilization.[116] For bone marrow harvest recommendations, refer to the National Marrow Donor Program/Be the Match. If feasible, consider rest for 2 to 4 weeks before a remobilization attempt.

Hematopoietic Cell Mobilization for Allogeneic Donors

G-CSF alone should be used to mobilize allogeneic donors. Initially, there were concerns about using G-CSF for mobilization in the allogeneic setting due to toxicity for the donor and the risk for GVHD in the recipient. However, studies have demonstrated filgrastim to be well-tolerated by donors without an effect on long-term survival in the recipient.[117-119] Data supporting the use of filgrastim biosimilars in the allogeneic setting are sparse. Some studies have suggested that filgrastim biosimilars are effective for mobilization in healthy donors with no short-term safety issues,[120-124] but long-term data are needed. In a study by the World Marrow Donor Association (WMDA), mobilization of CD34+ cells and incidence of treatment-related adverse events were found to be similar between filgrastim biosimilars and reference filgrastim in 1287 healthy volunteers,[125] although the authors cite a lack of long-term follow-up for both. Tbo-filgrastim has also been shown to effectively mobilize PBPCs for allogeneic transplantation in healthy donors.[82,126,127] Based on these data, the NCCN Panel endorses the use of filgrastim, tbo-filgrastim, and filgrastim biosimilars for the mobilization of PBPCs in healthy allogeneic donors, but cautions physicians to closely follow patients receiving tbo-filgrastim or filgrastim biosimilars during the follow-up period in order to identify any potential complications or unexpected outcomes. The minimum target yield for PBPC collection in allogeneic donors is 4 to 5 x 10^6 CD34+ cells/kg.[77]

Dosing and Administration

Single-agent filgrastim, tbo-filgrastim, or a filgrastim biosimilar should be administered at a dose of 10 mcg/kg per day in daily or twice daily (split) dosing by subcutaneous injection for 4 to 5 days. Apheresis usually commences on the fourth or fifth day following mobilization initiation.

Additional Therapy

If CD34+ cell yield is inadequate (<4 × 10^6 CD34+ cells/kg), consider addition of plerixafor to G-CSF. Bone marrow harvest is an alternative option.[116] For bone marrow harvest recommendations, refer to the National Marrow Donor Program/Be the Match.

Principles of Conditioning for HCT

Conditioning regimens are categorized into three groups based on their intensity.[128] MA regimens cause irreversible (or near irreversible) pancytopenia. Hematopoietic cell support is required to rescue marrow function and prevent aplasia-related death. Regimens that include total body irradiation (TBI) (≥5 Gy single dose or ≥8 Gy fractionated) or busulfan (Bu) >8 mg/kg orally (>6.4 mg/kg IV) or Bu plasma exposure unit (BPEU) equivalent are MA regimens.[129] NMA conditioning regimens produce moderate-to-minimal cytopenia, and graft rejection, if it occurred, would be followed by autologous hematopoietic recovery. Examples include TBI ≤2 Gy ± purine analog, fludarabine + cyclophosphamide ± antithymocyte globulin (ATG), fludarabine + cytarabine + idarubicin, cladribine + cytarabine, and total lymphoid irradiation + ATG. A reduced-intensity conditioning (RIC) regimen is one that does not fulfill the criteria for either an MA or NMA regimen.

The choice among an MA, NMA, or RIC regimen is a nuanced decision that should be made by the transplant team at the time of pre-transplant recipient evaluation or upon review of pre-transplant organ testing, frailty/geriatric assessment, or other evaluation. The selection of conditioning regimen intensity depends on many factors including patient age (chronologic and physiologic),[74] performance status, HCT-CI score,[75] disease type, remission status (including measurable residual disease), and history of prior HCT. In patients who are young and fit, MA regimens may be preferred for ALL, AML, CML, and MDS.[130] See *HCT-A 3 of 9* for a non-exhaustive list of MA regimens commonly used in autologous, allogeneic, and UCB transplants.

If UCB transplant is being used, referral to a center with experience in UCB transplants is strongly recommended. If a myeloablative conditioning regimen is planned for a recipient of UCB, omidubicel-onlv, an ex vivo nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from a single cord blood unit, has been shown to shorten the time to engraftment and reduce the risk of some infections.[131] In a phase III trial, median time to neutrophil engraftment for UCB transplantation with omidubicel-onlv was 12 days compared to 22 days for standard UCB transplantation ($P < .001$).[131] Similarly, platelet recovery was shorter in the omidubicel-onlv arm (55% vs. 35% recovery at 42 days; $P = .028$). Grade 2–3 bacterial or invasive fungal infections were also less common in the omidubicel-onlv arm (37% vs. 57%; $P = .027$).

NMA or RIC regimens may be preferred for patients undergoing allogeneic HCT for treatment of lymphoma (NHL or HL), CLL and plasma cell disorders such as MM and plasma cell leukemia. NMA/RIC regimens may also be preferred for patients who have received a prior autologous HCT and patients who are not candidates for MA regimens. See *HCT-A 3 of 9* for a non-exhaustive list of NMA regimens commonly used in allogeneic transplant and *HCT-A 4 of 9* for a non-exhaustive list of RIC regimens commonly used in allogeneic and UCB transplants. Conditioning regimens commonly used in autologous transplants are listed by disease type on *HCT-A 6 of 9*). Suggested dose modifications by weight for many of the drugs commonly used in conditioning regimens are given in the *Principles of Conditioning for Hematopoietic Cell Transplant: Suggested Doses/Modifications by Weight* section of the algorithm.[132]

There are certain special situations that warrant more caution. For example, use of high-dose Bu, BCNU, or high-dose TBI in patients with significant pulmonary dysfunction should be carefully considered due to the substantial additional risk to the lungs.[133-135] The use of high-dose Bu and high-dose TBI has been associated with an increased risk of sinusoidal obstruction syndrome (SOS) in patients with significant liver dysfunction.[136] An increased risk of SOS has also been associated with the use of dual alkylator-based regimens with pre-transplant inotuzumab or gemtuzumab.[137] Additionally, the alkylating agent thiotepa can be

excreted through the skin and requires special skin care.[138] The combination of sirolimus and tacrolimus may be also associated with higher risk of SOS and thrombotic microangiopathy (TMA), especially if used with MA regimens.[139-142] Importantly, an increased risk of GVHD has been associated with treatment with immune checkpoint inhibitors (pre- or post-HCT) and mogamulizumab.[143-146]Therefore, the panel recommends considering a minimum 8- to 12-week window between these treatments and the start of transplant conditioning if clinically feasible.

Conditioning Regimens Without Fludarabine

There have been intermittent shortages of fludarabine, which is a component of many conditioning regimens.[147] To address this, the panel has developed recommendations for non-fludarabine RIC regimens for use during times of shortage (see *Principles of Conditioning for Hematopoietic Cell Transplant: Conditioning Regimens Without Fludarabine* in the algorithm for a non-inclusive list).The panel suggests that the choice of regimen should be based on institutional preference and experience due to the lack of comparative data with fludarabine-based regimens.

Some of the regimens recommended by the panel are associated with certain adverse events. For example, a systemic inflammatory syndrome has been reported with the use of clofarabine-based regimens, although concomitant steroid use may mitigate this risk.[148] Additionally, use of certain cladribine-based regimens may be associated with increased risk of graft failure.[149-151] The pentostatin + Bu + cyclophosphamide regimen was reported with primary immunodeficiency disorders using post-transplant cyclophosphamide[152] and pentostatin + TBI 4 Gy was reported for second transplant after engraftment failure.[153]

Post-Transplant Follow-Up

Advances in HCT methods and supportive care have led to improved survival following HCT.[154] However, disease relapse and post-transplant complications continue to pose a major threat to HCT survivors. Disease relapse is more frequent in patients with advanced disease and in those receiving NMA conditioning regimens.[155] Intensive supportive care is required for all post-transplant recipients until engraftment occurs. Post-transplant complications are common after both allogeneic and autologous HCT and are often caused by the conditioning regimen,[156,157] delayed immune reconstitution, and/or GVHD (for allogeneic HCT and very rarely autologous HCT). The risk and type of complications are also influenced by patient-related factors such as age, performance status, and comorbidities.[40,158,159] Early complications (generally occurring within the first 100 days post-HCT) include prolonged cytopenia/delayed engraftment, infections, SOS, and other organ toxicities such as cardiomyopathy or idiopathic pneumonia syndrome (IPS).[156,160] Late complications (after the first 100 days) include infections; late radiation-related toxicities (eg, cataracts and hypothyroidism); late chemotherapy-related toxicities (eg, heart failure); organ dysfunction; secondary malignancies including therapy-related myeloid neoplasms, breast and thyroid cancer, melanoma and non-melanoma skin cancers; endocrinopathies and infertility; among others.[156,160] Allogeneic HCT recipients may also develop acute and/or chronic GVHD, in which the donor lymphocytes recognize the recipient's tissues as foreign, resulting in immune-mediated cellular injury of several organs, such as the skin, gastrointestinal (GI) tract, and liver.

Common causes of NRM after allogeneic HCT include GVHD, infections, cardiovascular disease, secondary malignancies, and organ toxicity.[161-164] Common causes of NRM after autologous HCT include organ toxicity, cardiovascular disease, and infectious complications.[165-167] Therefore,

post-transplant care plans, including optimal supportive and survivorship care, are essential to optimize long-term outcomes in both autologous and allogeneic HCT recipients.

Management of Graft-Versus-Host Disease

The development of acute and/or chronic GVHD is a common complication of allogeneic HCT and may be associated with significant morbidities and NRM in allogeneic HCT recipients.[168-170] The incidence of GVHD has been increasing in recent years, primarily due to the increased use of unrelated and/or HLA-mismatched donors and G-CSF–mobilized PBPCs, among other factors.[8,171-173] Mild manifestations limited to a single organ are often managed with close observation, topical treatment, or by slowing the tapering of immunosuppressive agents.[174] More severe manifestations or multi-organ involvement typically requires systemic corticosteroid treatment; addition of secondary agents may be required for patients who do not experience response to initial steroid therapy.[170] Management of GVHD can be optimized by providing coordinated care from a multidisciplinary team, preferably in medical centers with access to specialized transplant services.

