National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Cell Transplantation (HCT):

Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease

Version 4.2021 — September 9, 2021

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Hematopoietic Cell Transplantation

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NCCN Guidelines Panel Disclosures

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NCCN Guidelines Version 4.2021
Hematopoietic Cell Transplantation

NCCN Panel Members
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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.

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NCCN Guidelines Version 4.2021
Hematopoietic Cell Transplantation

Updates in Version 4.2021 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 3.2021 include:

HCT-1
- **Link added: Stem Cell Mobilization (HCT-4)**

HCT-4
- **New algorithm added: Stem Cell Mobilization**

HCT-4A
- **New page added: Stem Cell Mobilization Regimens**

Updates in Version 3.2021 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 2.2021 include:

GVHD-E (1 of 3)
- **Systemic agents for steroid-refractory chronic GVHD**
  - **Agent added: Belumosudil**
  - **Footnote c added: 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.**
  - **Reference added: Cutler CS, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease (cGVHD) after 2 or more prior lines of therapy: The ROCKstar Study. Blood 2021:blood.2021012021. Epub ahead of print.**

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

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NCCN Guidelines Version 4.2021
Hematopoietic Cell Transplantation

Updates in Version 2.2021 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 1.2021 include:

MS-1

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

Updates in Version 1.2021 of the NCCN Guidelines for Hematopoietic Cell Transplantation from Version 2.2020 include:

HCT-2

- Laboratory tests
  - Toxoplasma serology (for allogeneic HCT) moved to the recommended laboratory tests (previously listed on HCT-3, under "as clinically indicated").
- Footnote added: For acute leukemia, bone marrow biopsy is ideally performed within 4 weeks of starting a conditioning regimen.

GVHD-1

- Footnote modified: GI biopsy *(EGD, colonoscopy and/or flexible sigmoidoscopy) is recommended for the diagnosis of GI acute GVHD.* ~~and/or~~ Stool testing may be used to rule out other possible causes of GI symptoms (eg, bacterial/viral infection, drug-induced injury, other differential diagnoses).

GVDH-2

- Footnote added: For recommendations on antibiotic prophylaxis during immunosuppressive therapy, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

GVHD-3

- First-line therapy for upper GI only modified: changed from "methylprednisolone ± topical steroids," to "methylprednisolone + topical steroids."
- Option added for grade II–IV acute GVHD: Consider sirolimus for standard-risk acute GVHD.
  - Footnote added: Standard-risk acute GVHD as defined by clinical risk score and biomarker status (CTN1501 trial: Pidala J, et al. Blood 2020;135:97-107).

GVHD-4

- Footnote modified: 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.

GVHD-A (1 of 2)

- Bullets modified: *Commonly used* criteria ~~are commonly used~~ for the staging/grading of adults with acute GVHD *include:*
  - Keystone (modified Glucksberg) *criteria (see below)*
  - MAGIC criteria *(see GVHD-A, 2 of 2)* ~~(Harris AC, et al. Biol Blood Marrow Transplant 2016;22:4-10).~~
  - Minnesota criteria (MacMillan ML, et al. Biol Blood Marrow Transplant 2015;21:761-767; https://z.umn.edu/MNAcuteGVHDRiskScore

GVHD-A (2 of 2)

- Table added: MAGIC Criteria: Acute GVHD Target Organ Staging & Overall Clinical Grade (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).

GVHD-C (3 of 5)

- Footnote modified: ~~To be completed by specialist or trained medical providers.~~ *Referral and close surveillance by a specialist is recommended for early detection of chronic GVHD and full assessment of disease.*

GVHD-D (1 of 2)

- Table heading modified: ~~NIH~~ Response Criteria for ~~Chronic~~ GVHD Clinical Trials

GVHD-E (1 of 3)

- Systemic agents for steroid-refractory acute GVHD
  - Ruxolitinib was changed from a category 2A to a category 1 recommendation; and moved to the top of the list.
- Footnote added: An FDA-approved biosimilar is an appropriate substitute for rituximab.

GVHD-E (2 of 3)

- Reference added: Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 2020;382:1800-1810.

INTRODUCTION

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

The initial version of the Guidelines addresses pre-transplant recipient evaluation and management of acute/chronic graft-versus-host disease (GVHD). Additional topics will be addressed in subsequent versions.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

INDICATIONS FOR TRANSPLANTATION

Indications for hematopoietic cell transplantation (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 Lymphoma
- 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

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

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PRE-TRANSPLANT RECIPIENT EVALUATION[a]

- **Clinical Assessment:**
  - **Confirm histologic diagnosis**
  - **History & physical exam, including evaluation of performance status (ECOG or KPS) and body mass index (BMI)**
  - **Assess disease status[b] (including cytogenetic/molecular testing for risk stratification and assessment of minimal residual disease, if applicable)**
  - **Bone marrow aspiration & biopsy[c] 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 (DLCO)[d,e]**
  - **ECG (with QTc interval assessment)**
  - **Measure left ventricular ejection fraction (LVEF)[f] with echocardiogram (if valvular assessment required) or MUGA scan**
  - **Psychosocial evaluation[g]**
  - **HCT Comorbidity Index (HCT-CI)[h] score (in particular for allogeneic HCT)**
- **Imaging:**
  - **Disease-specific restaging studies (See NCCN Guidelines for Treatment of Cancer by Site)**
  - **Chest x-ray (if no other chest imaging done)**
- **Laboratory Tests:**
  - **CBC with differential**
  - **ABO/Rh typing**
  - **Chemistry profile (including blood glucose, creatinine/GFR,[i] electrolytes, and liver function tests (LFTs) [transaminases and bilirubin])[j,k]**
  - **Prothrombin time (PT)/partial thromboplastin time (PTT)**
  - **Urinalysis**
  - **Infectious disease testing: CMV, HSV, VZV, HBV, HCV, and HIV serology**
  - **HLA typing per FACT (Foundation for the Accreditation of Cellular Therapy) guidelines[l]**
  - **Toxoplasma serology (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 the choice of the preparative regimen (drug choice, dose intensity, and immunosuppressive regimen).

[b] 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.

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

[d] Diffusing capacity of the lungs for carbon monoxide (DLCO) should be corrected for hemoglobin concentration (Hb) using the Dinakara method. In patients with significantly reduced DLCO, caution should be exercised when using busulfan or carmustine-based regimens.

[e] Consider pulmonary consultation and/or arterial blood gas (ABG) analysis if DLCO <60%.

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

[g] Assess medication adherence, high-risk behavior, and caregiver availability to ensure patient compliance to treatment.

[h] 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;121:2854-63]. 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.

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

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

[k] 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.

[l] 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 (7th edition); 2018.

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

As clinically indicated:

- **Additional Clinical Assessment**
  - **Lumbar puncture for cerebrospinal fluid (CSF) analysis**
  - **Discuss fertility preservation/sperm banking**
  - **Pregnancy test for women of childbearing potential**
  - **Physical therapy evaluation (strength, flexibility, function)**
  - **Nutritional evaluation**
  - **Consider geriatric assessment for select patients (category 2B) (see NCCN Guidelines for Older Adult Oncology)**
  - **Dental evaluation (in particular for allogeneic HCT)**
- **Additional Imaging**
  - **CT (chest and/or sinuses)**
- **Additional Laboratory Tests**
  - **Epstein-Barr virus (EBV) testing or other infectious disease testing (if high risk) (eg, tuberculosis [TB], strongyloides, human T-cell lymphotropic virus [HTLV] types I and II [for allogeneic HCT])**
  - **Human leukocyte antigen (HLA) antibody assessment if using HLA-mismatched donor (allogeneic HCT)**
  - **24-hour urine creatinine clearance (for borderline renal dysfunction or low muscle mass)**
  - **Urine toxicology screen if history of illicit drug use**
  - **Thyroid-stimulating hormone (TSH) 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 the choice of the preparative regimen (drug choice, dose intensity, and immunosuppressive regimen).

