NCCN Continuing Education

Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

Accreditation Statements

In support of improving patient care, National Comprehensive Cancer Network (NCCN) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Physicians: NCCN designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses: NCCN designates this educational activity for a maximum of 1.0 contact hour.

Pharmacists: NCCN designates this knowledge-based continuing education activity for 1.0 contact hour (0.1 CEUs) of continuing education credit. UAN: JA4008196-0000-23-002-H01-P

PAs: NCCN has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1.0 AAPA Category 1 CME credit. Approval is valid until February 10, 2024. PAs should only claim credit commensurate with the extent of their participation.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: (1) review the educational content; (2) take the posttest with a 66% minimum passing score and complete the evaluation at **https://education.nccn.org/node/92893**; and (3) view/print certificate.

Pharmacists: You must complete the posttest and evaluation within 30 days of the activity. Continuing pharmacy education credit is reported to the CPE Monitor once you have completed the posttest and evaluation and claimed your credits. Before completing these requirements, be sure your NCCN profile has been updated with your NAPB e-profile ID and date of birth. Your credit cannot be reported without this information. If you have any questions, please email education@nccn.org.

Release date: February 10, 2023; Expiration date: February 10, 2024

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Hematopoietic Cell Transplantation
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Hematopoietic Cell Transplantation

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.
Marco Mielcarek, MD, Panel Member
Frankie Algieri, Guidelines Layout Specialist, NCCN
Lenora A. Pluchino, PhD, Oncology Scientist/Medical Writer, NCCN

The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

Ayman Saad, MD, Panel Chair, has disclosed receiving grant/research support from Kadmon Corporation and Orca Bio; receiving consulting fees from Kite Pharma; and receiving royalty income from IN8bio Inc.
Alison Loren, MD, MSCE, Panel Vice Chair, has disclosed receiving grant/research support from Equillium, Inc.
Areej El-Jawahri, MD, Panel Member, has disclosed receiving consulting fees from GlaxoSmithKline, Incyte Corporation, and Novartis Pharmaceuticals Corporation.
Mohamed Kharfan Dabaja, MD, Panel Member, has disclosed receiving grant/research support from Bristol Myers Squibb Company and Novartis Pharmaceuticals Corporation.
Mark Schroeder, MD, Panel Member, has disclosed receiving consulting fees from Equillium, Inc., Incyte Corporation, Inmagene Biopharmaceuticals, Janssen Pharmaceutica Products, LP, and sanofi-aventis U.S.; and serving as a scientific advisor for Advarra, Inc., CareDx, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, and sanofi-aventis U.S.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

This activity is supported by educational grants from AstraZeneca; Exact Sciences; Novartis; and Taiho Oncology, Inc. This activity is supported by an independent educational grant from Daiichi Sankyo. This activity is supported by independent medical education grants from Illumina, Inc. and Regeneron Pharmaceuticals, Inc.

Hematopoietic Cell Transplantation, Version 3.2022

Featured Updates to the NCCN Guidelines

Ayman Saad, MD[1,*]; Alison Loren, MD, MSCE[2,*]; Javier Bolaños-Meade, MD[3]; George Chen, MD[4]; Daniel Couriel, MS[5]; Antonio Di Stasi, MD[6]; Areej El-Jawahri, MD[7,*]; Hany Elmariah, MD, MS[8]; Sherif Farag, MD, PhD[9]; Krishna Gundabolu, MBBS, MS[10]; Jonathan Gutman, MD[11]; Vincent Ho, MD[12]; Rasmus Hoeg, MD[13]; Mitchell Horwitz, MD[14]; Joe Hsu, MD, MPH[15]; Adetola Kassim, MD, MS[16]; Mohamed Kharfan Dabaja, MD[17,*]; John Magenau, MD[18]; Thomas Martin, MD[19]; Marco Mielcarek, MD[20,*]; Jonathan Moreira, MD[21]; Ryotaro Nakamura, MD[22]; Yago Nieto, MD, PhD[23]; Cameron Ninos, PharmD[24]; Caspian Oliai, MD[25]; Seema Patel, PharmD[26]; Brion Randolph, MD[27]; Mark Schroeder, MD[28,*]; Dimitrios Tzachanis, MD, PhD[29]; Asya Nina Varshavsky-Yanovsky, MD, PhD[30]; Madhuri Vusirikala, MD[31]; Frankie Algieri[32,*]; and Lenora A. Pluchino, PhD[32,*]