Acute Graft-Versus-Host Disease

Despite prophylaxis with immunosuppressive agents, 20% to 80% of allogeneic HCT recipients develop acute graft-versus-host disease (aGVHD). Risk factors include degree of HLA-matching, donor type, and graft source.[170] The skin, GI tract (upper and lower), and liver are the three organs primarily affected by aGVHD, which is characterized by maculopapular rash, GI symptoms such as nausea, vomiting, and diarrhea, and hyperbilirubinemia.[175,176] Pathologic confirmation of aGVHD should be considered whenever possible, especially before escalating systemic immunosuppression. Although skin biopsy is not absolutely sensitive or diagnostic, biopsy of the GI tract and liver are usually diagnostic, and all biopsies may help exclude other diagnostic considerations.

Diagnosis and Grading

If aGVHD is suspected, organ-appropriate additional tests such as stool infectious disease testing, imaging studies, and/or viral testing should be performed to rule out non-GVHD causes of the symptoms. Organ-directed biopsies can then be performed as clinically indicated to support the presence of aGVHD or to exclude other diagnoses. GI biopsy (via esophagogastroduodenoscopy [EGD], colonoscopy, and/or flexible sigmoidoscopy) is recommended, whenever possible, for the diagnosis of GI aGVHD, particularly if stool testing is unrevealing. Rectosigmoid biopsies were shown in one study to have higher sensitivity and negative predictive value than biopsies at other sites, whether the patient presented with diarrhea, nausea, or vomiting.[177] Liver function tests (LFTs) should be routinely monitored after allogeneic HCT for early detection of hepatic aGVHD, which is often asymptomatic and can manifest with elevated transaminases without elevated bilirubin. Liver biopsy may be considered in patients presenting with unexplained abnormal LFTs without evidence of aGVHD elsewhere if the information obtained would inform treatment. Once the diagnosis of aGVHD is made, the organ staging and overall grade of aGVHD should be determined to guide choice of therapy and disease monitoring.

The clinical grade of aGVHD is predictive of survival. Glucksberg aGVHD grading criteria were first proposed in 1974.[178] Modified Glucksberg (consensus or Keystone) criteria were developed in 1994 (see *Acute GVHD: Staging and Grading* in the algorithm for modified Glucksberg grading criteria).[168] IBMTR Severity Index was subsequently developed,[179] and was shown to be more predictive of HCT outcome when compared with the original Glucksberg criteria.[180] Minnesota criteria have also been devised to identify patients with “high-risk” aGVHD who could benefit from

early escalated therapy.[181,182] More recently, MAGIC (Mount Sinai Acute GVHD International Consortium) criteria were developed (see *Acute GVHD: Staging and Grading* in the algorithm for MAGIC grading criteria).[183] A joint task force of the EBMT, National Institutes of Health (NIH), and CIBMTR has published a position statement on standardized terminology for GVHD.[184] Furthermore, blood biomarkers are being investigated for their utility as a predictive tool in aGVHD.[185-188]

First-Line Therapy of aGVHD

Grade I

Grade I aGVHD affects only the skin (stage 1–2, <50% body surface area [BSA] non-bullous rash), with no GI or liver involvement.[168] First-line therapy options for these patients include continuing (or restarting) the original immunosuppressive agent(s) and administering topical steroids (eg, triamcinolone, clobetasol) and/or topical tacrolimus. Medium- to high-potency topical steroid formulations are recommended, except on the face or intertriginous areas where low-potency hydrocortisone is to be used (to avoid skin atrophy, telangiectasia, and acneiform eruptions). Antihistamines may be used for symptomatic relief of itching as needed. Alternatively, the patient can be observed without treatment if the rash is asymptomatic and stable. If there is a response to first-line therapy, as indicated by a resolution of the rash and associated symptoms, the immunosuppressive agent(s) should be tapered as clinically feasible and topical steroids can be discontinued. Options for patients with no response to first-line therapy include enrollment in a well-designed clinical trial or continuing topical steroids. Patients with progression and/or symptomatic rash (eg, pruritus, pain, sloughing, increasing BSA involvement) should be treated according to the recommendations for grade II–IV aGVHD.

Grades II–IV

Enrollment in a well-designed clinical trial is encouraged for all patients presenting with grade II–IV aGVHD. The original immunosuppressive agent(s) should be restarted, continued, or escalated (with or without therapeutic drug monitoring) if aGVHD developed during tapering of immunosuppressive therapy. Administration of systemic corticosteroids (± topical steroids) is the standard first-line treatment option (unless contraindicated or associated with severe intolerance) for patients with grades II–IV aGVHD.[175,176,189] A phase III randomized controlled trial showed that initial treatment with low-dose systemic prednisone (0.5 mg/kg/day) in conjunction with GI topical steroids (beclomethasone dipropionate ± budesonide) was safe and effective for managing upper GI symptoms (ie, nausea, vomiting, anorexia) in patients with grade II aGVHD, with or without skin involvement (<50% BSA), with diarrhea volumes <1000 mL/day.[189] Of note, budesonide alone is less effective at treating the upper GI tract. In patients with higher grade aGVHD, use of low-dose prednisone was associated with an increased risk of requiring secondary immunosuppressive therapy, but with no difference in survival. Thus, patients with grade II aGVHD may be treated with 0.5–1 mg/kg/day of methylprednisone (or prednisone dose equivalent). Patients with higher grade aGVHD should be treated with higher doses of systemic steroids (1–2 mg/kg/day methylprednisolone or prednisone dose equivalent). There is no role for escalation of methylprednisolone above 2 mg/kg/day.[190] The addition of other systemic agents in conjunction with systemic corticosteroids as first-line therapy for aGVHD should only be done in the context of a well-designed clinical trial. Patients on high-dose steroids require significant supportive care (see *Supportive Care for All Patients with GVHD*).

The randomized phase II BMT CTN 1501 trial compared sirolimus to prednisone as initial treatment in 122 patients with standard-risk aGVHD as defined by the Minnesota GVHD Risk Score and Ann Arbor (AA1/2)

biomarker status.[191] At day 28, the overall response rate (ORR) for sirolimus and prednisone was similar (65% vs. 73%) and there were no differences in steroid-refractory aGVHD, disease-free survival, relapse, NRM, or overall survival (OS). Patients in the sirolimus group encountered less hyperglycemia and had reduced risk of infections but were at an increased risk for TMA as compared to patients in the prednisone group (10% vs. 1.6%). Thus, sirolimus can be considered as an alternative to systemic corticosteroids as first-line therapy for patients with standard risk aGVHD, as defined by clinical risk score and biomarker status.

Alternative regimens have been investigated as first-line therapy for aGVHD. BMT CTN 0302 was a randomized 4-arm phase II clinical trial (n = 180) that compared different agents (etanercept, mycophenolate mofetil [MMF], denileukin diftitox, and pentostatin) in combination with methylprednisolone at 2 mg/kg per day (or prednisone dose equivalent) for treatment of newly diagnosed aGVHD.[192] The day 28 ORRs were etanercept 26%, MMF 60%, denileukin diftitox 53%, and pentostatin 38%. The corresponding 9-month OS rates were 47%, 64%, 49%, and 47%, respectively. Risk of severe infections were etanercept 48%, MMF 44%, denileukin 62%, and pentostatin 57%. These results suggested that MMF plus corticosteroids would be a potentially promising regimen for initial therapy of aGVHD. Accordingly, a phase III multicenter double-blinded clinical trial (BMT CTN 0802) was initiated comparing the combination of methylprednisolone at 1.6 mg/kg per day (or prednisone dose equivalent) plus MMF versus methylprednisolone plus placebo as first-line therapy for aGVHD.[193] A futility rule for GVHD-free survival at day 56 was met at a planned interim analysis after 235 patients (of 372) were enrolled. Outcomes of both arms were equivalent in OS, 1-year incidence of cGVHD, and infection risk. Therefore, MMF provided no benefit when added to corticosteroids as first-line therapy for aGVHD.

If there is a response to first-line therapy, as indicated by a complete resolution of GVHD or improvement in at least one organ without any progression in any other organs, the steroids should be tapered as clinically feasible. Options for patients with no response to first-line therapy include enrollment in a well-designed clinical trial[194] or the addition of other systemic agent(s) to the corticosteroids, with steroid taper as clinically feasible. See *Suggested Agents for Steroid-Refractory aGVHD* below for more information.

Chronic Graft-Versus-Host Disease

cGVHD is the leading cause of NRM after allogeneic HCT and has a profound impact on quality of life.[164,195] cGVHD usually develops within the first year after HCT in most patients, but it can also develop many years later.[170] cGVHD affects multiple organ systems and is characterized by fibrosis and variable clinical features resembling autoimmune disorders.[196] The NIH Consensus Development Project has published detailed recommendations for the management of cGVHD including diagnosis, assessment of organ involvement, monitoring response to treatment, and supportive care interventions.[174,197-200] A thorough understanding of the various clinical manifestations of cGVHD is essential for the early recognition of signs and symptoms. Multidisciplinary care aimed at avoiding organ damage and preserving function is strongly recommended.

