Chapter e163: Hematopoietic Cell Transplantation

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UPDATE SUMMARY

Update Summary

December 1, 2023

The following updates were made to this chapter:

- Hematopoietic Stem Cells: include information on a recently FDA-approved generic for plerixafor and use of plerixafor in healthy donors
- Hematopoietic Stem Cells: inclusion of new CXCR4 inhibitor, motixafortide, indicated for mobilization in patients with multiple myeloma
- Transplant-related complications, Sinusoidal Obstruction Syndrome: updated clinical trial data evaluating the use of defibrotide to prevent sinusoidal obstructive syndrome
- Transplant-related complications, Pulmonary Complications: addition of belumosudil and ruxolitinib to agents useful in the treatment of pulmonary graft-vs-hosts disease
- Graft-versus-Host Disease, Acute Graft-versus-Host Disease, Prevention of Acute Graft-versus-Host Disease: added details for dosing and monitoring in patients receiving abatacept, infliximab, etanercept
- Graft-versus-Host Disease, Acute Graft-versus-Host Disease, Prevention of Acute Graft-versus-Host Disease: updated information on the use of post-transplant cyclophosphamide use in the prevention of acute graft-versus-host disease

KEY CONCEPTS

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1. Hematopoietic cell transplantation (HCT) is a procedure that involves intravenous infusion of hematopoietic stem cells from a donor into a recipient, after the administration of chemotherapy with or without radiation. The rationale is to increase tumor cell kill by increasing the dose of myelotoxic therapies and giving donor hematopoietic stem cells to "rescue" the recipient from the hematologic toxicity. Immune-mediated effects also contribute to the tumor cell kill observed after allogeneic HCT.

2. Hematopoietic stem cells used for transplantation can come from the recipient (autologous) or from a related or unrelated donor (allogeneic). If the related donor is a twin, the transplant is referred to as a syngeneic transplant.

3. Human leukocyte antigen (HLA) mismatching of allogeneic donor-recipient pairs at either class I or class II loci increases the risk of graft failure, graft-versus-host disease (GVHD), and worsens survival in the absence of effective GVHD prophylaxis. The ideal donor is one that is matched at HLA-A, B, C, and DRB1.

4. Hematopoietic stem cells are found in the bone marrow, peripheral blood, and umbilical cord blood. These stem cells express the CD34 antigen, and the number of $CD34^+$ cells is a clinically useful measure of the number of hematopoietic stem cells. Infusion of a minimum number of $CD34^+$ cells is necessary to ensure posttransplant engraftment. Due to the rarity of these cells in the peripheral blood, mobilization strategies are used to increase the number of $CD34^+$ cells prior to collection procedures.

5. Because of clinical and economic advantages, peripheral blood has replaced bone marrow as the most common source of hematopoietic stem cells in the autologous and adult allogeneic HCT setting.

6. The purpose of the preparative (or conditioning) regimen in traditional myeloablative transplants is twofold: (a) maximal tumor cell kill and (b) immunosuppression of the recipient to reduce the risk of graft rejection (allogeneic HCT only).

7. Reduced-intensity conditioning regimens (including those that are nonmyeloablative) have been developed to reduce early posttransplant morbidity and mortality while maximizing the graft-versus-malignancy (GVM) effect. The advantage of this approach is that patients who would otherwise not be eligible for allogeneic HCT can be offered a potentially curative therapy.

8. Transplant-related mortality associated with allogeneic HCT depends on recipient age, recipient performance status, donor source and degree of HLA matching, and disease status. Major causes of death include relapse, infection, organ toxicity, and GVHD. The most common cause of death after autologous HCT is disease relapse; transplant-related mortality is lower than after allogeneic HCT and depends on the conditioning regimen, age, underlying comorbidities, and disease status.

9. Patients undergoing allogeneic HCT receive immunosuppressive therapy to prevent GVHD, which inhibits T-cell activation, proliferation, or both. Commonly used GVHD prophylaxis regimens include combinations of tacrolimus, methotrexate, sirolimus, mycophenolate mofetil, or posttransplant cyclophosphamide.