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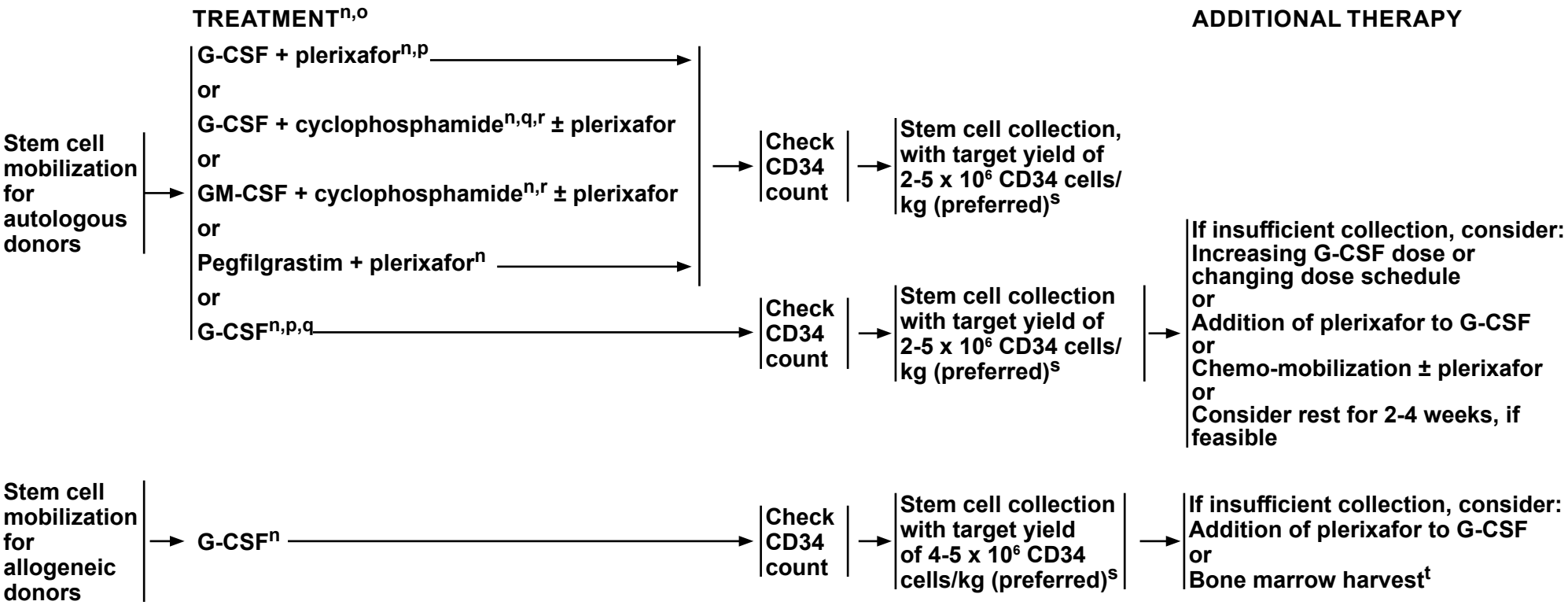
STEM CELL MOBILIZATION[m]



[m] 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)

[n] See Stem Cell Mobilization Regimens (HCT-4A).

[o] Alternative chemo-mobilization regimens with disease-specific activity are also appropriate.

[p] G-CSF + plerixafor is superior to single agent G-CSF in heavily pre-treated multiple myeloma and non-Hodgkin lymphoma.

[q] G-CSF + cyclophosphamide may be superior to single agent G-CSF in heavily pre-treated multiple myeloma and non-Hodgkin lymphoma.

[r] No difference was observed between G-CSF/cyclophosphamide and GM-CSF/cyclophosphamide (Gazitt, Callander et al. 2000).

[s] 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 desirable. Stem cell yields <2 x 10^6 CD34 cells/kg may cause delayed engraftment, while larger cell doses have been associated with a more rapid time to platelet and neutrophil recovery.

[t] For bone marrow harvest recommendations, refer to the National Marrow Donor Program/Be the Match.

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STEM CELL MOBILIZATION REGIMENS

Autologous Donors

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

Filgrastim[u] + Cyclophosphamide ± Plerixafor
- Cyclophosphamide: 1500-3000 mg/m2 IV for one dose
- Filgrastim: 10 mcg/kg SC
  - Start on day 1-5 after cyclophosphamide and continue daily until apheresis starts and collection goal is met
- Plerixafor: 0.24mg/kg actual body weight SC (max 40mg/day) on the day before apheresis[v]

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
  - Start on day 1-5 after cyclophosphamide and continue daily until apheresis starts and collection goal is met
- Plerixafor: 0.24mg/kg actual body weight SC (max 40mg/day) on the day before apheresis[v]

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

Allogeneic Donors

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

[u] Tbo-filgrastim or an FDA-approved biosimilar is an appropriate substitute for filgrastim.
[v] Plerixafor is generally administered 11 hours prior to stem cell collection.
[w] An FDA-approved biosimilar is an appropriate substitute for pegfilgrastim.

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POST-TRANSPLANT FOLLOW-UP

Monitoring for post-transplant complications such as GVHD, infections,[x] and disease relapse is recommended for all patients who have undergone HCT.

Additional recommendations for post-HCT follow-up will be addressed in subsequent versions of the NCCN Guidelines for Hematopoietic Cell Transplantation.

If GVHD is suspected, see Diagnosis/Workup of GVHD (GVHD-1).

[x] See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

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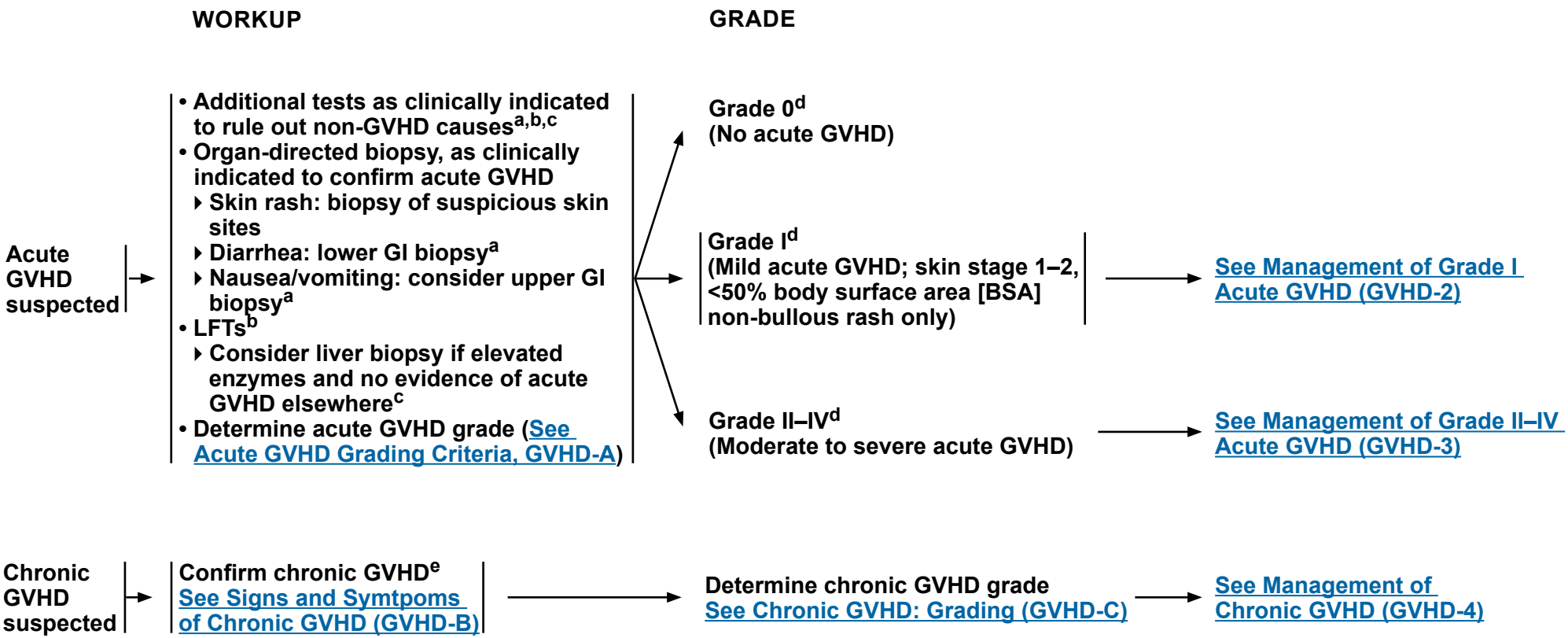
DIAGNOSIS/WORKUP OF GVHD



[a] GI biopsy (EGD, colonoscopy and/or flexible sigmoidoscopy) is recommended for the diagnosis of GI acute GVHD. Stool testing may be used to rule out other possible causes of GI symptoms (eg, bacterial/viral infection, drug-induced injury, other differential diagnoses).
[b] Consider imaging as clinically indicated for 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] See 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).