Diagnosis and Grading

In all cases of suspected cGVHD, additional tests are often performed to rule out non-GVHD causes of the symptoms, such as infection, drug-induced injury or toxicity, malignancy, or other causes. While a biopsy may be done to confirm the presence of cGVHD, this is not always feasible and is not mandatory if the patient has at least one of the diagnostic findings of cGVHD defined by the NIH Consensus Development Project (see *GVHD-B* in the algorithm for diagnostic signs and symptoms of cGVHD).[174] Manifestations of cGVHD include bronchiolitis obliterans syndrome (BOS),

an inflammatory lung condition. Unless it is pathologically diagnosed (via lung biopsy), clinical characteristics of BOS (assessed by pulmonary function tests [PFTs]) are only diagnostic of lung cGVHD if distinctive features of cGVHD are present in another organ (see *GVHD-B 2 of 3* in the algorithm for the complete criteria required for diagnosis of BOS). cGVHD grading is done according to the NIH Consensus Development Project criteria (see *Chronic GVHD: Grading* in the algorithm).[174] A predictive score including day +100 levels of gamma-glutamyl transferase (GGT), creatinine, cholinesterase, and albumin is being investigated for its utility as a predictive tool for cGVHD, though it requires further validation.[201]

First-Line Therapy of cGVHD

Enrollment in a well-designed clinical trial is encouraged for all patients presenting with cGVHD. Options for first-line therapy include restarting, continuing, or escalating the original immunosuppressive agent(s) and/or administration of systemic corticosteroids (0.5–1 mg/kg/day methylprednisolone or prednisone dose equivalent). The initial corticosteroid dose may vary depending on the organs involved, the severity of GVHD, and patient comorbidities. Topical steroids, such as triamcinolone or clobetasol, topical estrogen (for vulvovaginal cGVHD), topical tacrolimus, or dexamethasone oral rinse (for oral cGVHD) may be used as clinically indicated. Patients with lung involvement should receive inhaled steroids (eg, budesonide or fluticasone) ± montelukast ± azithromycin (eg, FAM [fluticasone, azithromycin, and montelukast]). Azithromycin should be used only for the treatment of BOS and not for BOS prophylaxis due to data suggesting increased risks for leukemic relapse and secondary neoplasms in patients undergoing HCT receiving azithromycin for BOS prophylaxis.[202,203] Patients with progressive or worsening lung cGVHD following two to three lines of therapy may be evaluated for lung transplant.

If there is a response to first-line therapy according to the NIH Response Criteria,[184] steroids should be tapered as clinically feasible to mitigate long-term side effects and risk of infection. Options for patients with no response to first-line therapy include enrollment in a well-designed clinical trial[194] or the addition of other systemic agent(s) to the corticosteroids, with steroid taper as clinically feasible. See *Suggested Agents for Steroid-Refractory cGVHD* below for more information. Supportive care interventions for controlling organ-specific symptoms or complications should be an integral part in the long-term management of patients with cGVHD.[198]

Steroid-Refractory GVHD

Approximately 40% to 50% of patients with acute or chronic GVHD present with steroid-refractory disease, which is associated with high mortality.[175,204] The NIH has defined criteria for steroid-refractory acute and chronic GVHD (see *GVHD Steroid Response Definitions/Criteria* in the algorithm).[184] Enrollment in a well-designed clinical trial is strongly encouraged for these patients. The selection of therapy for steroid-refractory GVHD should be based on institutional preferences, physician experience, the agent's toxicity profile, the effects of prior treatments, drug interactions, convenience/accessibility, and patient tolerability. Agent selection may also depend on organ involvement and overall grade of cGVHD.

Suggested Agents for Steroid-Refractory aGVHD

The following systemic agents, listed in alphabetical order (except for the category 1 recommendation), can be used in conjunction with the original immunosuppressive agent(s) and corticosteroids (typical first-line therapy) for steroid-refractory aGVHD. Slow taper of systemic corticosteroids is recommended if deemed ineffective therapy. In patients with steroid-dependent disease, corticosteroid therapy may be continued until an alternative steroid-sparing agent induces a response. The following are

the most commonly used agents among NCCN Member Institutions. Currently, ruxolitinib is the only therapy approved by the U.S. Food and Drug Administration (FDA) for treatment of steroid-refractory aGVHD.[205]

Ruxolitinib

Ruxolitinib is a selective inhibitor of JAK1 and JAK2, which are intracellular tyrosine kinases that play critical roles in cytokine signaling as well as the development and function of several types of immune cells.[206] In 2019, the FDA approved ruxolitinib for the treatment of steroid-refractory aGVHD in adult and pediatric patients aged ≥12 years based on data from the single-arm phase II REACH1 trial in which 71 patients with grade II–IV steroid-refractory aGVHD were treated with 5 mg ruxolitinib twice daily with an optional increase to 10 mg.[205,207] The ORR at day 28 was 55%, with 27% of patients achieving a complete response (CR). Responses were seen across the skin (61%), GI tract (46%), and liver (27%). The randomized phase III REACH2 trial compared ruxolitinib (10 mg twice daily) to investigator's choice of regimen in 309 patients with steroid-refractory aGVHD.[208] The ORR at day 28 was significantly higher in the ruxolitinib group compared to the control group (62% vs. 39%; $P < .001$). Similar results were observed for the durable ORRs at day 56 (40% vs. 22%; $P = .001$). Median failure-free survival and median OS were substantially longer with ruxolitinib than with control (5 vs. 1 month; hazard ratio [HR], 0.46 and 11 vs. 6.5 months; HR, 0.83). The most common adverse events in the ruxolitinib group were thrombocytopenia (33%), anemia (30%), and cytomegalovirus infection (26%). Based on these data, ruxolitinib is a category 1 recommended option for patients with steroid-refractory aGVHD.

Alemtuzumab

Alemtuzumab is a humanized anti-CD52 monoclonal antibody that has been successfully used as part of a pre-transplant preparative regimen for GVHD prophylaxis.[209,210] The safety and efficacy of alemtuzumab for the treatment of steroid-refractory aGVHD was evaluated in a prospective clinical study of 18 patients with grade II–IV steroid-refractory aGVHD treated subcutaneously with 10 mg alemtuzumab daily for 5 consecutive days.[211] The ORR to alemtuzumab was 83%, with 33% of patients achieving CR. Importantly, univariate analyses of clinical characteristics between those who experienced response and those who did not experience response showed no differences in the main organ involved, grade of GVHD, or time between HCT and GVHD onset. After a median follow-up of 9 months, 78% of patients had one or more infectious episodes. In a retrospective analysis of 20 patients with steroid-refractory grade III–IV aGVHD receiving 10 mg of intravenous alemtuzumab weekly, the ORR was 70% with a CR of 35%.[212] One-year OS was 50%. Although infectious complications were common, infection was not a significant predictor of survival in this study. These data suggest that alemtuzumab has favorable activity in the treatment of steroid-refractory aGVHD and emphasizes the need for anti-infective prophylaxis and close monitoring for patients receiving this therapy. Currently in the United States, alemtuzumab is only available via the Campath Distribution Program and drug supply is patient-specific.

Alpha-1 Antitrypsin

Alpha-1 antitrypsin (AAT) (also known as alpha-1 proteinase inhibitor) is a circulating protease inhibitor that inactivates serine proteases from neutrophils and macrophages to protect tissues from proteolytic degradation.[213] AAT is most commonly used to treat patients with AAT deficiency, an inherited condition that causes lung and liver damage.[214] The safety and efficacy of AAT to treat steroid-refractory aGVHD was evaluated in a prospective, multicenter phase II trial of 40 patients treated with intravenous AAT twice weekly for up to 4 weeks at a dose of 60 mg/kg/day.[213] The ORR and CR rate at 28 days were 65% and 35%, respectively. After 60 days, responses were maintained in 73% of patients.

OS at 6 months was 45% and did not differ by grade or site of organ involvement. Infectious mortality was 10% at 6 months. No infusion reactions or drug-related grade 3–4 toxicities were reported. These data suggest that AAT is an effective treatment option for patients with steroid-refractory aGVHD.

Anti-Thymocyte Globulin

Anti-thymocyte globulin is a T-cell–depleting antibody that has been commonly used for immunosuppression in the solid organ transplant setting and for GVHD prophylaxis.[215-222] Two non-interchangeable ATG products are currently approved by the FDA: anti-thymocyte globulin (rabbit), a polyclonal immunoglobulin G (IgG) derived from rabbits, and anti-thymocyte globulin (equine), a polyclonal IgG derived from horses.[223,224] An early retrospective study analyzed the clinical response and survival outcomes of 79 patients with steroid-refractory aGVHD treated with 1 to 5 courses of equine ATG at a dose of 15 mg/kg/day twice daily for 5 days.[225] At day 28 of treatment, the ORR was 54% with 20% of patients achieving a durable CR. Response to ATG was not associated with the initial grade of GVHD; however, it was associated with the site of GVHD. Patients with skin aGVHD were more likely to experience response to ATG. Of the 64 patients with skin involvement, 61% achieved a CR or partial response compared to 27% without skin involvement (P = .02). The probability of survival at 1 year for all patients was 32% (95% CI, 22%–42%). Bacterial, viral, and fungal infections occurred in 37%, 10%, and 18% of patients, respectively. Another early retrospective study analyzed the efficacy of rabbit ATG in 36 patients with steroid-refractory GVHD treated at a single institution.[226] Patients, most of whom (89%) had grade III–IV aGVHD, received rabbit ATG at 2.5 mg/kg/day for either 4 to 6 consecutive days (group 1; n = 13) or on days 1, 3, 5, and 7 (group 2; n = 21). The ORR was 59%, with a CR rate of 38%. The response rate was higher in patients in group 1 (77%) compared to patients in group 2 (48%); however, this difference was not statistically significant (P = .15). As seen in the aforementioned study, skin aGVHD was more responsive (96% of patients) than GI (46%) or liver aGVHD (36%). Common adverse events included hepatic dysfunction (25%), viral infections (26%), fungal infections (32%), and bacteremia (21%). Of the 36 original patients enrolled in the study, only 2 (6%) were alive 34 months post-HCT. A more recent retrospective analysis of 11 patients with steroid-refractory aGVHD reported an ORR of 55% for rabbit ATG administered at a median dose of 3 mg/kg/day, and a median of 2 doses (range105).[227] In this study, high response rates were observed in patients with skin (100%) and GI (83%) aGVHD as compared to those with liver aGVHD (25%). One-year OS and TRM were 55% and 45%, respectively. These data suggest that ATG may be an effective treatment option for patients with steroid-refractory aGVHD, especially for those with skin involvement. However, long-term survival appears to be low, even in those who experience response.[226] A comprehensive review on the use of ATG for GVHD treatment has been published.[228]

Basiliximab

Basiliximab is a chimeric monoclonal antibody that functions as an immunosuppressive agent by binding to and blocking the interleukin-2 (IL-2) receptor.[229] IL-2 plays a key role in the development of aGVHD by stimulating the activation of donor T cells in the graft, which can attack the cells and tissues of the recipient.[230] The efficacy and feasibility of basiliximab for the treatment of steroid-refractory aGVHD was evaluated in a prospective phase II trial of 23 patients treated with intravenous basiliximab at a dose of 20 mg on days 1 and 4.[230] The ORR was 83% with 18% of patients achieving a CR. The percentage of patients achieving a minimum one-grade reduction in aGVHD varied with organ involvement (77% of patients with skin GVHD, 14% of patients with liver involvement, and 67% of patients with GI involvement). While administration of basiliximab did not cause any infusion-related toxicity, infections occurred in 65% of patients. The rates of malignancy recurrence and 1-year

treatment-related mortality were 10% and 45%, respectively, following immunosuppression with basiliximab. Therefore, basiliximab appears to have some activity in the treatment of steroid-refractory aGVHD.