ABSTRACT

The NCCN Guidelines for Hematopoietic Cell Transplantation (HCT) provide an evidence- and consensus-based approach for the use of autologous and allogeneic HCT in the management of malignant diseases in adult patients. HCT is a potentially curative treatment option for patients with certain types of malignancies; however, recurrent malignancy and transplant-related complications often limit the long-term survival of HCT recipients. The purpose of these guidelines is to provide guidance regarding aspects of HCT, including pretransplant recipient evaluation, hematopoietic cell mobilization, and treatment of graft-versus-host disease—a major complication of allogeneic HCT—to enable the patient and clinician to assess management options in the context of an individual patient's condition. These NCCN Guidelines Insights provide a summary of the important recent updates to the NCCN Guidelines for HCT, including the incorporation of a newly developed section on the Principles of Conditioning for HCT.

J Natl Compr Canc Netw 2023;21(2):108–115
doi: 10.6004/jnccn.2023.0007

[1]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [2]Abramson Cancer Center at the University of Pennsylvania; [3]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [4]Roswell Park Comprehensive Cancer Center; [5]Huntsman Cancer Institute at the University of Utah; [6]O'Neal Comprehensive Cancer Center at UAB; [7]Massachusetts General Hospital Cancer Center; [8]Moffitt Cancer Center; [9]Indiana University Melvin and Bren Simon Comprehensive Cancer Center; [10]Fred & Pamela Buffett Cancer Center; [11]University of Colorado Cancer Center; [12]Dana-Farber/Brigham and Women's Cancer Center; [13]UC Davis Comprehensive Cancer Center; [14]Duke Cancer Institute; [15]Stanford Cancer Institute; [16]Vanderbilt-Ingram Cancer Center; [17]Mayo Clinic Cancer Center; [18]University of Michigan Rogel Cancer Center; [19]UCSF Helen Diller Family Comprehensive Cancer Center; [20]Fred Hutchinson Cancer Center; [21]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [22]City of Hope National Medical Center; [23]The University of Texas MD Anderson Cancer Center; [24]University of Wisconsin Carbone Cancer Center; [25]UCLA Jonsson Comprehensive Cancer Center; [26]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [27]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [28]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [29]UC San Diego Moores Cancer Center; [30]Fox Chase Cancer Center; [31]UT Southwestern Simmons Comprehensive Cancer Center; and [32]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

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 noted.

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.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

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

Definitions of Conditioning Regimen Intensity[a]

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

[a] Bacigalupo A, et al. Biol Blood Marrow Transplant 2009;15:1628-1633.
[b] BPEU should be reported as area under the curve (AUC) in mg x h/L. For example, AUC 5,000 µM x min is equivalent to 20.5 mg x h/L (McCune JS, et al. Biol Blood Marrow Transplant 2019;25:1890-1897).

Continued

Overview

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

The Center for International Blood and Marrow Transplant Research (CIBMTR) estimates that 8,326 allogeneic transplants and 11,557 autologous transplants were performed in the United States in 2020.[2] Acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndromes (MDS) were the most common malignancies treated with allogeneic HCT, whereas autologous HCT was used most frequently in multiple myeloma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL).[2] Difficult logistics and high costs create significant barriers to access for many patients. A recent systematic review found older age, lower socioeconomic status, and non-White race to be associated with reduced access to HCT.[3]

Outcomes of HCT vary according to the type and stage of the disease being treated, the overall health and comorbidities of the patient, the degree of HLA-mismatch between donor and recipient (for allogeneic HCT), and the source of the hematopoietic cells.[1] Hematopoietic cells can be obtained from peripheral blood, bone marrow, or umbilical cord blood (UCB). Several clinical factors should be considered when determining the optimal graft source for an individual patient, including disease type, disease stage, patient comorbidities, and the urgency for transplantation.[4] Use of peripheral blood progenitor cells (PBPCs) has largely replaced the use of bone marrow grafts (in particular for autologous HCT)

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Allogeneic Conditioning Regimen Selection