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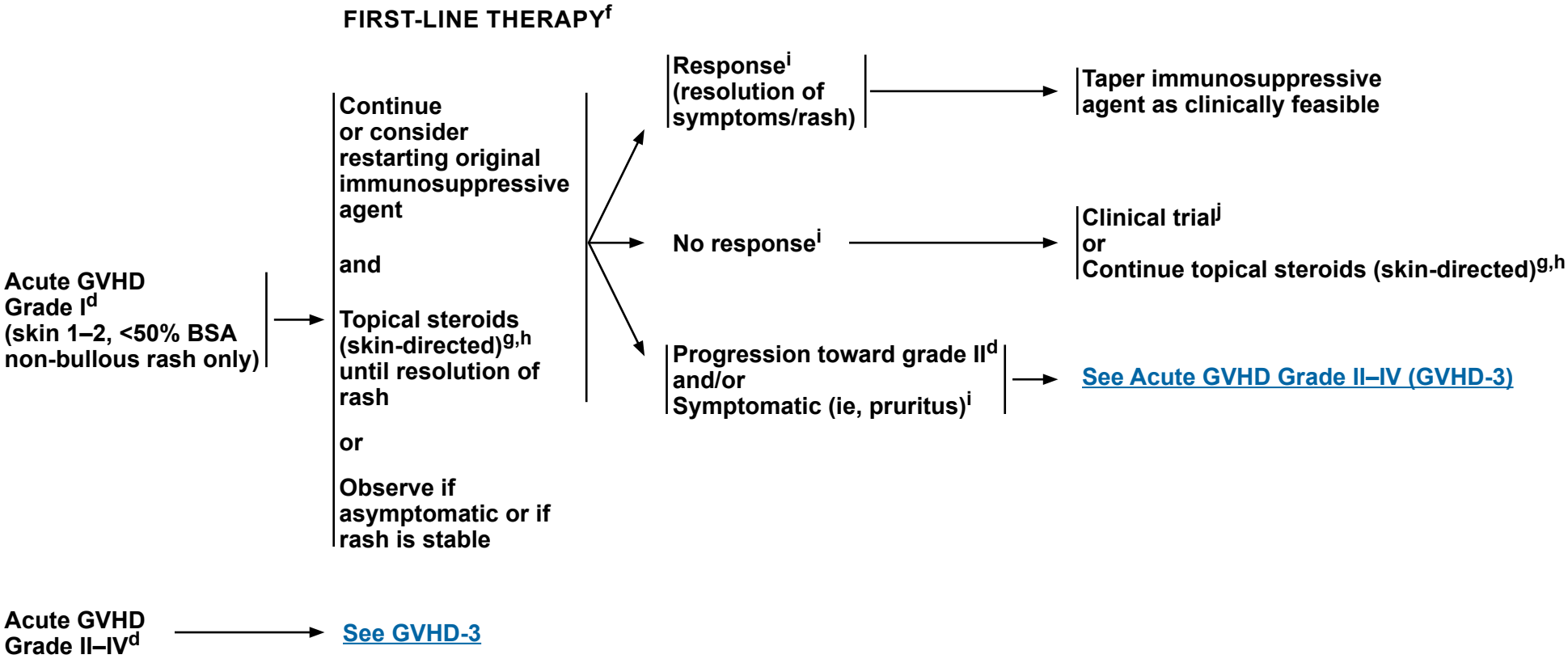
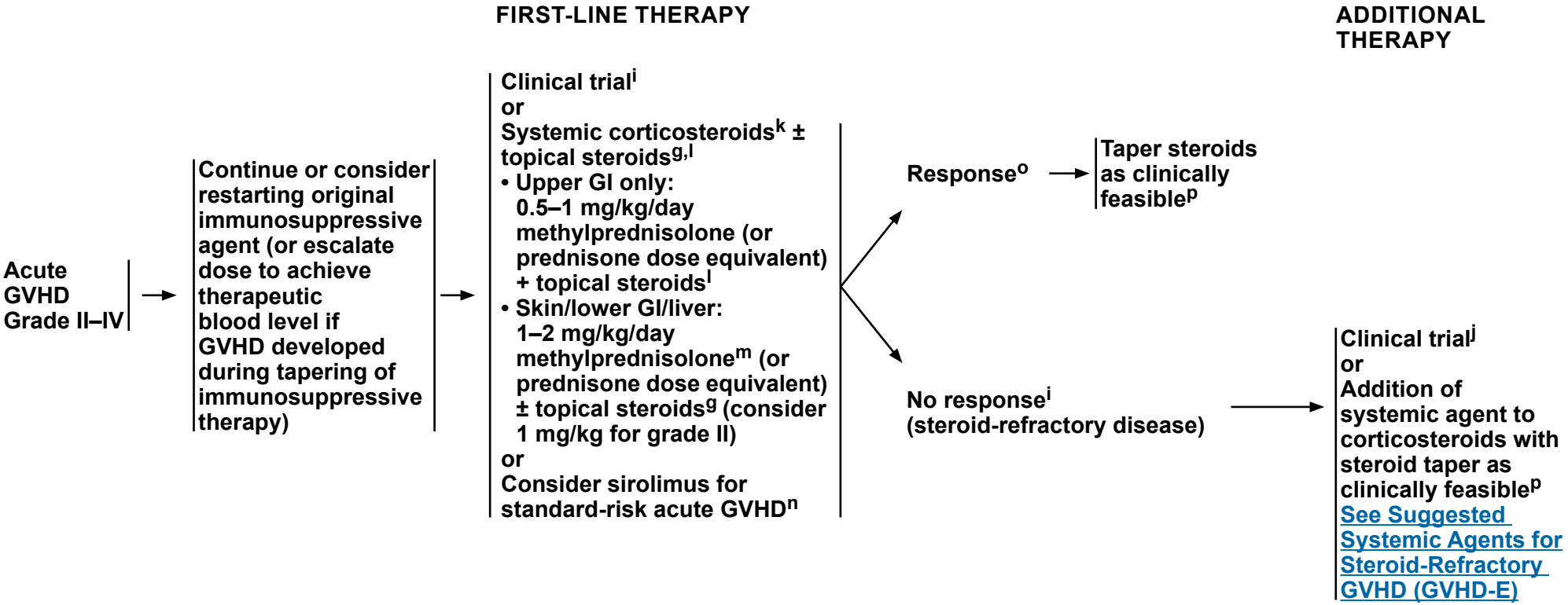
MANAGEMENT OF ACUTE GVHD



[d] See 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] See GVHD Steroid Response Definitons/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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

[j] Enrollment in well-designed clinical trials should be encouraged. 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 RCT, initial treatment with systemic prednisone at 0.5 mg/kg/day in conjunction with GI topical steroids (beclomethasone dipropionate ± 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 <1,000 mL/day. (Mielcarek M, et al. Haematologica 2015;100:842-848.)

[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 1 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.