Calcineurin Inhibitors

Calcineurin inhibitors (CNI), such as tacrolimus and cyclosporine, are immunosuppressive agents that inhibit the action of calcineurin, an enzyme involved in the activation of T cells. CNI are commonly used for the prevention and initial treatment of GVHD, often in conjunction with other agents.[142,231-239] However, limited data exist for their use in the treatment of steroid-refractory aGVHD. In a small phase II trial, 18 patients with aGVHD that developed or progressed during therapy with cyclosporine and/or other immunosuppressive agents were treated with tacrolimus at an initial dose of 0.05 mg/kg intravenously or 0.15 mg/kg orally twice daily (targe trough 15-25 ng/mL).[240] In the 13 patients with evaluable data, the ORR was 54%. The most common adverse events were renal toxicity (53% of patients), followed by nausea and vomiting (31%). A retrospective analysis involving 42 patients with steroid-refractory aGVHD treated with tacrolimus (target concentration 4-8 ng/mL) in combination with sirolimus reported an ORR of 49% (CR rate = 42%) for patients treated in the second-line (n = 31) and an ORR of 27% (CR = 0) for patients treated in the third-line (n = 11).[241] One-year OS was 42% in patients treated in the second-line and 0% in patients treated in the third-line. Infectious complications occurred in 90% of patients. Therefore, CNI may be a reasonable option for the treatment of patients with steroid-refractory aGVHD, including when they have not been used in prophylaxis or initial therapy.

Etanercept

Etanercept is a recombinant tumor necrosis factor-alpha (TNF-α) receptor fusion protein.[242] Etanercept acts by inhibiting the activity of TNF-α, a proinflammatory cytokine that acts as the master regulator of immune response and is a major mediator in the pathogenesis of aGVHD.[243] The efficacy of etanercept for the treatment of steroid-refractory aGVHD was retrospectively evaluated in a cohort of 13 patients.[244] Etanercept at 25 mg was given subcutaneously twice weekly for 4 weeks followed by 25 mg weekly for 4 weeks. The ORR was 46%, with 4 patients achieving CR. Responses correlated with the overall grade of aGVHD, with patients with grade II aGVHD showing higher response rates than those with grades III–IV aGVHD, and were most commonly observed in patients with GI involvement (64% of clinical responses). No immediate treatment-related side effects were observed; however, bacterial and fungal infections occurred in 14% and 19% of patients, respectively. At a median follow-up of 429 days, OS was 67%. These results suggest that etanercept has favorable activity in steroid-refractory aGVHD.

Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is a form of immunotherapy that involves ex vivo exposure of mononuclear cells obtained by apheresis to the photosensitizing agent 8-methoxypsoralen and ultraviolet A (UVA) light, followed by reinfusion of the cells back into the patient.[245] The clinical activity of ECP is thought to be mediated by the immunomodulatory effects of UV light.[246] The exact mechanism by which ECP ameliorates GVHD (acute or chronic) is unclear, but may involve the normalization of $CD4^+/CD8^+$ lymphocyte populations, an increase in the number of CD3-/CD56+ natural killer (NK) cells, and/or a decrease in circulating dendritic cells.[245,247]

A phase II trial in patients with grade II–IV steroid-refractory aGVHD found that weekly ECP therapy resulted in complete resolution of aGVHD symptoms in 82% of patients with skin involvement and 61% of patients with liver or GI involvement.[248] In a prospective single-center study involving 21 patients with grade III–IV aGVHD, second- or third-line

treatment with ECP resulted in an ORR of 84%.[249] After a median follow-up of 17 months, 1-year OS was 53% and was independently associated with a higher number of ECP sessions. A systematic review of prospective studies reported a pooled ORR of 69% for ECP in the treatment of steroid-refractory aGVHD.[245] The ORR for skin manifestations was highest at 84%, followed by 65% for GI involvement. Reported rates of ECP-related mortality were extremely low. Another systematic review largely reached the same conclusions, reporting a pooled ORR of 71% and ORRs of 86%, 60%, and 68% for skin, liver, and GI involvement, respectively.[250] These data suggest that ECP is an effective therapy for steroid-refractory aGVHD, especially for patients with skin involvement. If ECP is not available or feasible, the NCCN Panel recommends the use of psoralen plus UVA (PUVA) irradiation as an alternative treatment option for sclerotic or cutaneous steroid-refractory GVHD.

Infliximab

Infliximab is a genetically constructed immunoglobulin G1 (IgG1) chimeric monoclonal antibody that binds to membrane-bound TNF-α, blocking its activity and triggering lysis of TNF-α–producing cells.[243,251] In a retrospective evaluation of 21 patients with steroid-refractory aGVHD who had received treatment with single-agent infliximab (10 mg/kg once weekly for at least 4 doses), the ORR was 67%, with 62% of patients achieving CR.[243] No toxic reactions to infliximab were observed; however, bacterial, fungal, and viral infections occurred in 81%, 48%, and 67% of patients, respectively. OS was 38% at a median follow-up of 21 months. Another retrospective analysis of 32 patients with steroid-refractory aGVHD treated with infliximab administered intravenously at the dose of 10 mg/kg once weekly for a median of three courses reported an ORR of 59%.[252] Infections developed in 72% of patients. A third, more recent retrospective analysis involving 35 patients with steroid-refractory aGVHD reported an ORR of 40% for infliximab administered intravenously at 10 mg/kg weekly for a median of four doses, with 83% of patients developing infectious complications.[253] These data suggest that infliximab is active in the treatment of steroid-refractory aGVHD; however, the potential for excessive infections should be evaluated.

mTOR Inhibitors

Sirolimus (rapamycin) is a macrolide compound derived from the bacteria *Streptomyces hygroscopicus* that possesses immunosuppressive, antibiotic, and antitumor properties. Sirolimus functions as a potent immunosuppressant by inhibiting the activity of mTOR, a serine/threonine kinase that acts as a master regulator of cell growth, proliferation, metabolism, and survival.[254,255] By inhibiting mTOR, sirolimus disrupts the cytokine signaling that promotes the growth and differentiation of T cells.[256] Sirolimus is also used for GVHD prophylaxis, often in conjunction with the CNI tacrolimus.[142,236,237,257-260] The safety and efficacy of sirolimus in the treatment of steroid-refractory aGVHD was evaluated in a phase I trial involving 21 patients with grade III–IV steroid-refractory aGVHD.[261] The ORR was 57%, with a CR rate of 24%. However, only 11 patients completed the full course of treatment due primarily to extensive toxicities including cytopenias, hyperlipidemia, severe TMA, and renal failure. In a retrospective analysis of 31 patients with steroid-refractory aGVHD treated with sirolimus (target therapeutic range 4-12 ng/mL) in combination with tacrolimus, the ORR was 76% and 42% of patients achieved CR.[262] Median OS was 5.6 months and 1-year OS was 44%. TMA and hyperlipidemia occurred in 21% and 44% of patients, respectively, but were manageable. Another retrospective study involving 22 patients with steroid-refractory aGVHD treated with sirolimus (target therapeutic range 7-13 ng/mL) reported similar results.[263] The ORR was 72% and OS was 41% after a median follow-up of 13 months. TMA occurred in 36% of patients when sirolimus was combined with tacrolimus or other CNI. A third, more recent retrospective analysis involving 42 patients with steroid-refractory aGVHD treated with sirolimus (target concentration 4-8 ng/mL) and tacrolimus reported an ORR of 48.5% (CR

rate = 42%) for patients treated in the second-line (n = 31) and an ORR of 27% for patients treated in the third-line (n = 11).[241] For patients treated in the second-line, 1-year OS was 42% (0% for patients treated in the third-line). Infectious complications were common (90% of patients). These data suggest that sirolimus is an effective option for the treatment of patients with steroid-refractory aGVHD, but may result in significant toxicities.

Mycophenolate Mofetil

MMF is a prodrug of mycophenolic acid (MPA) that acts as an immunosuppressant by inducing apoptosis in lymphocytes through inhibition of the de novo synthesis of purines.[264] MMF is indicated for the prevention of organ rejection in solid organ transplants and is a standard component of GVHD prophylaxis regimens.[265] In a prospective phase II trial completed in the mid-1990s, Furlong et al reported an ORR of 47% and a CR rate of 31% in 19 patients with steroid-refractory aGVHD treated with MMF at an initial dose of 1 g twice daily for 35 days.[266] OS at 6 and 12 months was 37% and 16%, respectively. MMF treatment was discontinued in 4 patients because of toxicities including neutropenia, abdominal pain, and pulmonary infiltrate. The same group conducted a retrospective analysis of more recent patients with steroid-refractory aGVHD (n = 29) and found a similar ORR to MMF therapy (48%).[266] However, OS at 6 and 12 months was much higher (55% and 52%, respectively). Possible explanations for the improved OS may include improved management of GVHD and longer experience with the use of MMF. In another retrospective analysis of 13 patients with steroid-refractory aGVHD, the ORR to MMF (1.5 or 2 g daily) was 31% and the estimated 2-year OS rate was 33%.[267] Responses were observed in 31% of cases with skin involvement, 44% of cases with liver involvement, and 23% of cases with GI involvement. Another retrospective study reported a 3-year OS rate of 40% and a CR rate of 26% in 27 patients with steroid-refractory aGVHD treated with MMF at a dose of 1–1.5 g twice daily orally or intravenously.[268] The CR rates observed with MMF therapy were typically higher in patients with lower grade GVHD (40% for grades I–II vs. 8% for grades III–IV). These data suggest that MMF has some efficacy for treating steroid-refractory aGVHD, especially in those with lower grade GVHD at the start of treatment.