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

Special Situations

- For patients with significant pulmonary dysfunction, caution is recommended if using high-dose busulfan, BCNU, and high-dose TBI.
- Increased risk of sinusoidal obstruction syndrome (SOS) has been associated with the use of:
  - High-dose busulfan and high-dose TBI in patients with significant liver dysfunction.
  - Akylator-based regimens with pre-transplant inotuzumab or gemtuzumab.
- The combination of sirolimus and tacrolimus may be associated with higher risk of SOS and thrombotic microangiopathy (TMA), especially if used with myeloablative regimens.[d,e]
- Increased risk of GVHD has been associated with patients treated with checkpoint inhibitors (pre- or post-HCT), and mogamulizumab.
  - Consider 8- to 12-week window between the use of these treatments and the start of transplant conditioning.[e]
- Thiotepa can be excreted through the skin and requires special skin care. Refer to the package insert.

[c] The HCT-CI predicts the risk of NRM after transplant more accurately than age and performance status; however, it does not predict the risk of relapse. Detailed explanation of the HCT-CI has been published [Sorror ML. Blood 2013;121:2854-2863]. Allogeneic HCT: Increased HCT-CI scores were predictive for increased risks of NRM and overall mortality. Autologous HCT: Scores ≥3 were predictive for increased risks of NRM and overall mortality. See HCT-CI score calculator: http://hctci.org.
[d] Pidala J, et al. Haematologica 2012;97:1882-1889; Khimani F, et al. Bone Marrow Transplant 2017;52:1003-1009.
[e] Ijaz A, et al. Biol Blood Marrow Transplant 2019;25:94-99; Merryman R, et al. Blood 2017;129:1380-1388; Kamada Y, et al. Leuk Lymphoma 2022 Feb 27;1-7.

Continued

HCT-A
2 OF 9

due to the ease of collection, avoidance of general anesthesia, more rapid engraftment rates, and reduced risk of graft failure.[5–7] However, allogeneic PBPC transplants are associated with an increased risk of chronic graft-versus-host disease (GVHD) compared with bone marrow transplants.[7–9]

Advantages of using UCB grafts include rapid cell procurement, lower incidence of chronic GVHD, and less stringent HLA-matching requirements.[10] Disadvantages include delayed engraftment, higher risk for graft failure, higher rates of infectious complications, and higher costs for procurement. Additionally, use of UCB is also limited by the cell doses that can be achieved in recipients with high body weight. Therefore, UCB transplantation is typically reserved for patients without an HLA-matched donor and should be performed in centers with expertise in this procedure. Patients without an HLA-matched donor may also be candidates for HCT from a haploidentical, or half HLA-matched, related donor. Advantages of haploidentical HCT include lower costs for procurement and rapid availability of the cell products, whereas disadvantages include increased risk of graft failure and GVHD compared with HLA-matched HCT. Several investigators have advocated for the use of bone marrow grafts for haploidentical HCT and HLA-mismatched unrelated donor HCT to reduce the risk of GVHD.[8,9,11]

The purpose of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HCT is 2-fold: (1) to provide guidance for various aspects of the HCT procedure in adult patients with malignant disease, and (2) to enable the patient and clinician to assess management options in the context of an individual patient's condition. These NCCN Guidelines Insights provide a summary of the important recent updates to the NCCN Guidelines for HCT, including the incorporation of a newly developed section on the Principles of Conditioning for HCT. The most complete and recent version of these guidelines is available at NCCN.org.

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 NCCN.org). The American Society for Transplantation and Cellular Therapy (ASTCT) has also published clinical practice guidelines on indications for autologous and allogeneic HCT.[4]

Principles of Conditioning for HCT

Conditioning regimens are categorized into 3 groups based on their intensity.[12] Myeloablative regimens cause irreversible (or near irreversible) pancytopenia. Hematopoietic cell support is required to rescue marrow function and prevent aplasia-related death. Examples of myeloablative regimens

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Examples of Commonly Used Conditioning Regimens
- **This list is not comprehensive. Other options can be considered.**
- **See Suggested Doses/Modifications by Weight (HCT-A 7 of 9)**