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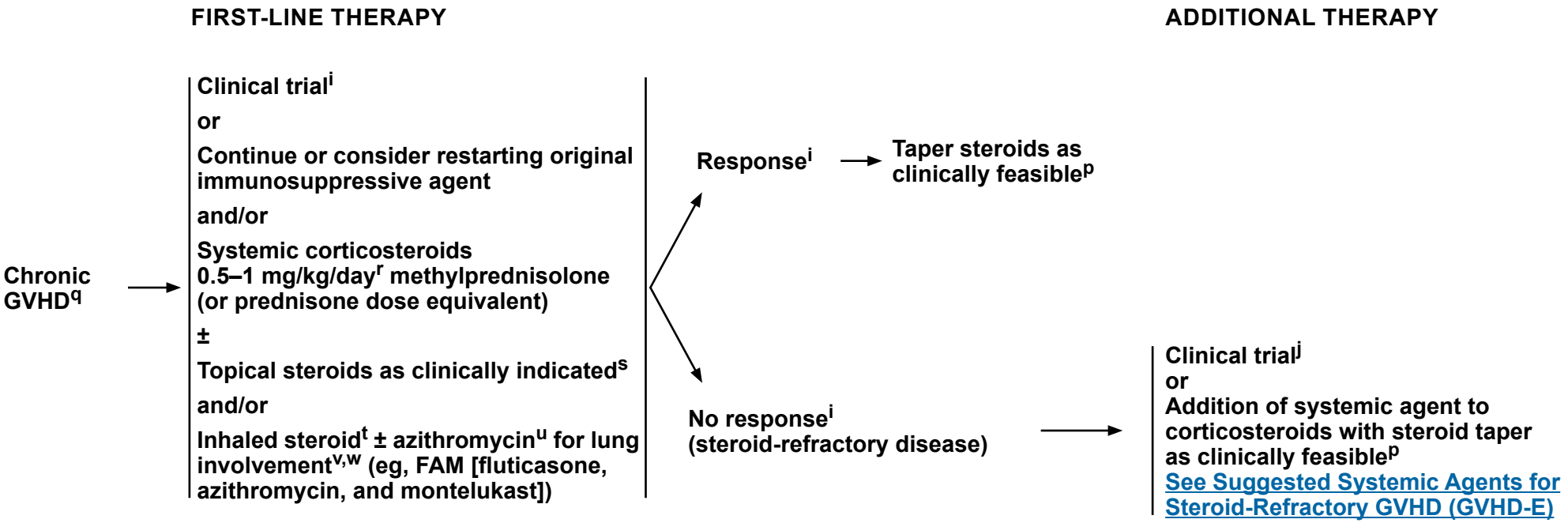
MANAGEMENT OF CHRONIC GVHD



[i] See GVHD Steroid Response Definitions/Criteria (GVHD-D).
[j] Enrollment in well-designed clinical trials should be encouraged. 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] 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.
[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.

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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 (see 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 body surface area. 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.

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ACUTE GVHD: STAGING AND GRADING

MAGIC Criteria: Acute GVHD Target Organ Staging & Overall Clinical Gradeg

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).

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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.

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Continued

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 (females) • Phimosis or urethral/meatus scarring or stenosis (males)	• 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 > 2 × upper limit of normal • ALT > 2× upper limit of normal
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (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. FEV1/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, computed tomographic (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 PFTs: 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.

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Continued

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 (AIHA, 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.

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CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]	Score 0	Score 1	Score 2	Score 3
Performance Score: _____ KPS ECOG LPS (circle one)	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <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 total body surface (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

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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

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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 discrepency 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.

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Continued

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

Keypoints:

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

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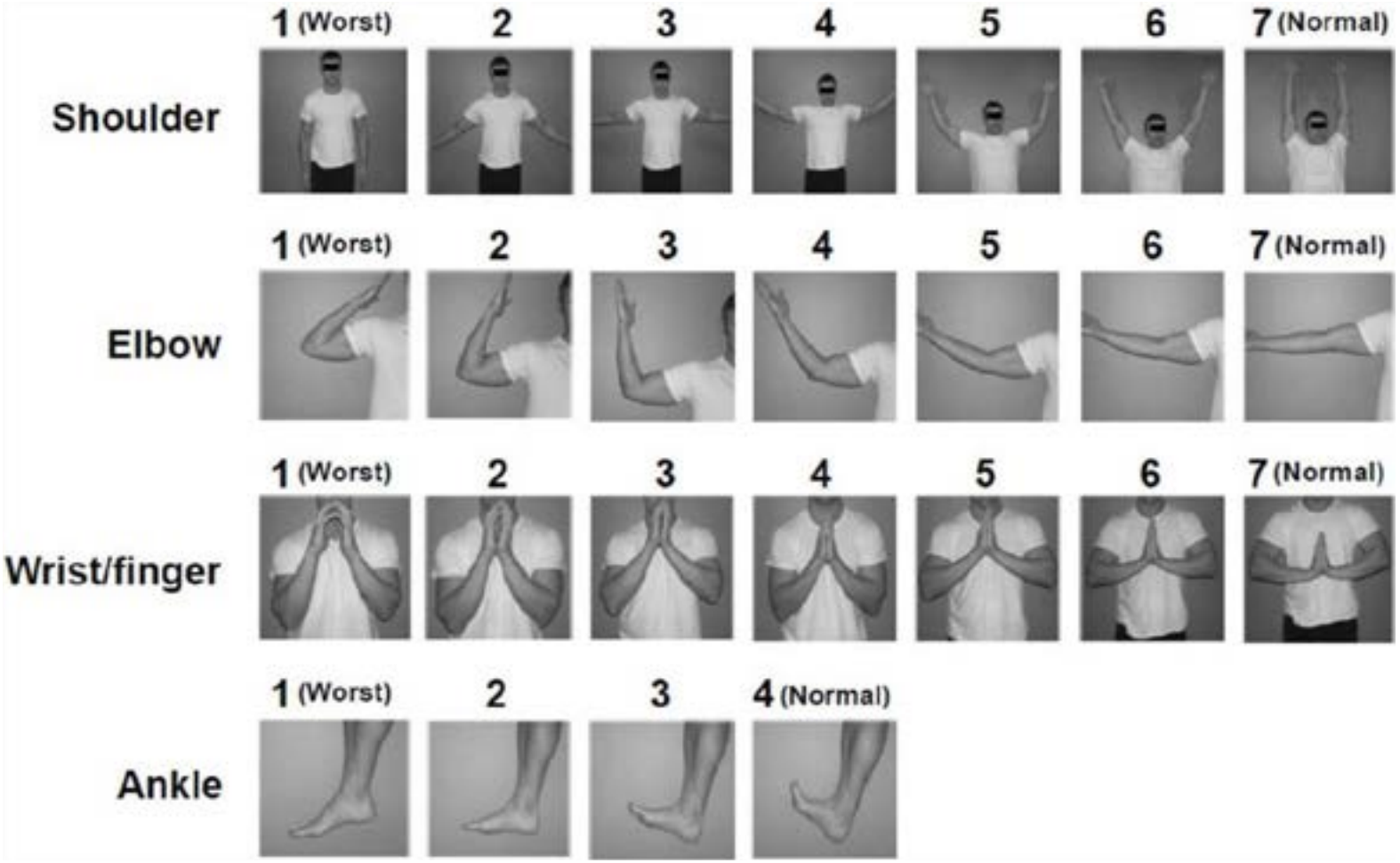
CHRONIC GVHD: GRADING

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.

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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	

See 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.

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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.