Pentostatin

Pentostatin is a purine analogue that acts as an immunosuppressant by inducing lymphocyte apoptosis through inhibition of adenosine deaminase.[269] A large retrospective analysis of 60 patients treated with pentostatin for steroid-refractory aGVHD reported an ORR of 33% and a CR rate of 18%.[270] All patients received pentostatin at a dose of 1.5 mg/m^2 on days 1 to 3, repeated every 2 weeks, for a median of three courses. OS at 18 months was 21% and NRM was 72%. Stratified analysis revealed that patients <60 years of age with isolated lower GI GVHD had the best outcomes with an ORR of 48% and 18-month OS of 42%. An earlier retrospective study reported similar results, with an ORR of 38% and 2-year OS of 17% in 24 patients treated with pentostatin at a daily dose of 1 mg/m^2 given intravenously on 3 consecutive days.[271] A smaller retrospective analysis of 12 patients reported a higher ORR of 50% and a CR rate of 33%.[272] Discrepancies in the results of these studies may be attributed to variability in the patient populations, pentostatin doses and number of treatment cycles, use of additional therapies, or the assessment of treatment response.[270]

A phase I dose-escalation study involving 22 patients with steroid-refractory aGVHD reported a high CR rate of 63%.[273] However, late infections observed at the 2 mg/m^2/day dose used in the study were considered to be dose-limiting toxicities. In a follow-up phase II study of eight patients receiving a lower dose of 1.5 mg/m^2/day of pentostatin, four patients died from progressive hepatic GVHD and three patients died from sepsis secondary to infections, pancytopenia, progressive hepatic GVHD, and/or acute renal failure.[274] Two patients with renal insufficiency

demonstrated excessive pentostatin exposure, as determined by measurement of the area under the curve (AUC), despite a 50% reduction in pentostatin dose. Although this trial was terminated before efficacy could be assessed, the data suggest that pentostatin is ineffective in treating liver manifestations of GVHD and may be inappropriate for patients with renal insufficiency. The limited available data suggest activity for pentostatin in the treatment of steroid-refractory aGVHD without liver involvement; however, serious adverse events have been reported. The renal function of patients receiving pentostatin should be monitored throughout the course of treatment.

Tocilizumab

Tocilizumab is a humanized anti-IL-6 receptor antibody that functions as an immunosuppressive agent by blocking IL-6 signaling.[275] IL-6 is a pro-inflammatory cytokine produced by a variety of cell types that plays a key role in the development of aGVHD. Elevations of IL-6 have been detected in the serum of patients with GVHD, and polymorphisms that result in increased IL-6 production have been associated with an increase in GVHD severity.[276,277] The efficacy of tocilizumab for the treatment of steroid-refractory aGVHD was evaluated in several studies.[278-282] A small study of eight patients (6 patients had aGVHD, the majority of whom had grade IV) showed an ORR of 67%, with a CR rate of 33%.[282] Tocilizumab was administered intravenously at a dose of 8 mg/kg once every 3 to 4 weeks. The most common adverse event in this study was infectious complications (69% were bacterial in origin). A retrospective study of nine patients with grade III–IV steroid-refractory aGVHD treated with the same dose and schedule of tocilizumab reported a lower ORR of 44% and a CR rate of 22%.[281] Another retrospective analysis of 15 patients conducted at the same institution reported improved results with the use of tocilizumab for steroid-refractory aGVHD, with a CR rate of 40%.[280] In this study, the patients received tocilizumab every 2 to 3 weeks (majority received tocilizumab every 2 weeks), compared to every 3 to 4 weeks as in the previous studies. Patients with skin and/or GI involvement had the greatest response, while those with liver involvement demonstrated no response. Another retrospective study conducted at a different institution reported a CR rate of 63% to tocilizumab (8 mg/kg given every 2 weeks) in 16 patients with steroid-refractory aGVHD of the lower GI tract.[278] These data suggest that tocilizumab has activity in the treatment of patients with steroid-refractory aGVHD, especially in patients with skin or GI involvement. An FDA-approved biosimilar is an appropriate substitute for tocilizumab.

Vedolizumab

Vedolizumab is a monoclonal antibody that is currently FDA approved for the treatment of moderate to severe inflammatory bowel disease.[283] Vedolizumab inhibits trafficking of T-cells to the GI mucosa by blocking the activation of α4β7 integrin, a process involved in the pathogenesis of GI aGVHD.[284-286]

Several studies have investigated the safety and efficacy of vedolizumab for steroid-refractory GI aGVHD.[284-286] In a small retrospective study that analyzed the outcomes of 29 patients, the ORR following vedolizumab was 79%, with a CR rate of 29% and a PR rate of 52%.[285] ORR was 100% when vedolizumab was given as a second-line agent, compared to 63% when given as third-line or later (P = .012) When given early, vedolizumab was also associated with a greater likelihood of coming off of immunosuppression (69% vs. 19%; P = .007) as well as fewer fatal infections (38% vs. 88%; P = .0006) In another small retrospective study analyzing the outcomes of 29 patients with steroid refractory GI aGVHD, ORR was 64% at 6 to 10 weeks following vedolizumab administration.[286] At 6 months, OS was 54%. There were 29 serious adverse events (SAEs), 12 of which were infectious in nature (3 possibly related to vedolizumab) and 13 of which were fatal (1 possibly related to vedolizumab). In a more recent meta-analysis, the use of vedolizumab for GI aGVHD was

associated with significantly improved pooled ORR at 14 days (60.53%), 28 days (50%), and 12 months (76.92%).[284] While improvement in CR rates at 14 and 28 days were not significant, improvement at 12 months was significant (pooled CR, 27.27%).

Suggested Agents for Steroid-Refractory cGVHD

The following systemic agents, listed in alphabetical order (except for the category 1 recommendation and FDA approved recommendations), can be used in conjunction with corticosteroids for steroid-refractory cGVHD. Although prolonged systemic corticosteroid therapy is better avoided, some patients may require prolonged steroid therapy (preferably using ≤0.5 mg/kg/day) for steroid-dependent cGVHD. The following are the most commonly used agents among NCCN Member Institutions. Currently, ruxolitinib, ibrutinib, and belumosudil are the only FDA-approved agents for treatment of steroid-refractory cGVHD.[287-289] While the following agents may be used in any site, some agents are more commonly used with particular organ involvement.

Ruxolitinib

In 2021, the FDA approved ruxolitinib for the treatment of steroid-refractory cGVHD after failure or one or two lines of systemic therapy in adult and pediatric patients aged ≥12 years.[290] The approval was based on data from the randomized phase III REACH3 trial, which compared ruxolitinib (10 mg twice daily) to investigator's choice of best available therapy in 329 patients with steroid-refractory or steroid-dependent cGVHD.[288] At week 24, the ORR was higher in patients in the ruxolitinib group compared to those in the control group (50% vs. 26%; $P < .001$). Ruxolitinib also led to longer median failure-free survival (>19 vs. 6 months; HR = .37; $P < .001$) and higher symptom response (24% vs. 11%; $P = .001$) than control. The median durations of response were 4.2 months and 2.1 months for the ruxolitinib and control arms, respectively. The median times from first response to death or new systemic therapies for cGVHD were 25 months and 5.6 months, respectively. The most common grade 3 or higher adverse events were thrombocytopenia (15% in the ruxolitinib group and 10% in the control group) and anemia (13% and 8%, respectively). Based on these data and the FDA approval, ruxolitinib is a category 1 recommended option for patients with steroid-refractory cGVHD.

Ibrutinib

Ibrutinib is a potent and irreversible inhibitor of Bruton's tyrosine kinase (BTK), which regulates B-cell survival.[287] It also inhibits IL-2–inducible T-cell kinase (ITK), which is involved in the selective activation of T-cell subsets.[291] In 2017, ibrutinib was approved by the FDA for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy and in 2022 was approved for pediatric patients ≥1 year of age with the same indication.[292, 2022 #624] The initial approval in adults was based on data from a single-arm multicenter trial that included 42 patients with steroid-refractory cGVHD.[287] Patients received 420 mg ibrutinib daily until cGVHD progression. The majority of patients (88%) had at least two organs involved at baseline, the most common being mouth (86%), skin (81%), and GI tract (33%). At a median follow-up of 14 months, the ORR was 67% and the most commonly reported adverse events were fatigue, bleeding/bruising, diarrhea, muscle spasms, nausea, thrombocytopenia, and anemia. After a median follow-up of 26 months, the ORR was 69%, with 31% of patients achieving a CR.[293] Sustained responses of ≥44 weeks were seen in 55% of the those who experienced response. Of the patients with multiorgan involvement, 73% of those with ≥2 organs involved showed responses in ≥2 organs and 60% of those with ≥3 organs involved showed responses in ≥3 organs. Corticosteroid dose was reduced to <0.15 mg/kg/day in 64% of patients and was completely discontinued in 19% of patients. The most common grade 3 adverse events were pneumonia, fatigue, and diarrhea. These data suggest that ibrutinib is effective and may produce durable responses in patients with

steroid-refractory cGVHD. However, ibrutinib should be used with caution in patients with a history of heart arrhythmias, due to a heightened risk of atrial fibrillation, and in patients on anticoagulation or antiplatelet therapy, due to a heightened risk of bleeding. Given the high risk of bleeding, patients should hold ibrutinib for 3 to 7 days prior to and after surgical procedures.

Belumosudil

In 2021, belumosudil was approved by the FDA for the treatment of adult and pediatric patients aged ≥12 years with cGVHD after failure of two or more lines of systemic therapy.[294] This approval was based on data from the randomized, multicenter phase II ROCKstar study, which evaluated the efficacy of belumosudil 200 mg taken once or twice daily in patients with cGVHD who had received two to five prior lines of therapy.[289] After a median follow-up of 14 months, the ORR was 76%, with 5% of patients achieving a CR. Response, including CR, was observed in all organs, including pulmonary GVHD. The median duration of response was 54 weeks and 44% of patients remained on belumosudil therapy for more than 1 year. Adverse events were consistent with those observed in patients with cGVHD receiving immunosuppressants and included infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, and musculoskeletal pain. Sixteen patients (12%) discontinued belumosudil due to possible drug-related adverse events. These data suggest that belumosudil is a promising therapy for steroid-refractory cGVHD that is well tolerated and produces clinically meaningful responses.