Myeloablative (MA) Regimens		
Allogeneic Transplant	**TBI-Based** **Cyclophosphamide + TBI[1]** • Cyclophosphamide 120 mg/kg over 2 days • TBI 12–13.2 Gy fractionated **Fludarabine + TBI[2]** • Fludarabine 120 mg/m^2 over 4 days • TBI 12–13.2 Gy fractionated **Etoposide + TBI[3]** • Etoposide 60 mg/kg in 1 dose • TBI 12–13.2 Gy fractionated	**Busulfan-Based** **Busulfan + Cyclophosphamide[g,4]** • Busulfan 3.2 mg/kg/day for 4 days • Cyclophosphamide 60 mg/kg/day for 2 days **Fludarabine + Busulfan[5]** • Busulfan 3.2 mg/kg/day (12.8 mg/kg total) for 4 days • Fludarabine 150–160 mg/m^2 over 5 days **Fludarabine + Busulfan + Thiotepa[6,7]** • Fludarabine 120–160 mg/m^2 over 3–4 days; • Busulfan 3.2 mg/kg/day total for 3–4 days; • Thiotepa 5 mg/kg/day for 1–2 days
Umbilical Cord[f]	**TBI-Based** **Fludarabine + Cyclophosphamide + TBI[2]** • Fludarabine 120–180 mg/m^2 over 4 days; • Cyclophosphamide 120 mg/kg over 2 days; • TBI 13.2 Gy fractionated **Fludarabine + Thiotepa + TBI[8,9]** • Fludarabine 160 mg/m^2 over 4 days; • Thiotepa 5 mg/kg/day for 2 days; • TBI 13.2 Gy fractionated	**Busulfan-Based** **Fludarabine + Busulfan + Thiotepa[10]** • Thiotepa 5 mg/kg/day for 2 days • Busulfan 3.2 mg/kg/day for 3 days • Fludarabine 50 mg/m^2/day for 3 days
Non-Myeloablative (NMA) Regimens		
Allogeneic Transplant	**TBI-Based** **Fludarabine + TBI[11]** • Fludarabine 30 mg/m^2/day for 3 days • TBI 2 Gy	**Other** **Fludarabine + Cyclophosphamide ± Rituximab[12]** • Fludarabine 30 mg/m^2/day for 3 days • Cyclophosphamide 750 mg/m^2/day for 3 days • Rituximab ▸ 375 mg/m^2 IV for 1 day before transplant; and ▸ 1000 mg/m^2 IV on days 1,8, and 15 after transplant

[f] Referral to a center with experience in umbilical cord transplants is strongly recommended.
[g] Cyclophosphamide/busulfan is different than busulfan/cyclophosphamide (Rezvani AR, et al. Biol Blood Marrow Transplant 2013;19:1033-1039).

References Continued

HCT-A 3 OF 9

include total body irradiation (TBI) (≥5 Gy single dose or ≥8 Gy fractionated) and busulfan >8 mg/kg orally (>6.4 mg/kg intravenously) or busulfan plasma exposure unit equivalent (see HCT-A 1 of 9, page 110).[13] Nonmyeloablative conditioning regimens produce moderate-to-minimal cytopenia, and graft rejection, if it occurred, would be followed by autologous hematopoietic recovery. Examples include TBI ≤2 Gy ± purine analog; fludarabine + cyclophosphamide ± antithymocyte globulin (ATG); fludarabine + cytarabine + idarubicin; cladribine + cytarabine; and total lymphoid irradiation + ATG. A reduced-intensity conditioning (RIC) regimen is one that does not fulfill the criteria for either a myeloablative or a nonmyeloablative regimen.