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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]
(listed in alphabetical order, except for category 1)

Acute GVHD[1]	Chronic GVHD
The following agents are often used in conjuction with the original immunosuppressive agent.	*While the following systemic agents may be used in any site, some agents are used more commonly in certain sites based on available data (see Discussion).*
• Ruxolitinib (category 1)[b,2] • Alemtuzumab[3,4] • Alpha-1 antitrypsin (AAT)[5] • Anti-thymocyte globulin (ATG)[6] • Basiliximab[7] • Calcineurin inhibitors (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[18-21]	• Abatacept[22] • Alemtuzumab[23,24] • Belumosudil[c,25] • Calcineurin inhibitors (eg, tacrolimus, cyclosporine) • Etanercept[26] • ECP[d,9] • Hydroxychloroquine[27] • Ibrutinib[e,28] • Imatinib[29,30] • Interleukin-2 (IL-2)[31] • Low-dose methotrexate[32-34] • mTOR inhibitors (eg, sirolimus)[35-37] • Mycophenolate mofetil[38] • Pentostatin[39-41] • Rituximab[42,f] • Ruxolitinib[43,44]

[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 patients with steroid-refractory acute GVHD.
[c] 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.
[d] Psoralen and ultraviolet A irradiation (PUVA) may be used for sclerotic or cutaneous GVHD if ECP is not available or feasible.
[e] Ibrutinib is FDA approved for the treatment of adult patients 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] An FDA-approved biosimilar is an appropriate substitute for rituximab.

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References

SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD
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[2] Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 2020;382:1800-1810.
[3] Gomez-Almaguer D, Ruiz-Arguelles GJ, del Carmen Tarin-Arzaga L, et al. Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 2008;14:10-15.
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Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD
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Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus 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 Guidelines Version 4.2021
Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease

Discussion

This discussion corresponds to the NCCN Guidelines for Hematopoietic Cell Transplantation. Last updated on July 26, 2021.

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Overview

Hematopoietic cell transplantation (HCT) involves the infusion of hematopoietic progenitor cells after cytotoxic conditioning regimens in order to re-establish normal hematopoietic and immune function.[1] HCT is a potentially curative treatment option 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 donor. Prior to HCT, most patients receive chemotherapy, serotherapy, and/or radiation for pre-transplant conditioning (preparative regimen). In allogeneic HCT, preparative regimens are administered in order to eradicate malignant cells in the bone marrow (if using a myeloablative regimen) and induce immunosuppression so that engraftment of healthy donor cells occurs.[1] In autologous HCT, high-dose myeloablative regimens are used to treat the malignancy. This is followed by rescue infusion of the patient's own cells, which are collected before high-dose therapy, in order to restore hematopoiesis and reconstitute the immune system.[1]

The number of HCTs has increased in the United States in recent years.[2] The Center for International Blood and Marrow Transplant Research (CIBMTR) estimated that 9,028 allogeneic transplants and 14,006 autologous transplants were performed in the United States in 2018.[3] Acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndromes (MDS) were the most common malignancies treated with allogeneic HCT, while autologous HCT was used most frequently in multiple myeloma, non-Hodgkin lymphoma, and Hodgkin lymphoma.[3] Although the overall number of HCTs has increased, difficult logistics and high costs create significant barriers to access for many patients. A recent systematic review also found older age, lower socioeconomic status, and non-White race to be associated with reduced access to HCT.[4]

Outcomes of HCT vary according to the type and stage of the disease being treated, the overall health of the patient, the degree of HLA-mismatch between donor and recipient (for allogeneic HCT), and the source of the hematopoietic cells.[5] Hematopoietic cells can be obtained from either 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.[6] Mobilization of peripheral blood progenitor cells (PBPCs) by granulocyte-colony stimulating factor (G-CSF) has largely replaced use of bone marrow grafts (in particular for autologous HCT) due to the ease of collection, avoidance of general anesthesia, more rapid engraftment rates, reduced risk of graft failure, and lower transplant-related mortality (TRM).[7-9] However, allogeneic PBPC transplants are associated with an increased risk of graft-versus-host disease (GVHD) compared to BM transplants.[9-11] Allogeneic BM transplant continues to be indicated in certain conditions such as severe aplastic anemia and other non-malignant disorders, owing to a lower risk of GVHD. Furthermore, several investigators have advocated for the use of BM grafts for haploidentical HCT[12] and unrelated donor HCT.[10,11]

Advantages of using UCB grafts include rapid cell procurement, lower incidence of GVHD, 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. The outcome of UCB transplant is more favorable in pediatric populations, likely due to the feasibility of using higher graft cell doses (given smaller body weight) and lower incidence of comorbidities in pediatric populations. UCB

transplant is typically reserved for patients without an HLA-matched donor. Patients without an HLA-matched donor may also be candidates for haploidentical HCT. 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.

Advances in HCT methods and supportive care have led to improved survival following HCT.[13] However, disease relapse and long-term complications continue to pose a major threat to HCT survivors. Disease relapse is higher with advanced disease and with the use of non-myeloablative conditioning regimens. Post-transplant complications are common after both allogeneic and autologous HCT and are often caused by the preparative regimen,[14,15] delayed immune reconstitution, and/or GVHD (only for allogeneic). The risk and type of complications are also influenced by patient-related factors such as age, performance status, and comorbidities.[16-18] Early complications (generally occurring within the first 100 days post-HCT) include prolonged cytopenia/graft failure, infections, sinusoidal obstruction syndrome (SOS), and organ toxicities.[14,19] 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 dysfunctions, and secondary malignancies including MDS.[14,19] 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 bodily organs, such as the skin, gastrointestinal (GI) tract, and liver. Common causes of non-relapse mortality (NRM) after allogeneic HCT include GVHD, infections, interstitial pneumonia, and organ toxicity.[20-23] Common causes of NRM after autologous HCT include organ toxicity and infectious complications.[3,24,25] Therefore, post-transplant care plans including optimal supportive care are essential to optimize long-term outcomes in both autologous and allogeneic HCT recipients.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Cell Transplantation focus on the management of adult patients with malignant disease. The initial version of the Guidelines addresses pre-transplant recipient evaluation as well as the management of acute and chronic GVHD. Additional topics will be addressed in subsequent versions of the Guidelines.

Literature Search Criteria and Guidelines Update Methodology

Prior to this publication of the NCCN Guidelines for Hematopoietic Cell Transplantation, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: hematopoietic cell transplant; stem cell transplant; bone marrow transplant; allogeneic cell transplant; autologous cell transplant; acute graft-versus-host disease; and chronic 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.[26]

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; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level

evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

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 re-infused back into the patient after administration of the preparative regimen. High-dose chemotherapy with autologous HCT is an effective treatment for several hematologic malignancies, including multiple myeloma,[27-31] relapsed/refractory Hodgkin lymphoma,[32,33] and relapsed/refractory non-Hodgkin lymphoma.[34-36] Autologous HCT is also used in patients undergoing high-dose chemotherapy for the treatment of certain solid tumors, including testicular germ cell tumors[37-40] and some central nervous system tumors,[41-45] for whom hematologic toxicity would otherwise limit chemotherapy administration. Additionally, autologous HCT is sometimes used as consolidation therapy for certain patients with AML or ALL.

Since autologous HCT uses the patient's own cells, these patients do not develop GVHD. Additionally, these patients often have a lower risk of infectious complications since they do not receive post-transplant immunosuppression. Therefore, autologous HCT is associated with less morbidity and mortality than allogeneic HCT; however, risk of disease relapse is often higher with autologous HCT when compared to allogeneic HCT. Furthermore, clinical studies demonstrated no benefit of graft purging (*ex vivo* manipulation to eliminate residual neoplastic cells) prior to autologous HCT. [46,47]

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is performed to replace malignant (or defective) hematopoietic tissue using a healthy donor's hematopoietic cells. A preparative regimen consisting of chemotherapy (often high-dose), serotherapy, 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. HLA matching is the most imperative factor when choosing a donor. An HLA-matched sibling remains the preferred donor source. However, post-transplant survival is comparable among patients receiving hematopoietic cells from HLA-matched unrelated donors for several diseases.[16,48] When a patient has no HLA-matched related or unrelated donors, as is common among minority ethnic groups, a haploidentical donor or UCB may be used. A haploidentical donor is a first-degree relative who matches half the HLA markers of the patient. Emerging data suggest that haploidentical HCT may yield comparable outcomes to HLA-matched HCT.[49,50] However, a recent study found that use of haploidentical donors beyond first-degree relatives may negatively affect survival.[51] UCB transplant was first reported to cure a child with Fanconi anemia,[52] and was subsequently utilized successfully in patients with hematologic malignancies.[53,54] Although the outcomes of UCB transplants have been comparable to HLA-matched transplants in some reports,[48,55-58] 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.[48,55-59]