Axatilimab-csfr

In August 2024, axatilimab-csfr was approved by the FDA for the treatment of pediatric and adult patients with cGVHD weighing ≥40 kg after failure of at least two prior lines of systemic therapy.[295] Approval was based on data from the randomized, multicenter phase II AGAVE-201 study, which investigated the efficacy and safety of 3 different doses (0.3 mg/kg every 2 weeks, 1 mg/kg every 2 weeks, or 3 mg/kg every 3 weeks) of axatilimab-csfr in 239 patients with recurrent or refractory cGVHD.[296] Simultaneous use of corticosteroids, CNIs, or mTOR inhibitors was permitted. Median duration of response was not reached at any dose, with 60%, 60%, and 53% of patients at doses of 0.3 mg/kg, 1 mg/kg, and 3 mg/kg maintaining response at 12 months, respectively. However, ORR was superior in the 0.3 mg/kg arm, at 74%, compared to 67% and 50% with the 1 mg/kg and 3 mg/kg doses, respectively. Treatment-related adverse events, including fatal events, were also less common in the 0.3 mg/kg arm. The most common treatment-related adverse events included headache, elevation in LFTs and CPK, and infections. Of note, there are currently no randomized data comparing axatilimab-csfr with other agents utilized for steroid-refractory cGVHD.

Abatacept

Abatacept is a T-cell costimulatory inhibitor. It is a recombinant soluble fusion protein composed of the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) linked to the modified fragment crystallizable (Fc) region of IgG1.[297,298] Abatacept acts as an immunomodulatory drug by selectively inhibiting T-cell activation via binding to (blocking) the costimulation receptors (CD80 and CD86) on antigen-presenting cells (costimulation blockade). The safety and efficacy of abatacept in the treatment of steroid-refractory cGVHD were evaluated in a phase I clinical trial involving 16 patients.[297] The study followed a 3+3 design with two escalating abatacept doses to determine the maximum tolerated dose (MTD). The partial response rate to abatacept was 44% and no dose-limiting toxicities were observed at the MTD of 10 mg/kg. The affected sites with greatest improvement were the mouth, GI tract, joints, skin, eyes, and lungs. The most common adverse events were pulmonary infections (all of which resolved), diarrhea, and fatigue. Importantly,

treatment with abatacept resulted in a 51% reduction in prednisone usage. These data suggest that abatacept is an effective treatment option for patients with steroid-refractory cGVHD.

Alemtuzumab

The safety and efficacy of alemtuzumab for the treatment of steroid-refractory cGVHD was evaluated in a phase I dose-escalation trial involving 13 patients.[299] Six patients had moderate and seven patients had severe cGVHD per NIH consensus global scoring criteria; all patients had involvement of skin and subcutaneous tissues. Alemtuzumab dosing was investigated in a 3+3 study design. The MTD of alemtuzumab was 3 mg×1, then 10 mg×5 administered over 4 weeks. The most common adverse events were infections and hematologic toxicities. Of the 10 patients evaluable for response, the ORR was 70%, with a 30% CR rate. The median decrease in steroid dose at 1 year was 62%. A prospective study of 15 patients with steroid-refractory cGVHD treated with one cycle of subcutaneous alemtuzumab at 10 mg/day for 3 days followed by 100 mg intravenous rituximab on days +4, +11, +18, and +25 reported an ORR of 100% and a CR rate of 33% at day +30 evaluation.[300] At day +90 evaluation, the partial response rate was 50%, the CR rate was 28%, and 21% of patients had relapsed cGVHD. Of the five patients with evaluable data at 1 year, two (40%) had a partial response, two had a CR, and one experienced cGVHD progression. These data indicate that alemtuzumab is active in steroid-refractory cGVHD. Currently in the United States, alemtuzumab is only available via the Campath Distribution Program and the drug supply is patient-specific.

Calcineurin Inhibitors

Limited data exist for the efficacy of CNI, such as tacrolimus and cyclosporine, for the treatment of steroid-refractory cGVHD. The most common adverse events typically seen with CNI use are renal toxicity, hypomagnesemia, hypertension, and tremors. In a phase II trial, 31 patients with cGVHD that developed or progressed during therapy with cyclosporine and/or other immunosuppressive agents were treated with tacrolimus at an initial dose of 0.05 mg/kg intravenously or 0.15 mg/kg orally twice daily (target trough 15-25 ng/mL). In the 26 patients with evaluable data, the ORR was 46%.[240] Another trial evaluated the efficacy of tacrolimus administered at 0.15 mg/kg twice daily orally or 0.15 mg/kg/day intravenously in 17 patients with severe steroid-refractory cGVHD.[301] The ORR was 35% and OS was 65% at a median follow-up of 8.4 months. The greatest responses were observed in the skin, liver, and GI tract; musculoskeletal and lung cGVHD showed no response to treatment. Commonly reported adverse events included renal toxicity, hypertension, and infections. In a third report, 39 patients with cGVHD refractory to cyclosporine and prednisone were treated with tacrolimus.[302] The ORR was 21% with a CR rate of 13%. However, 56% of patients discontinued tacrolimus due to progression/persistence of cGVHD or treatment-related toxicity and 23% died during continued tacrolimus treatment. Infectious complications were the most common adverse event followed by renal toxicity, which led to treatment discontinuation in two patients. Three-year estimated OS was 64% and 41% of patients had discontinued all immunosuppressive treatment at 3 years post-HCT. Therefore, CNI may provide clinical benefit for steroid-refractory cGVHD, in particular when they have not been used for GVHD prophylaxis or initial therapy.

Etanercept

The efficacy of etanercept for the treatment of steroid-refractory cGVHD was retrospectively evaluated in a cohort of eight patients treated with subcutaneous etanercept at 25 mg twice weekly for 4 weeks followed by 25 mg once weekly for 4 weeks.[244] Patients were also continued on CNI, MMF, and/or sirolimus. The ORR was 62%, with one patient achieving CR. Three of the eight patients (37%) treated with etanercept died of

progressive disease or sepsis. In three of the five patients who experienced response to etanercept, corticosteroids were reduced by >50%. In a phase II trial, 34 patients with either obstructive (n = 25) or restrictive (n = 9) lung dysfunction following allogeneic HCT were treated with etanercept subcutaneously at 0.4 mg/kg/dose twice weekly for 4 (group A) or 12 (group B) weeks.[303] Obstructive lung dysfunction is commonly associated with cGVHD, with BOS being the most common histopathology reported. All patients had clinical signs or symptoms of cGVHD at the onset of treatment with diffuse skin, oral mucosal, ocular, and/or hepatic involvement. All patients received concurrent immunosuppressive therapy with either CNI alone (n = 5), CNI plus corticosteroids ± MMF (n = 22), MMF ± corticosteroids (n = 5), or sirolimus (n = 2). Clinical response, defined as a ≥10% improvement in the absolute value for forced expiratory volume (FEV1; for obstructive defects) or forced vital capacity (FVC; for restrictive defects), was obtained in 32% of patients. There was no difference in ORR based on the duration of treatment (29% in group A vs. 35% in group B; *P* = .99) or the presence of restrictive or obstructive lung dysfunction (33% vs. 32%, respectively; *P* = .73). No bacterial or viral infections were observed. Thus, etanercept seems to be effective for treating steroid-refractory cGVHD of the lung (especially if associated with BOS).

Extracorporeal Photopheresis

In a prospective single-center study involving 88 patients with extensive cGVHD, second- or third-line treatment with ECP resulted in an ORR of 73%.[249] Cutaneous and sclerotic manifestations were associated with higher response rates. After a median follow-up of 68 months, 5-year OS was 65% and was independently associated with a higher number of ECP sessions and cutaneous manifestations. A multicenter randomized phase II trial involving 95 patients with cutaneous manifestations of steroid-refractory cGVHD found that 8% of patients receiving ECP therapy experienced at least a 25% reduction in total skin score from baseline compared to 0% of patients in the control group (*P* = .04).[304] Treatment with ECP resulted in an ORR of 61% in a retrospective analysis of 71 patients with severe steroid-refractory cGVHD; the best responses were seen in the skin, liver, oral mucosa, and eyes.[305] A systematic review of prospective studies reported a pooled ORR of 64% for ECP in the treatment of steroid-refractory cGVHD.[245] Similar response rates were seen with skin and GI involvement; however, the ORR for cGVHD with lung involvement was only 15%, suggesting that ECP may not effectively treat lung manifestations of cGVHD. Reported rates of ECP-related mortality were extremely low. Another systematic review largely reached the same conclusions, reporting a pooled ORR of 64% and pooled response rates of 74% and 48% for skin and lung involvement, respectively.[306] This review also reported activity for ECP in treating cGVHD with GI involvement (ORR = 53%). These data suggest that ECP is an effective therapy for steroid-refractory cGVHD, especially in those with skin involvement. If ECP is not available or feasible, the NCCN Panel recommends the use of PUVA irradiation as an alternative treatment option for sclerotic or cutaneous steroid-refractory cGVHD.

Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline immunosuppressive and anti-parasitic agent that is commonly used for the treatment of malaria.[307] Hydroxychloroquine is believed to exert its immunomodulatory effects by interfering with cytokine production and antigen processing and presentation.[308,309] The efficacy of hydroxychloroquine for the treatment of steroid-refractory cGVHD was evaluated in a phase II trial involving 40 patients treated with hydroxychloroquine at 800 mg (12 mg/kg) per day.[309] The ORR was 53% among the 32 patients with evaluable data, with three patients achieving a CR. All patients who experienced response tolerated a >50% reduction in their steroid dose while receiving hydroxychloroquine. The highest response rates were observed in patients with skin, oral,

and/or liver involvement; efficacy in the treatment of GI manifestations was limited.