10. Initial treatment of acute and chronic GVHD consists of prednisone, either alone or combined with other immunosuppressants. New agents are available for the treatment of steroid-refractory GVHD.

BEYOND THE BOOK

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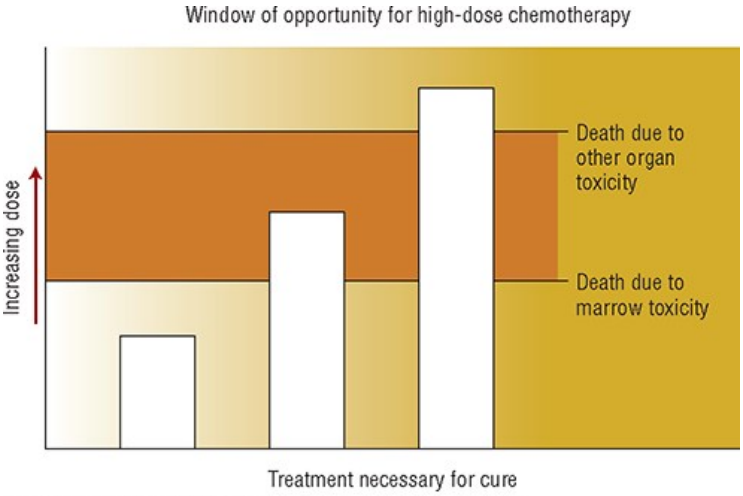
Watch the "What is GVHD?" video available on YouTube and visit the "Hematopoietic Cell Transplantation (HCT)—Clinicians Resource" (select posttransplant care, then chronic GVHD) on bethematchclinical.org. The video gives a brief overview of GVHD for the purposes of patient education. The Website provides more detail about the clinical manifestations of chronic GVHD. Both will help students to learn the basics about GVHD in preparation for a more in-depth discussion provided by the chapter.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a procedure that involves intravenous infusion of hematopoietic stem cells from a compatible donor into a recipient, usually after the administration of high-dose chemotherapy with or without radiation (called the conditioning or preparative regimen). The original rationale for HCT in the treatment of malignant disease is based on studies showing that many anticancer drugs and radiation have a steep dose–response relationship and that myelosuppression limits the chemotherapy dosage that can be safely administered. Although standard-dose chemotherapy can prolong survival in many cancer patients, most patients are not cured of their disease with this strategy alone. Infusion of hematopoietic stem cells allows the administration of high doses of chemotherapy (as much as 10-fold higher) by reestablishing hematopoiesis. If tumor cells that are resistant to standard doses are sensitive to higher doses of chemotherapy, then tumor cell kill will be greatly increased, and the likelihood of cure would be higher with HCT compared with standard-dose chemotherapy. However, the chemotherapy dose cannot be escalated indefinitely due to the risk of death caused by nonhematologic toxicity (see Fig. e163-1).

FIGURE e163-1

Patients represented by the middle bar are the best candidates for hematopoietic cell transplantation because the technique allows for administration of chemotherapy or radiation in doses that otherwise would be intolerable because of severe myelosuppression.



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HCT is an important modality to treat a variety of malignant and nonmalignant diseases. In the United States, the estimated annual number of allogeneic HCTs exceeds 8,000 while the annual number of autologous HCTs has steadily increased since 2000 with over 12,000 HCTs performed in 2019.[1] The total number of HCTs per year has grown steadily over the past decade because of an increase in the number of patients receiving alternative donor transplants and an increase in the number of patients older than 60 years undergoing transplantation.[1]

The most common malignancies treated with HCT are multiple myeloma, lymphomas, and leukemias and other blood disorders such as myelodysplasia and myeloproliferative syndromes. Many nonmalignant hematologic disorders, including aplastic anemia, thalassemia, and sickle cell anemia; immunodeficiency disorders; and other genetic disorders are also potentially curable with allogeneic HCT. Autologous HCT can also be used

to treat select patents with autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematous. The role and indications for HCT are discussed in detail within individual disease chapters of this text.