The choice of a myeloablative, nonmyeloablative, or RIC regimen is a nuanced decision that should be made by the transplant team at the time of pretransplant recipient evaluation. The selection of conditioning regimen intensity depends on many factors, including patient age (chronologic and physiologic),[14] performance status, HCT comorbidity index score,[15] disease type, remission status (including measurable residual disease), and history of prior HCT (see HCT-A 2 of 9, page 111). In young, fit patients, myeloablative regimens are preferred for ALL, AML, chronic myeloid leukemia (CML), and MDS. See HCT-A 3 of 9 (above) for a nonexhaustive list of myeloablative regimens commonly used in allogeneic and UCB (autologous or allogeneic) transplants. If UCB transplant is being used, the panel strongly recommends referral to a center with experience in UCB transplants. Nonmyeloablative/RIC regimens may be preferred for patients undergoing allogeneic HCT for treatment of lymphoma (NHL or HL), chronic lymphocytic leukemia (CLL), and plasma cell disorders such as multiple myeloma and plasma cell leukemia. Nonmyeloablative/RIC regimens may also be preferred for patients who have received a prior autologous HCT and those who are older or unfit. See HCT-A 3 of 9 (above) for a nonexhaustive list of nonmyeloablative regimens commonly used in allogeneic transplant, and HCT-A 4 of 9 (opposite page) for a nonexhaustive list of RIC regimens commonly used in allogeneic and UCB transplants. Conditioning regimens commonly used in autologous transplants are listed by disease type (see HCT-A 5 of 9; page 114). Suggested dose modifications by weight for many of the drugs commonly used in conditioning regimens are provided on HCT-A 7 of 9 (available in these guidelines at NCCN.org).[16]

In developing this section, the panel decided to add recommendations for patients in certain special situations that warrant more caution (see HCT-A 2 of 9, page 111). For example, caution is recommended if using high-dose busulfan, BCNU, or high-dose TBI in patients with significant pulmonary dysfunction. Use of high-dose busulfan

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Examples of Commonly Used Conditioning Regimens
- **This list is not comprehensive. Other options can be considered.**
- **See Suggested Doses/Modifications by Weight (HCT-A 7 of 9)**

Reduced-Intensity Conditioning (RIC) Regimens		
Allogeneic Transplant	**Fludarabine + Melphalan[13]** • Fludarabine 100–180 mg/m^2 over 5 days • Melphalan 100–140 mg/m^2 over 1–2 days **Fludarabine + Busulfan[14]** • Fludarabine 30 mg/m^2/day for 5–6 days • Busulfan 3.2 mg/kg/day IV for 2–3 days	**Commonly Used with PTCy** **Fludarabine + Cyclophosphamide + TBI[15]** • Fludarabine 150 mg/m^2 over 5–6 days • Cyclophosphamide 14.5 mg/kg/day for 2 days • TBI 2–4 Gy **Fludarabine + Melphalan + TBI[16]** • Fludarabine 150 mg/m^2 over 5–6 days; • Melphalan 100–140 mg/m^2 over 1–2 days • TBI 2–4 Gy **Fludarabine + Melphalan + Thiotepa[17,18]** • Fludarabine 160 mg/m^2 over 4 days; • Melphalan 140 mg/m^2 for 1 day; • Thiotepa 10 mg/m^2 for 1 day **Fludarabine + Busulfan + Thiotepa[6]** • Thiotepa 5 mg/kg/day for 1 day • Busulfan 130 mg/m^2/day IV for 2 days[h] • Fludarabine 30–40 mg/m^2/day for 4 days
Umbilical Cord[f]	**Fludarabine + Cyclophosphamide + Thiotepa + TBI[19]** • Fludarabine 150 mg/m^2 • Cyclophosphamide 50 mg/kg • Thiotepa 10 mg/kg/day • TBI 4 Gy **Fludarabine + Cyclophosphamide + TBI[20]** • Fludarabine 200 mg/m^2 • Cyclophosphamide 50 mg/kg • TBI 2 Gy	

[f] Referral to a center with experience in umbilical cord transplants is strongly recommended.
[h] Typically, this is equivalent to 3.2 mg/kg/day.

References Continued

HCT-A 4 OF 9

and high-dose TBI has also been associated with an increased risk of sinusoidal obstruction syndrome (SOS) in patients with significant liver dysfunction. An increased risk of SOS has also been associated with the use of alkylator-based regimens with pretransplant inotuzumab or gemtuzumab. Additionally, the alkylating agent thiotepa can be excreted through the skin and requires special skin care. The combination of sirolimus and tacrolimus may be also associated with higher risk of SOS and thrombotic microangiopathy, especially if used with myeloablative regimens.[17–20] Importantly, an increased risk of GVHD has been associated with checkpoint inhibitor treatment (pre- or post-HCT) and mogamulizumab. Therefore, the panel recommends considering an 8- to 12-week window between the use of these treatments and the start of transplant conditioning.[17,18]

Conditioning Regimens Without Fludarabine

There is currently an international shortage of fludarabine, which is a component of many conditioning regimens recommended in the NCCN Guidelines.[21] To address the shortage, the panel convened for an interim meeting on September 2, 2022. During this meeting, the panel developed recommendations for nonfludarabine RIC regimens for use during the ongoing shortage (see HCT-A 6 of 9; available in these guidelines at NCCN.org). However, the panel suggests that the choice of regimen should be based on institutional preference and experience due to the lack of comparative data with fludarabine-based regimens.