One of the most serious adverse events reported with the long-term use (>2 years) of hydroxychloroquine is chloroquine retinopathy, a form of toxic retinopathy caused by the binding of hydroxychloroquine to melanin in the retinal pigment epithelium, which can result in vision loss. The retinal toxicity of hydroxychloroquine was evaluated in a cohort of 12 patients with cGVHD treated with 800 mg hydroxychloroquine per day for a median duration of 22.8 months.[310] Seven patients developed vortex keratopathy and three patients developed retinal toxicity; retinal structure and color vision were abnormal in two of the three patients. These data suggest that hydroxychloroquine is an effective treatment option for patients with steroid-refractory cGVHD, especially in those with skin or oral involvement, but may not be appropriate for long-term use due to the risk of retinal toxicity. Periodic ophthalmologic assessment is recommended during treatment.

Imatinib

Imatinib is a small molecule tyrosine kinase inhibitor indicated for the treatment of several types of cancer, including CML.[311] Imatinib has activity against several tyrosine kinase enzymes, including platelet-derived growth factor receptor (PDGFR), which is implicated in skin fibrosis.[312] Stimulatory antibodies against PDGFR have been identified in patients with cGVHD with cutaneous sclerosis; however, neither anti-PDGFR antibody level, nor phosphorylation of tissue PDGFR, correlated with response to imatinib in patients with cGVHD.[313] The efficacy of imatinib to treat sclerotic manifestations of cutaneous steroid-refractory cGVHD was assessed in a pilot phase II trial involving 20 patients.[312] Eight patients received a standard dose of 400 mg daily while 12 patients underwent a dose escalation study due to poor tolerability (100 mg daily initial dose up to 200 mg daily maximum). Of the 14 patients evaluable for primary response, 5 (36%) had a partial response, 7 (50%) had stable disease, and 2 (14%) had progressive disease. After treatment with imatinib for 6 months, range of motion (ROM) deficit was improved in 79% of patients by an average of 24%. Common adverse events included hypophosphatemia, fatigue, nausea, diarrhea, and disrupted fluid homeostasis leading to edema. A randomized phase II crossover study compared imatinib (200 mg daily) to rituximab (375 mg/m^2 intravenously weekly for 4 weeks) for the treatment of patients (n = 35) with cutaneous sclerosis associated with cGVHD.[314] Significant clinical response, defined as quantitative improvement in skin sclerosis or joint ROM, was observed in 26% of patients randomized to imatinib and 27% of patients randomized to rituximab. Treatment success, defined as significant clinical response at 6 months without crossover, recurrent malignancy, or death, was achieved in 17% of patients on imatinib and 14% of patients on rituximab. In a prospective trial of 39 patients with steroid-refractory cGVHD treated with imatinib, the partial response rate was 36%.[315] The best responses were seen in the skin (32%), GI tract (50%), and lungs (35%). After a median follow-up of 40 months, the 3-year OS and event-free survival rates were 72% and 46%, respectively. These data suggest that low-dose imatinib (200 mg) is active in the treatment of patients with steroid-refractory cGVHD, especially in those with cutaneous sclerosis.

Interleukin-2

IL-2 is a naturally occurring pleiotropic cytokine that regulates the growth of T cells and is a key mediator of immune response.[316] The efficacy of IL-2 in the treatment of steroid-refractory cGVHD was evaluated in a phase I study involving 29 patients.[317] Patients received daily subcutaneous IL-2 at escalating dose levels for 8 weeks. The MTD was determined to be 1×10^6 IU/m^2. Of the 23 patients evaluable for a response, 12 had a significant clinical response involving multiple organs. Clinical responses were sustained in patients who received IL-2 for an extended period, allowing their corticosteroid dose to be tapered by a mean of 60%. In a follow-up

phase II trial, 35 patients with steroid-refractory cGVHD were treated with IL-2 at 1×10^6 IU/m^2 for 12 weeks.[316] The ORR in 33 patients with evaluable data was 61%. There were CRs and three patients developed progressive cGVHD. All those who experienced response experienced improvement in multiple sites of cGVHD, including the liver, skin, GI tract, lungs, and joints/muscle/fascia. Extended IL-2 therapy for up to 2 years was well tolerated and resulted in durable clinical responses in most patients. However, two patients in this study withdrew and five required dose reductions of IL-2 due to adverse events including thrombocytopenia, fatigue, flu-like symptoms, malaise, and thrombocytopenia. A phase I dose-escalation trial showed that escalation above the previously defined MTD did not improve clinical response in 10 patients with steroid-refractory cGVHD.[318] These data suggest that low-dose IL-2 has durable clinical activity in treating steroid-refractory cGVHD and is generally safe for long-term use.

Low-Dose Methotrexate

Methotrexate is an antimetabolite that exerts immunosuppressive effects by inhibiting the activity of dihydrofolic acid reductase, resulting in impaired DNA synthesis and lymphocyte proliferation.[319] In a retrospective study of 14 patients who had received low-dose methotrexate (7.5 mg/m^2/week for 3–50 weeks) for the treatment of steroid-refractory cGVHD, 71% of patients were able to reduce their prednisone dose to <1 mg/kg every other day without the addition of other agents.[320] In this study, the most frequently involved sites were the oral mucosa (n = 14) and skin (n = 11) and no grade 3 or higher toxicities were observed. The steroid-sparing effects of methotrexate were also observed in a prospective study of eight patients with steroid-refractory cGVHD, which reported a reduction in corticosteroid dose in the range of 25% to 80% in patients treated with low-dose methotrexate (5 mg/m^2/infusion).[321] The ORR was 75% and few toxicities were observed, the most serious being grade 3–4 cytopenias reported in two patients. Another retrospective review of 21 patients with steroid-refractory cGVHD reported an ORR of 76% in patients treated with low-dose methotrexate (5 or 10 mg/m^2 infusion every 3–4 days).[322] The response rates were particularly high in patients with extensive cGVHD (ORR = 92%) and were significantly higher in patients with skin involvement (92%) compared to those with liver involvement (43%; P = .009). Among patients with cGVHD in a single organ (skin or liver), 58% experienced response compared to 100% of patients with ≥2 organs involved. Although this trial reported severe hematologic toxicities associated with methotrexate, these toxicities were reversible and did not result in treatment discontinuation. These data suggest that low-dose methotrexate is active in the treatment of patients with steroid-refractory cGVHD, especially in those with skin and oral manifestations.

mTOR Inhibitors

The safety and efficacy of sirolimus for the treatment of steroid-refractory cGVHD was evaluated in a phase II trial involving 35 patients.[323] Patients with steroid-refractory cGVHD received sirolimus at a loading dose of 6 mg orally followed by a maintenance dose of 2 mg/day targeting a concentration between 7-12 ng/mL while continuing immunosuppressive treatment with tacrolimus and methylprednisolone. The ORR was 63%, with six patients achieving CR. The highest response rates were observed in patients with sclerotic skin involvement (73%) and involvement of the oral mucosa (75%), but responses were also observed in the lower GI tract (67%), liver (33%), and eyes (64%). Major adverse events included hyperlipidemia, renal dysfunction, cytopenias, TMA, and infectious complications. Median survival was 15 months and estimated actuarial survival at 2 years was 41%. In another phase II trial, 19 patients with steroid-refractory cGVHD were treated with sirolimus, CNI, and prednisone.[324] Sirolimus was administered orally at a loading dose of 10 mg followed by a daily dose of 5 mg without a defined target range. Of the 16 patients with evaluable data, 15 had an initial clinical response to this regimen. However, five patients discontinued treatment due to renal

toxicity. Of the 10 patients who continued with this regimen, three had a prolonged response and were able to successfully taper off immunosuppressive agents. A retrospective study analyzed 47 patients with steroid-refractory cGVHD treated with sirolimus (2 mg/day, target concentration 5-10 ng/mL) in combination with other immunosuppressive agents (CNI [n = 33], MMF [n = 9], or prednisone [n = 5]).[325] The ORR was 81%, with a CR rate of 38%. The main toxicity was mild impairment of renal function, which was more common in patients receiving sirolimus and CNI (33%) compared to sirolimus and other immunosuppressive agents (7%). Estimated 3-year OS in all patients was 57%. These data suggest that sirolimus is an effective agent for the treatment of patients with steroid-refractory cGVHD and should be investigated further to find the best dose schedule and combination of additional agents to optimize clinical response while limiting toxicity.

Although it has not been studied extensively, the sirolimus derivative everolimus has shown activity in the treatment of steroid-refractory cGVHD. Preliminary data from two retrospective studies showed that treatment with everolimus resulted in significant improvement in the NIH Severity Score and patient-reported quality of life.[326,327] However, more data are necessary to confirm the role of everolimus in the treatment of steroid-refractory cGVHD.

Mycophenolate Mofetil

The safety and efficacy of MMF for the treatment of steroid-refractory cGVHD was evaluated in a retrospective study of 24 patients treated with MMF at a dose of 500 mg twice daily (escalated to 1 g twice daily if tolerated) in combination with cyclosporine, tacrolimus, and/or prednisone.[328] The ORR was 75%, with a CR rate of 21%. Only two patients experienced progressive disease. The highest response rates were seen in patients with involvement of the skin or oral mucosa. Of the 22 patients receiving prednisone, 14 (64%) had their prednisone dose decreased by a median of 50% by the end of the 6-month observation period. The most common adverse events were abdominal cramps (which resulted in discontinuation of MMF in 3 patients) and infections. At a median follow-up of 24 months, 83% of patients were alive. In a prospective phase II trial involving 23 patients with steroid-refractory cGVHD, the cumulative incidence of disease resolution and withdrawal of all immunosuppressive treatment was 26% at 36 months after starting treatment with MMF (initial dose of 1 g twice daily).[266] After a median follow-up of 9.5 years, 52% of patients remained alive with only one patient requiring continued treatment with immunosuppressive agents. In another retrospective analysis of 13 patients with steroid-refractory cGVHD, the ORR to MMF (1.5 or 2 g daily) was 77% and the estimated 2-year OS rate was 54%. The most common adverse events were GI disturbances (27%) and infectious complications (23%). These data suggest that MMF is an effective therapy option for patients with steroid-refractory cGVHD.