Allogeneic HCT has been shown to improve outcomes in patients with malignancies such as refractory AML,[60] ALL,[61] MDS,[62] chronic myeloid leukemia (CML),[63] chronic lymphocytic leukemia (CLL),[64] multiple myeloma,[65] primary and secondary myelofibrosis,[66] Hodgkin lymphoma,[67] and non-Hodgkin lymphoma.[68] 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 2,000 patients that showed a reduced relapse risk among patients with GVHD.[69] Graft-versus-tumor effect is considered a major mechanism for sustained response following allogeneic HCT, in particular with reduced intensity or non-myeloablative HCT.[70,71]

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.[6]

Pre-Transplant Recipient Evaluation

The pre-transplant recipient evaluation generates data to estimate the risks of relapse, NRM, and overall mortality. Physiological age rather than chronological age should be used to determine eligibility for HCT.[6] Selected older patients with limited comorbidities and good functional status can safely receive HCT with a relatively low and acceptable risk of NRM.[72-75] Ongoing studies, such as BMT CTN 1704, are assessing the utility of geriatric assessment tools in predicting outcome of HCT in elderly patients (Clinical Trial ID: NCT03992352). Determining functional status (Karnofsky's or ECOG performance status) and HCT-Comorbidity Index (HCT-CI) score[76] 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.[77,78] HCT-CI has also been shown to predict survival after autologous transplant.[79,80] Furthermore, an updated composite-age HCT-CI has also been shown to have the same utility.[81] Detailed clinical assessment of HCT-CI has been published.[82] HLA typing of the donor and recipient per FACT (Foundation for the Accreditation of Cellular Therapy) guidelines[83] is necessary prior to allogeneic HCT.

Management of Graft-Versus-Host Disease

The development of acute and/or chronic GVHD is a major complication of allogeneic HCT and is associated with significant morbidities and NRM in allogeneic HCT recipients.[84-86] Increasing incidence of GVHD has been observed in recent years, primarily due to the increased use of unrelated and/or HLA-mismatched donors and G-CSF–mobilized PBPCs, among other factors.[9,87-89] Mild manifestations limited to a single organ are often managed with close observation, with topical treatment, or by slowing the tapering of immunosuppressive agents.[90] More severe manifestations or multi-organ involvement typically require systemic corticosteroid treatment (with or without secondary systemic agents).[86] 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 (aGVHD)

Despite prophylaxis with immunosuppressive agents, 20% to 80% of allogeneic HCT recipients develop aGVHD depending on several factors, including donor source and graft source. The skin, GI tract (upper and lower), and liver are the three organs primarily affected by aGVHD, which is characterized by maculopapular rash, GI complications, and

hyperbilirubinemia.[91,92] Although pathologic confirmation of aGVHD should be considered whenever possible, especially before escalating systemic immunosuppression, reliance on pathologic diagnosis is not required for the diagnosis or treatment of aGVHD because biopsy is not absolutely sensitive.

Diagnosis and Grading

If aGVHD is suspected, additional tests such as stool testing, imaging studies, and/or viral reactivation testing should be performed to rule out non-GVHD causes of the symptoms. Organ-directed biopsies can then be performed as clinically indicated to confirm the presence of aGVHD (ie, skin biopsy for rash). GI biopsy (EGD, colonoscopy, and/or flexible sigmoidoscopy) is recommended, whenever possible, for the diagnosis of GI aGVHD. 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.[93] Liver function tests (LFTs) should be routinely monitored after allogeneic HCT for early detection of hepatic aGVHD, which is often asymptomatic. 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. Grading criteria for aGVHD have been developed over the last several decades. Glucksberg aGVHD grading criteria were first proposed in 1974.[94] Modified Glucksberg (consensus or Keystone) criteria were further developed in 1994 (see *GVHD-A 1 of 2* in the algorithm for modified Glucksberg grading criteria).[84] IBMTR Severity Index was subsequently developed,[95] and was shown to be more predictive of HCT outcome when compared with the original Glucksberg criteria.[96] Minnesota criteria have also been devised to identify patients with “high-risk” aGVHD who could benefit from early escalated therapy.[97,98] More recently, MAGIC (Mount Sinai Acute GVHD International Consortium) criteria were developed (see *GVHD-A 2 of 2* in the algorithm for MAGIC grading criteria).[99] A joint task force of the European Society for Blood and Marrow Transplantation (EBMT), National Institutes of Health (NIH), and CIBMTR has published a position statement on standardized terminology for GVHD.[100] Furthermore, blood biomarkers are being actively investigated for their utility as a predictive tool in aGVHD.[101-103]

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.[84] First-line therapy options for these patients include continuing (or restarting) the original immunosuppressive agent and administering topical skin-directed steroids (eg, triamcinolone, clobetasol) and/or topical tacrolimus. Medium- to high-potency topical steroid formulations are recommended, except on the face 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 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 skin-directed steroids. Patients with progression toward grade II and/or symptomatic rash (eg, refractory pruritic rash) 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 should be restarted, continued, or escalated (with or without therapeutic drug targeting) 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.[91,92,104] 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 <1,000 mL/day.[104] 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.[105] 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.

The randomized phase II 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.[106] At day 28, the overall response rate (ORR) for sirolimus and predisone 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 thrombotic microangiopathy 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.[107] The day 28 ORRs were etanercept 26%, MMF 60%, denileukin 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 suggest that MMF plus corticosteroids is 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.[108] 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 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.

Additional Therapy

Due to a lack of high-quality evidence, the NCCN Panel does not prefer any specific agent(s) for second-line therapy and encourages that patients with steroid-refractory aGVHD be managed as part of a clinical trial.[92] Currently, ruxolitinib is the only therapy approved by the United States Food and Drug Administration (FDA) for steroid-refractory aGVHD with outcomes, in particular 6-month survival, seemingly comparable to other agents.[109] See *Suggested Agents for Steroid-Refractory aGVHD* below for more information.

Chronic Graft-Versus-Host Disease (cGVHD)

cGVHD is the leading cause of NRM after allogeneic HCT and has a profound impact on quality of life.[23,110] cGVHD usually develops within the first year after HCT in most patients, but it can also develop many years later. cGVHD affects multiple organ systems and is characterized by fibrosis and variable clinical features resembling autoimmune disorders.[111] 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.[90,112-115] 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, a biopsy 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).[90] Manifestations of cGVHD include bronchiolitis obliterans syndrome (BOS), a devastating 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 *GVHD-C* in the algorithm).[90]

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 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, 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) ± 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 an increased risk for cancer relapse in HCT patients receiving azithromycin for BOS prophylaxis.[116] 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,[100] 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 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.

Additional Therapy

Due to a lack of high-quality evidence, the NCCN Panel does not prefer any specific agent(s) for second-line therapy and encourages that patients with steroid-refractory cGVHD be managed as part of a clinical trial.[92] Currently, ibrutinib is the only FDA-approved second-line therapy for patients with steroid-refractory cGVHD.[117] Other novel agents are being evaluated in ongoing clinical trials.[118] 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.[113]

Steroid-Refractory GVHD

Approximately 40% to 50% of patients with acute or chronic GVHD develop steroid-refractory disease, which is associated with high mortality.[91,119] The NIH has defined criteria for steroid-refractory acute and chronic GVHD (see *GVHD-D* in the algorithm).[100] 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 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 category 1), can be used in conjunction with the original immunosuppressive agent 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 shows a response. Currently, there is insufficient evidence to recommend one systemic agent as preferred over another. However, it is worth noting that ruxolitinib is currently the only FDA-approved therapy for steroid-refractory aGVHD. The following are the most commonly used agents among NCCN Member Institutions.