This chapter summarizes the procedures involved in HCT and the common complications associated with HCT. More detailed information on HCT can be found in published reviews and books.[2–4] Information on HCT also can be found on several Websites, including http://www.cibmtr.org (Center for International Blood and Marrow Transplant Research [CIBMTR]) and https://bethematch.org/ (National Marrow Donor Program [NMDP]).

HISTOCOMPATIBILITY TESTING AND DONOR SELECTION

2 Different types of donors are used in HCT. The choice of donor depends on the diagnosis and disease status of the recipient as well as their age, concurrent comorbidities, and performance status. In *autologous* transplants, patients receive their own hematopoietic stem cells, which were collected and stored before administration of the transplant conditioning regimen. In *syngeneic* transplants, an identical twin serves as the donor. In *allogeneic* transplants, the donor is genetically not identical to the recipient but shares some common cell surface antigens called human leukocyte antigens (HLAs). These antigens are encoded by the major histocompatibility complex (MHC), a cluster of genes located on the sixth chromosome.[5] The MHC contains three distinct regions designated as class I, class II, and class III. Class I and class II genes encode for HLA; products of class III genes have other important roles in the immune system. Class I and class II HLA antigens differ in their tissue distribution, structure, and function. Their primary function is to aid the immune system in recognizing cells or tissues as “self” or “nonself.” The genes (and the corresponding antigens they encode for) important in HCT are the class I antigens, HLA-A, HLA-B, and HLA-C and the class II antigen, HLA-DRB1.[5] Class II antigens also include HLA-DQ and -DP. Because of the polymorphism of the HLA system, there are many different HLA antigens within each different class of HLA. To reduce the chance of graft rejection and graft-versus-host disease (GVHD), a donor is chosen based on how many of these HLA antigens are the same as those of the recipient.[5] Thus, an ideally matched donor would be an “8/8” match, matching at HLA-A, -B, -C, and -DRB1.

To identify a suitable allogeneic donor, both the recipient and potential donors are HLA typed (ie, specific HLA antigens are identified); the potential donor who is most closely matched is generally chosen to be the transplant donor. HLA typing is accomplished by DNA-based techniques that use polymerase chain reaction (PCR) amplification of specific HLA genes from genomic DNA. DNA typing methods are categorized by the level of discrimination they provide in defining the sequence of an HLA gene.[5] Low-resolution methods provide limited sequence information about a particular HLA gene and are typically used to identify sibling donors. However, low-resolution techniques cannot distinguish the extremely polymorphic nature of many of the HLA antigens. HLA antigens are characterized by thousands of genetic variations (alleles), and each allele may correspond to a unique HLA molecule. High-resolution typing techniques (eg, sequence-specific priming or next-generation sequencing) can characterize different alleles and are used to identify suitable unrelated donors.

3 The degree of HLA mismatching correlates with the risk of graft rejection, GVHD, and survival.[5] Mismatches at HLA-A, HLA-B, HLA-C, and HLA-DRB1 are similarly associated with increased risk of GVHD and mortality.[5] HLA-DQB1 and -DPB1 mismatching are less predictive of negative outcomes, which suggests an 8/8 match is as beneficial as a 10/10 or 12/12 match. As the number of mismatches increases, the risk of GVHD and transplant-related mortality also increases. In the search for an allogeneic donor, the patient’s siblings are typed first. About 30% of Americans have an HLA-identical sibling. In an effort to offer allogeneic HCT to patients who lack an HLA-identical sibling donor, alternative donors are being used. The most common type of alternative donor is an individual unrelated to the recipient who is fully HLA matched. With improved HLA typing techniques and better supportive care, most reported outcomes with matched unrelated donors are not significantly different than those reported with related sibling donors.[6] To facilitate the identification of unrelated donors, the NMDP (https://bethematch.org) was started in 1986. To date, the NMDP has access to more than 39 million donors worldwide through agreements with international cooperative registries and has facilitated more than 105,000 unrelated donor transplants. Although it is the transplant center’s responsibility to select the donor, the NMDP recommends that selected donor and recipient be matched at HLA-A, B, C, and DRB1 by high-resolution typing when possible for bone marrow or peripheral blood HCT.[7,8] If more than one suitable HLA-matched unrelated donor is identified, other factors can be used to select the donor, such as younger age, being male or a nulliparous female, and negative cytomegalovirus (CMV) serostatus.