Pentostatin

In a phase II trial involving 58 patients with steroid-refractory cGVHD, treatment with pentostatin at 4 mg/m^2 given intravenously every 2 weeks for a median of 12 doses resulted in an ORR of 55%.[329] Most patients had skin involvement and more than half had oral and GI involvement. The highest response rates were observed in patients with lichenoid cutaneous manifestations (69%) followed by patients with oral involvement (62%); the lowest response rates were seen in patients with liver involvement. A total of 11 grade 3–4 infections were reported and four patients withdrew from treatment due to adverse events including nausea/vomiting, renal toxicity, and fatigue. OS at 1 and 2 years was 78% and 70%, respectively. In a retrospective analysis of 18 patients with steroid-refractory cGVHD, 12 of whom had severe cGVHD, treatment with pentostatin at 4 mg/m^2 every 2 weeks resulted in an ORR of 56%; CR was achieved in one patient.[272] Activity was observed in all affected organs, with CRs observed in GI (CR

= 3), skin (CR = 4), and muscle/fascia (CR = 1) manifestations. The median decrease in corticosteroid dose over 24 months after pentostatin initiation was 38% and median OS was 5 months. Estimated 1-year OS was 34%. Common adverse events included renal toxicity and infections. These data suggest that pentostatin is active in the treatment of steroid-refractory cGVHD.

Rituximab

Rituximab is an anti-CD20 chimeric monoclonal antibody used to treat NHL and CLL that exerts immunosuppressive effects by binding to CD20 on the surface of B cells, facilitating their destruction.[330] Since B cells are implicated in the pathogenesis of cGVHD, the efficacy of rituximab in the treatment of steroid-refractory cGVHD has been evaluated in several studies.[308,331] In a systematic review and meta-analysis of seven studies (3 prospective and 4 retrospective) including 111 patients, the pooled ORR to rituximab was 66%.[331] The majority of studies used rituximab at a dose of 375 mg/m^2 once per week for 4 to 8 infusions, although similar results were reported with rituximab administered at 50 mg/m^2 per week for 4 weeks (ORR = 69%). The pooled ORR for patients with skin cGVHD was 60%, compared to 36% for oral mucosal cGVHD, 29% for liver cGVHD, and 30% for lung cGVHD, suggesting that skin manifestations of cGVHD are particularly susceptible to rituximab treatment. However, it should be noted that the site-specific response rates varied greatly among studies. Administration of rituximab facilitated corticosteroid dose reductions in the range of 75% to 86%, depending on the study. The steroid-sparing effect of rituximab was more pronounced in patients with skin and oral mucosal GVHD. The most common adverse events were related to infusion reactions or infectious complications. Therefore, rituximab is an effective treatment option for patients with steroid-refractory cGVHD, especially in those with skin involvement. An FDA-approved biosimilar is an appropriate substitute for rituximab.

GVHD Supportive Care

Supportive Care for All Patients with GVHD

Supportive care is essential for all patients with GVHD. Special attention is required for prevention of infection, as infection is the most common cause of death in those with cGVHD.[198] The NCCN Panel recommends initiation of appropriate antimicrobial prophylaxis with escalating immunosuppressive therapy as outlined in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections. Surveillance for cytomegalovirus reactivation, which is associated with significant morbidity and mortality among allogeneic HCT recipients,[198,332] is also recommended in appropriate patients. Consideration can be made for additional viral surveillance. Live vaccines should be avoided for all patients on immunosuppressive therapy or those with active GVHD.[198] Re-vaccination for COVID-19 is recommended in all allogeneic HCT recipients, though with a delay until 3 months post-transplant given the likelihood of a blunted immune response affecting the efficacy of vaccination prior to this time point.[333] Routine use of prophylactic intravenous immunoglobulin (IVIG) replacement is not recommended given lack of clear evidence of benefit, higher risks of SOS and thrombosis, and possible reduced efficacy of vaccinations post-transplant; however, there may be subsets of patients where prophylactic IVIG may be considered, such as in UCB transplant recipients, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in patients with cGVHD with recurrent sinopulmonary infections.[334]

The use of high-dose steroid therapy for management of GVHD may be associated with infections (including viral, fungal, and bacterial), glucose intolerance, hypertension, adrenal insufficiency, poor wound healing, myopathy, osteoporosis, vitamin D deficiency, insomnia, anxiety, and mood swings.[335] Vitamin D and calcium supplementation should be

considered for patients on high-dose steroids. [335] Allogeneic HCT, even without the use of high-dose steroids, is associated with bone resorption and decreased bone formation, which can lead to osteoporosis. Thus, monitoring of vitamin D levels and measurement of bone mineral density by dual-energy x-ray absorptiometry (DEXA) scans is recommended for those with current or past exposure to high-dose steroids and those with cGVHD, with treatment and repeat imaging as indicated based on results.[198]

Dermatology, dental, and ophthalmology exams are recommended at baseline and at appropriate intervals beginning 6-12 months post-transplant for all patients with GVHD for both GVHD-related symptoms and other increased risk factors, such as increased risks of skin cancer and oral squamous cell carcinoma in those with cGVHD.[198]

For patients with liver GVHD, prophylaxis with ursodiol, a hydrophilic bile acid, can be considered. In a randomized trial, ursodiol was found to reduce the incidence of bilirubin elevation, severe aGVHD, liver GVHD, and GI GVHD, as well as improve survival.[336,337]

Supportive Care for Acute GVHD

Acute GVHD of the Skin

Supportive care recommendations for aGVHD of the skin include avoidance of direct sunlight and photosensitizing agents, such as voriconazole, as well as the use of sunscreen.[338] Those with advanced skin aGVHD should be evaluated by a dermatologist.[339]

Acute GVHD of the GI Tract

Acute GVHD of the GI tract can lead to symptoms such as severe abdominal pain and diarrhea. Abdominal pain from aGVHD can be difficult to treat and opioids are often required, though should be used with caution given the increased risk of ileus associated with their use.[340] Similarly, the use of octreotide can be considered for control of severe diarrhea, though given the risk of ileus should be stopped once diarrhea resolves, or after 7 days of treatment.[341]

Patients with aGVHD of the gut may suffer from malnutrition and protein-losing enteropathy with deficiency of trace elements (eg, magnesium and zinc) and vitamins (eg, thiamine, and vitamins B12 and D).[340,342] In addition, bowel rest is a critical component of supportive care for high grade aGVHD of the GI tract. Total parenteral nutrition should be considered in patients with voluminous diarrhea or poor tolerance to oral intake.[340,342] Monitoring for thiamine deficiency should be considered for patients with altered mental status.

GI topical steroids such as oral beclomethasone or budesonide are frequently administered in the setting of aGVHD of the gut, but prolonged use can lead to adrenal insufficiency. Thus, it is critical for providers to be familiar with symptoms of adrenal insufficiency and to keep a high index of suspicion in the setting of non-specific symptoms, such as fatigue, malaise, and muscle aches.[343]

Supportive Care for cGVHD

Chronic Oral GVHD

Xerostomia is a common complication of oral cGVHD. Sialogogues such as cevimeline can be considered for severe xerostomia in the absence of contraindications.[198] Patients with oral cGVHD are also at higher risk of developing oral squamous cell carcinoma[198]; thus, all suspicious oral lesions should be examined by a dentist or oral surgeon, in addition to routine surveillance dental examinations. Dexamethasone mouth rinses (swish and spit) can be considered[198]; patients should be monitored for oral thrush and appropriate anti-fungal topical therapy should be initiated as indicated.

Chronic Ocular GVHD

Supportive care for ocular cGVHD centers around increasing ocular surface moisture to reduce dry eye and reduction of inflammation.[198] Autologous serum drops may improve ocular surface inflammation but are not widely available. Methods to alleviate dry eye include artificial tears and, in severe cases, punctal plugs or gas-permeable scleral lenses. Assessment and follow-up by an ophthalmologist, ideally with experience in GVHD, is recommended.

Chronic Gut GVHD

Although diarrhea is a well-known symptom of gut cGVHD, a workup for malabsorption is indicated in patients with prolonged diarrhea. Pancreatic atrophy leading to fat malabsorption may occur in the setting of gut cGVHD and oral pancreatic enzyme supplementation may be beneficial.[198,344]

Upper intestinal cGVHD is associated with the development of esophageal webs and strictures, for which GI consultation for endoscopic esophageal dilation may be beneficial.[198]

cGVHD of the Genitalia

Vulvovaginal cGVHD often presents with symptoms of dryness, tenderness, dysuria, and dyspareunia.[198] All patients with vulvovaginal symptoms should be assessed by a gynecologist. Urology and dermatology assessment may also be required for genitourinary symptoms or sclerotic changes. Differential diagnosis includes post-menopausal changes and consideration may be given to starting topical estrogen or systemic estrogen/progestin-combined hormone therapy (or referral to gynecology for further evaluation).[345]

Foreskin and penile cGVHD are uncommon but may lead to lichenoid skin lesions and erectile dysfunction.[198,346] Appropriate referrals to urology and/or dermatology are recommended.

cGVHD of the Nervous System

Physical therapy consultation may be beneficial for patients experiencing myopathy and/or neuropathy from cGVHD, especially when symptoms such as muscle pain, weakness, or wasting or paresthesias limit activities of daily living or impair quality of life.[198] Patients with limited ROM from sclerotic skin changes may also benefit from physical therapy consultation.

Summary

The NCCN Guidelines® for Hematopoietic Cell Transplantation provide an evidence- and consensus-based approach for the use of HCT for the management of malignant disease in adult patients. HCT is a potentially curative treatment option for patients with certain types of malignancies. However, disease relapse and transplant-related complications often limit the long-term survival of HCT recipients. The leading cause of NRM in allogeneic HCT recipients is the development of GVHD.[164] Despite treatment with systemic corticosteroids, approximately 50% of patients with GVHD develop steroid-refractory disease.[204] Steroid-refractory GVHD is associated with high mortality and no standard, effective therapy has yet been identified. Therefore, the NCCN Panel strongly encourages patients with steroid-refractory acute or cGVHD to participate in well-designed clinical trials to enable further advancements for the management of these diseases and ultimately increase the long-term survival of HCT recipients.

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