Some of the regimens recommended by the panel are associated with certain adverse events. For example, cytokine release syndrome has been reported with the use of clofarabine-based regimens, although concomitant steroid use may mitigate this risk.[22] Additionally, use of certain cladribine-based regimens may be associated with increased risk of engraftment failure.[23–25] The panel also noted the clinical setting reported in the supporting reference for certain recommended regimens. The pentostatin + busulfan + cyclophosphamide regimen was reported with primary immunodeficiency disorders using posttransplant cyclophosphamide[26] and pentostatin + TBI 4 Gy was reported for salvage second transplant after engraftment failure.[27]

Summary

These NCCN Guidelines Insights highlight important recent updates to the NCCN Guidelines for HCT. The panel recently developed a new section for the inclusion of conditioning regimens, including condition regimens without fludarabine to address the ongoing international shortage. The incorporation of conditioning regimens into the NCCN

PRINCIPLES OF CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANT

Examples of Commonly Used Conditioning Regimens
- This list is not comprehensive. Other options can be considered.
- See Suggested Doses/Modifications by Weight (HCT-A 7 of 9)

Autologous Regimens by Disease Type	
Non-Hodgkin Lymphoma (NHL) (without CNS Disease) or Hodgkin Lymphoma (HL)	• BEAM (carmustine + etoposide + cytarabine + melphalan)[21] • BEAC (carmustine + etoposide + cytarabine + cyclophosphamide)[22-24] • Carmustine + thiotepa[25] • Busulfan + cyclophosphamide + etoposide[26] • TEAM (thiotepa + etoposide + cytarabine + melphalan)[27] • Bendamustine + etoposide + cytarabine + melphalan[28]
Primary Central Nervous System Lymphoma (PCNSL) or NHL (with CNS Disease)	• Thiotepa + busulfan + cyclophosphamide[25] • Carmustine + thiotepa[25]
Multiple Myeloma (MM)/Plasma Cell Leukemia (PCL)	• Melphalan (200 mg/m^2)[29] • Melphalan (70–140 mg/m^2 for select patients)[i,30-32] • Melphalan + busulfan (high risk)[33]
Germ Cell Tumors (GCT)	• Carboplatin + etoposide[34] • Paclitaxel + ifosfamide + carboplatin + etoposide[35]
Acute Promyelocytic Leukemia (APL)	• Busulfan + melphalan[36-38] • Cyclophosphamide + TBI[38] • Busulfan + cyclophosphamide[38]

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

References Continued

HCT-A 5 OF 9

Guidelines represents an opportunity to ensure the receipt of high-quality care for patients undergoing HCT for malignant disease. Because there is currently no consensus on the optimal condition regimens for various clinical settings, clinicians must make decisions on the appropriate use of conditioning regimens in the context of an individual patient's condition. Increased education and awareness of the available options, including fludarabine-free regimens, will help to ensure the acceptance and use of these agents in the clinical care of patients undergoing HCT.

To participate in this journal CE activity, go to https://education.nccn.org/node/92893