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.[120] In 2019, the FDA approved ruxolitinib for the treatment of steroid-refractory aGVHD in adult and pediatric patients aged 12 years and older.[121,122] The approval was based on data from the single-arm multicenter phase II REACH1 trial that included 71 patients with grade II–IV steroid-refractory aGVHD.[109] Patients received 5 mg ruxolitinib twice daily, with an optional increase to 10 mg BID in the absence of cytopenias. 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 commonly used regimens (control group) in 309 patients with steroid-refractory aGVHD.[123] 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 overall response rates at day 56 (40% vs. 22%; *P* .001). Median failure-free survival and median OS were substantially longer with ruxolitinib than with control (5 months vs. 1 month; hazard ratio [HR], 0.46; 95% CI, 0.35–0.60 and 11 months vs. 6.5 months; HR, 0.83; 95% CI, 0.60–1.15). The most common adverse events in the ruolitinib group were thrombocytopenia (33%), anemia (30%), and cytomegalovirus infection (26%). These data suggest that ruxolitinib is effective and may produce durable responses in patients with steroid-refractory aGVHD. The ongoing REACH3 trial (Clinical Trial ID: NCT03112603) will compare treatment with ruxolitinib to the best available therapy in patients with steroid-refractory cGVHD.[120]

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.[124,125] 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. [126] The ORR to alemtuzumab was 83%, with 33% of patients achieving CR. Importantly, univariate analyses of clinical characteristics between responders and nonresponders 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 ≥1 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%.[127] 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 (AAT)

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.[128] AAT is most commonly used to treat patients with AAT deficiency, an inherited condition that causes lung and liver damage.[129] 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.[128] 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 (ATG)

ATG is a T-cell–depleting antibody that has been commonly used for immunosuppression in the solid organ transplant setting and for GVHD prophylaxis.[130-135] Two ATG products are currently approved by the FDA: thymoglobulin (ATG-T), a polyclonal immunoglobulin G (IgG) derived from rabbits, and ATGAM (ATG-h), a polyclonal IgG derived from horses.[136,137] 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 (ATGAM) at a dose of 15 mg/kg/day BID for 5 days.[138] 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 respond to ATG. Of the 64 patients with skin involvement, 61% achieved a complete 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 (thymoglobulin) in 36 patients with steroid-refractory GVHD treated at at single institution.[139] Patients, most of whom (89%) had grade III–IV aGVHD, received thymoglobulin 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 group 1 patients (77%) compared to group 2 patients (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 thymoglobulin administered at a median dose of 3 mg/kg/day.[140] 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 responders.[139] A comprehensive review on the use of ATG for GVHD treatment has been published.[141]

Basiliximab

Basiliximab is a chimeric monoclonal antibody that functions as an immunosuppressive agent by binding to and blocking the interleukin-2 (IL-2) receptor.[142] 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.[143] 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.[143] 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 (CNI)

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.[144-153] 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 BID.[154] In the 13 evaluable patients, the ORR was 54%. The most common adverse events were renal toxicity (53% of patients), followed by nausea and vomiting (31%). A recent retrospective analysis involving 42 patients with steroid-refractory aGVHD treated with tacrolimus 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).[155] 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 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.[156] 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.[157] The efficacy of etanercept for the treatment of steroid-refractory aGVHD was retrospectively evaluated in a cohort of 13 patients.[158] 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 grade II aGVHD patients 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 (ECP)

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.[159] The clinical activity of ECP is thought to be mediated by the immunomodulatory effects of UV light.[160] 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.[159,161]

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.[162] In a recent 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%.[163] 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.[159] 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.[164] 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.

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.[157,165] 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.[157] 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 3 courses reported an ORR of 59%.[166] 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 4 doses, with 83% of patients developing infectious complications.[167] 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.[168,169] By inhibiting mTOR, sirolimus disrupts the cytokine signaling that promotes the growth and differentiation of T cells.[170] Sirolimus is also used for GVHD prophylaxis, often in conjunction with the CNI tacrolimus.[149-151,171-174] 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.[175] 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 thrombotic microangiopathy, and renal failure. In a retrospective analysis of 31 patients with steroid-refractory aGVHD treated with sirolimus in combination with tacrolimus, the ORR was 76% and 42% of patients achieved CR.[176] Median OS was 5.6 months and 1-year OS was 44%. Thrombotic microangiopathy 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 reported similar results.[177] The ORR was 72% and OS was 41% after a median follow-up of 13 months. Thrombotic microangiopathy 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 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).[155] 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)

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.[178] MMF is indicated for the prevention of organ rejection in solid organ transplants and is a standard component of GVHD prophylaxis regimens.[179] 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.[180] 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%).[180] 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%.[181] 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 BID orally or intravenously.[182] 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.[183] 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%.[184] 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 3 courses. OS at 18 months was 21% and NRM was 72%. Stratified analysis revealed that patients younger than 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 over 3 consecutive days.[185] A smaller retrospective analysis of 12 patients reported a higher ORR of 50% and a CR rate of 33%.[186] 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.[184]

A phase I dose-escalation study involving 22 patients with steroid-refractory aGVHD reported a high CR rate of 63%.[187] 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 8 patients receiving a lower dose of 1.5 mg/m^2/day of pentostatin, 4 patients died from progressive hepatic GVHD and 3 patients died from sepsis secondary to infections, pancytopenia, progressive hepatic GVHD, and/or acute renal failure.[188] Two patients with renal insufficiency demonstrated excessive pentostatin exposure, as determined by measurement of the 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.[189] 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.[190,191] The efficacy of tocilizumab for the treatment of steroid-refractory aGVHD was evaluated in several studies.[192-196] A small study of 8 patients (6 patients had aGVHD, the majority of whom had grade IV) showed an ORR of 67%, with a CR rate of 33%.[196] 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 9 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%.[195] 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%.[194] 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 recent 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.[192] These data suggest that tocilizumab has activity in the treatment of patients with steroid-refractory aGVHD, especially in patients with skin or GI involvement.

Anti-Integrins

Anti-integrin agents (natalizumab and vedolizumab) are currently being investigated as therapeutic modalities for steroid-refractory aGVHD.[197-199] These agents are monoclonal antibodies that impair homing of leukocytes (particularly T cells) to the GI endothelium via blocking leukocyte receptors alpha-4 integrin (natalizumab) or alpha-4/beta-7 integrin (vedolizumab).[200,201] A retrospective multicenter study evaluated the use of vedolizumab for steroid-refractory GI aGVHD in 29 patients.[198] The ORR was 79% with CR observed in 28% of patients. Early administration of vedolizumab was associated with a greater chance of discontinuing immunosuppression and a lower risk of fatal infectious complications. However, further studies are needed to confirm these findings. It should be noted that the NCCN Panel does not currently recommend the use of these agents for the treatment of steroid-refractory aGVHD.

Suggested Agents for Steroid-Refractory cGVHD

The following systemic agents, listed in alphabetical order, 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. Currently, there is insufficient evidence to recommend one systemic agent as preferred over another. However, it is worth noting that ibrutinib is currently the only FDA-approved therapy for steroid-refractory cGVHD. The following are the most commonly used agents among NCCN Member Institutions. While the following agents may be used in any site, some agents are more commonly used with particular organ involvement.

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.[202,203] 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.[202] The study followed a 3+3 design with 2 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 lung. 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.[204] Six subjects had moderate and 7 subjects had severe cGVHD per NIH consensus global scoring criteria; all subjects 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 1 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.[205] At day +90 evaluation, the partial response rate was 50%, the CR rate was 28%, and 21% of patients had relapsed cGVHD. Of the 5 evaluable patients at 1 year, 2 (40%) had a partial response, 2 had a CR, and 1 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.

Belumosudil

In 2021, belumosudil was approved by the FDA for the treatment of adult and pediatric patients aged 12 years and older with cGVHD after failure of two or more lines of systemic therapy.[206] This approval was based on data from the randomized, multicenter phase II ROCKstar study, which evaluated the efficacy of belumosudil 200 mg taken once daily in patients with cGVHD who had received 2 to 5 prior lines of therapy.[207] 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 subjects 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 subjects (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.

Calcineurin Inhibitors (CNI)

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 BID. In the 26 evaluable patients, the ORR was 46%.[154] Another trial evaluated the efficacy of tacrolimus administered at 0.15 mg/kg BID orally or 0.15 mg/kg/day intravenously in 17 patients with severe steroid-refractory cGVHD.[208] 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.[209] The ORR was 21% with a CR rate of 13%. However, 79% of patients experienced treatment failure 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 2 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 8 patients treated with subcutaneous etanercept at 25 mg twice weekly for 4 weeks followed by 25 mg once weekly for 4 weeks.[158] Patients were also continued on CNI, MMF, and/or sirolimus. The ORR was 62% with 1 patient achieving CR. Three of the 8 patients (37%) treated with etanercept died of progressive disease or sepsis. In 3 of the 5 patients who responded to etanercept, corticosteroids were reduced by greater than 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.[210] 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 greater than or equal to 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 (ECP)

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%.[163] 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).[211] 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.[212] A systematic review of prospective studies reported a pooled ORR of 64% for ECP in the treatment of steroid-refractory cGVHD.[159] 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.[213] 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.

Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline immunosuppressive and anti-parasitic agent that is commonly used for the treatment of malaria.[214] Hydroxychloroquine is believed to exert its immunomodulatory effects by interfering with cytokine production and antigen processing and presentation.[215,216] 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.[216] The ORR was 53% among the 32 evaluable patients, with 3 patients achieving a CR. All responders tolerated a greater than 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.[217] Seven patients developed vortex keratopathy and 3 patients developed retinal toxicity; retinal structure and color vision were abnormal in 2 of the 3 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.

Ibrutinib

Ibrutinib is a potent and irreversible inhibitor of Bruton's tyrosine kinase (BTK), which regulates B-cell survival.[117] It also inhibits IL-2–inducible T-cell kinase (ITK), which is involved in the selective activation of T-cell subsets.[218] 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.[219] This approval was based on data from a single-arm multicenter trial that included 42 patients with steroid-refractory cGVHD.[117] Patients received 420 mg ibrutinib daily until cGVHD progression. The majority of patients (88%) had at least 2 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.[220] Sustained responses of greater than or equal to 44 weeks were seen in 55% of the responders. 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.

Imatinib

Imatinib is a small molecule tyrosine kinase inhibitor indicated for the treatment of several types of cancer, including CML.[221] Imatinib has activity against several tyrosine kinase enzymes, including platelet-derived growth factor receptor (PDGFR), which is implicated in skin fibrosis.[222] Stimulatory antibodies against PDGFR have been identified in cGVHD patients with cutaneous sclerosis; however, neither anti-PDGFR antibody level, nor phosphorylation of tissue PDGFR, correlated with response to imatinib in cGVHD patients.[223] The efficacy of imatinib to treat sclerotic manifestations of cutaneous steroid-refractory cGVHD was assessed in a pilot phase II trial involving 20 patients.[222] 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.[224] 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%.[225] 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)

IL-2 is a naturally occurring pleiotropic cytokine that regulates the growth of T cells and is a key mediator of immune response.[226] The efficacy of IL-2 in the treatment of steroid-refractory cGVHD was evaluated in a phase I study involving 29 patients.[227] 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.[226] The ORR in 33 evaluable patients was 61%. There were CRs and 3 patients developed progressive cGVHD. All responders 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, 2 patients in this study withdrew and 5 required dose reductions of IL-2 due to adverse events including thrombocytopenia, fatigue, flu-like symptoms, malaise, and thrombocytopenia. A recent 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.[228] 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.[229] In a retrospective study of 14 patients who had received low-dose methotrexate (7.5 mg/m^2/week for 3 to 50 weeks) for the treatment of steroid-refractory cGVHD, 71% of patients were able to reduce their prednisone dose to less than 1 mg/kg every other day without the addition of other agents.[230] 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 8 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).[231] The ORR was 75% and few toxicities were observed, the most serious being grade 3–4 cytopenias reported in 2 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).[232] 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% responded compared to 100% of patients with greater than or equal to 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.[233] Patients with steroid-refractory cGVHD received sirolimus at a loading dose of 6 mg orally followed by a maintenance dose of 2 mg/day while continuing immunosuppressive treatment with tacrolimus and methylprednisolone. The ORR was 63% with 6 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, thrombotic microangiopathy, 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. Sirolimus was administered orally at a loading dose of 10 mg followed by a daily dose

of 5 mg. Of the 16 evaluable patients, 15 had an initial clinical response to this regimen. However, 5 patients discontinued treatment due to renal toxicity. Of the 10 patients who continued with this regimen, 3 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) in combination with other immunosuppressive agents (CNI [n = 33], MMF [n = 9], or prednisone [n = 5]).[234] 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 2 retrospective studies showed that treatment with everolimus resulted in significant improvement in the NIH Severity Score and patient-reported quality of life.[235,236] However, more data are necessary to confirm the role of everolimus in the treatment of steroid-refractory cGVHD.

Mycophenolate Mofetil (MMF)

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 BID (escalated to 1 g BID if tolerated) in combination with cyclosporine, tacrolimus, and/or prednisone.[237] The ORR was 75% with a CR rate of 21%. Only 2 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).[180] After a median follow-up of 9.5 years, 52% of patients remained alive with only one of them 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%. 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 4 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 1 patient. 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 non-Hodgkin lymphoma and CLL that exerts immunosuppressive effects by binding to CD20 on the surface of B cells, facilitating their destruction.[238] 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.[215,239] In a systematic review and meta-analysis of 7 studies (3 prospective and 4 retrospective) including 111 patients, the pooled ORR to rituximab was 66%.[239] 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.

Ruxolitinib

The activity of ruxolitinib in the treatment of steroid-refractory cGVHD has been retrospectively evaluated in several studies. A recent analysis of 46 patients with steroid-refractory cGVHD, the majority of whom had severe cGVHD, reported an ORR of 43% and a CR rate of 13% following 12 months of ruxolitinib therapy.[240] Organ-specific responses were observed in 25% of patients with skin involvement (n = 10), 60% of patients with mouth involvement (n = 15), 26% of patients with eye involvement (n = 23), 10% of patients with lung involvement (n = 1), and 41% of patients with joint/fascia involvement (n = 23). The 1-year probability of treatment failure-free survival was 54%. The most common adverse event was infectious complications. Another recent retrospective analysis reported better outcomes in 19 patients treated with ruxolitinib (5 mg orally BID) for moderate to severe steroid-refractory cGVHD.[241] The ORR was 100% with 18 patients achieving an overall partial response and 1 achieving CR. No cytopenias or infections were noted. Corticosteroids were successfully reduced or discontinued in 21% and 68% of patients, respectively. An earlier retrospective study of 41 patients who had received ruxolitinib at a dose of 5–10 mg orally BID for moderate to severe steroid-refractory cGVHD reported an ORR of 85% and a 6-month OS rate of 97%.[242] Cytopenias and CMV reactivation were observed in 17% and 15% of patients, respectively. These data suggest that ruxolitinib is capable of producing high response rates in patients with steroid-refractory cGVHD.

Summary

The NCCN Guidelines for Hematopoietic Cell Transplantation provide an evidence- and consensus-based approach for the pre-transplant

evaluation of potential HCT recipients and the management of GVHD. 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. To determine whether HCT is a potential treatment option, the pre-transplant recipient evaluation should be performed in each patient to estimate the risks of relapse, NRM, and overall mortality. Determining the HCT-CI score is essential to establish candidacy for HCT and has been validated to predict the risk of NRM and estimated survival after allogeneic transplant. The leading cause of NRM in allogeneic HCT recipients is the development of GVHD. Mild manifestations of GVHD limited to a single organ are often managed with close observation, topical treatment, or by slowing the tapering of immunosuppressive agents. More severe manifestations or multi-organ involvement typically require systemic corticosteroid treatment (with or without secondary systemic agents). Despite these treatments, approximately 40% to 50% of patients with GVHD develop steroid-refractory disease. 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 chronic GVHD 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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