References

1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813–1826.
2. Auletta JJ, Kou J, Chen M, Shaw BE. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021. Accessed January 5, 2023. Available at: https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/Pages/index.aspx
3. Flannelly C, Tan BE, Tan JL, et al. Barriers to hematopoietic cell transplantation for adults in the United States: a systematic review with a focus on age. Biol Blood Marrow Transplant 2020;26:2335–2345.
4. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2015;21:1863–1869.
5. Hosing C. Hematopoietic stem cell mobilization with G-CSF. Methods Mol Biol 2012;904:37–47.
6. Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. N Engl J Med 2001;344:175–181.
7. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med 2012;367:1487–1496.
8. Lee SJ, Logan B, Westervelt P, et al. Comparison of patient-reported outcomes in 5-year survivors who received bone marrow vs peripheral blood unrelated donor transplantation: long-term follow-up of a randomized clinical trial. JAMA Oncol 2016;2:1583–1589.
9. Alousi A, Wang T, Hemmer MT, et al. Peripheral blood versus bone marrow from unrelated donors: bone marrow allografts have improved long-term overall and graft-versus-host disease-free, relapse-free survival. Biol Blood Marrow Transplant 2019;25:270–278.
10. Brunstein CG, Eapen M, Ahn KW, et al. Reduced-intensity conditioning transplantation in acute leukemia: the effect of source of unrelated donor stem cells on outcomes. Blood 2012;119:5591–5598.
11. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 2008;14:641–650.
12. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009;15:1628–1633.
13. McCune JS, Quinones CM, Ritchie J, et al. Harmonization of Busulfan Plasma Exposure Unit (BPEU): a community-initiated consensus statement. Biol Blood Marrow Transplant 2019;25:1890–1897.

14. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. J Clin Oncol 2014;32:3249–3256.
15. Sorror ML. How I assess comorbidities before hematopoietic cell transplantation. Blood 2013;121:2854–2863.
16. Bubalo J, Carpenter PA, Majhail N, et al. Conditioning chemotherapy dose adjustment in obese patients: a review and position statement by the American Society for Blood and Marrow Transplantation practice guideline committee. Biol Blood Marrow Transplant 2014;20:600–616.
17. Ijaz A, Khan AY, Malik SU, et al. Significant risk of graft-versus-host disease with exposure to checkpoint inhibitors before and after allogeneic transplantation. Biol Blood Marrow Transplant 2019;25:94–99.
18. Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. Blood 2017;129:1380–1388.
19. Pidala J, Kim J, Jim H, et al. A randomized phase II study to evaluate tacrolimus in combination with sirolimus or methotrexate after allogeneic hematopoietic cell transplantation. Haematologica 2012;97:1882–1889.
20. Khimani F, Kim J, Chen L, et al. Predictors of overall survival among patients treated with sirolimus/tacrolimus vs methotrexate/tacrolimus for GvHD prevention. Bone Marrow Transplant 2017;52:1003–1009.
21. Maziarz RT, Diaz A, Miklos DB, et al. Perspective: an international fludarabine shortage: supply chain issues impacting transplantation and immune effector cell therapy delivery. Transplant Cell Ther 2022;28:723–726.
22. Chevallier P, Peterlin P, Garnier A, et al. Clofarabine-based reduced intensity conditioning regimen with peripheral blood stem cell graft and post-transplant cyclophosphamide in adults with myeloid malignancies. Oncotarget 2018;9:33528–33535.
23. Saito T, Kanda Y, Kami M, et al. Therapeutic potential of a reduced-intensity preparative regimen for allogeneic transplantation with cladribine, busulfan, and antithymocyte globulin against advanced/refractory acute leukemia/lymphoma. Clin Cancer Res 2002;8:1014–1020.
24. Saito T, Kanda Y, Nakai K, et al. Immune reconstitution following reduced-intensity transplantation with cladribine, busulfan, and antithymocyte globulin: serial comparison with conventional myeloablative transplantation. Bone Marrow Transplant 2003;32:601–608.
25. Markova M, Barker JN, Miller JS, et al. Fludarabine vs cladribine plus busulfan and low-dose TBI as reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation: a prospective randomized trial. Bone Marrow Transplant 2007;39:193–199.
26. Dimitrova D, Gea-Banacloche J, Steinberg SM, et al. Prospective study of a novel, radiation-free, reduced-intensity bone marrow transplantation platform for primary immunodeficiency diseases. Biol Blood Marrow Transplant 2020;26:94–106.
27. Gvajaia A, Langston A, Esiashvil N, et al. Pentostatin/TBI conditioning is well-tolerated and permits engraftment of a second allogeneic stem cell transplant following primary or secondary rejection of an allogeneic hematopoietic stem graft. Blood 2019;134(Suppl 1):Abstract 5657.