The likelihood of a patient finding an HLA-matched unrelated donor through NMDP ranges from 29% to 79% depending on the prevalence of the recipient’s HLA type, race, and ethnic background.[7] With the current size and racial make-up of the NMDP registry, the matching likelihood is higher for White patients than for patients from other racial or ethnic groups. Agreements between NMDP and international registries may improve the likelihood of finding donors for non-White patients, and NMDP actively promotes participation among non-White donor volunteers. Another potential limitation

in finding an unrelated donor is the time needed to search for a potential donor candidate. Patients with relatively common HLA genotypes have shorter search times than those with less common genotypes. Some donor searches may take several weeks and patients with acute leukemia can relapse while waiting for completion of the search. If an initial search yields few or no donors, transplant centers will usually begin to investigate alternative donor options.

Alternative donor options include mismatched unrelated donors, related haploidentical donors, or umbilical cord blood (discussed in the next section).[7] Potentially useful HLA-mismatched unrelated donors are those who are mismatched at one or, at most, two HLA loci. If minimal mismatching is allowed, the chance of finding an unrelated donor increases significantly. Although mismatched unrelated donor transplants are inferior with respect to GVHD, transplant-related mortality, and overall survival when compared to matched unrelated donors, these transplants do offer a curative therapeutic option in select patients.[7] Research is focused on evaluating the relative effect of mismatches at specific loci to determine if some are less detrimental (permissive) than others in order to improve outcomes. In addition, NMDP recommends testing the recipient for donor-specific HLA antibodies as graft failure is more common when the antibodies are present.[7,8]

Related haploidentical donors are relatives of the recipient with two or more antigen mismatches. Donors can be parents, children, or siblings who have one identical HLA haplotype and one nonidentical haplotype to the recipient. Historically, haploidentical allogeneic transplants (haplo-HCT) resulted in poor outcomes because of high rates of graft failure and GVHD. Strategies to reduce the incidence of graft failure and GVHD have included various methods of T-cell depletion including administration of anti-thymocyte globulin (ATG), alemtuzumab, or posttransplant cyclophosphamide (PTCy).[9,10] Several observational studies have compared outcomes after haplo-HCT to those seen after traditional matched related and unrelated donor transplants and have shown that GVHD and survival outcomes were similar.[11–13] Two parallel prospective studies with identical objectives, eligibility criteria, and clinical endpoints were conducted with reduced-intensity conditioning regimens in either haplo-HCT with PTCy or umbilical cord blood transplant (UCBT).[14] While the trials were not designed for results to be compared directly, patients receiving haplo-HCT had higher rates of engraftment, lower risk of acute and chronic GVHD and less nonrelapse mortality than reported in the UCBT trial. However, relapse rates were lower after UCBT leading to similar progression-free and overall survival between the two studies. These trials reproduce single-center results with haplo-HCT or UCBT and suggest that survival rates with these alternative donor sources are comparable to those observed after matched unrelated donors. Based on these results, a phase III study comparing haplo-HCT or UCBT showed no significant difference in progression-free survival at 2 years. However, overall survival, a secondary endpoint, was lower in patients receiving UBCT compared to those receiving haplo-HCT.[15] While this study suggests an advantage of haplo-HCT over UCBT, choosing an alternative donor in the absence of an HLA-matched sibling or unrelated donor depends on patient characteristics, physician preference, and center experience.

HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells serve as “mother” cells for all blood cells, including erythrocytes, leukocytes, and platelets (see Chapter e106). Stem cells have varying degrees of “stemness.” True pluripotent stem cells can replicate indefinitely and can give rise to stem and progenitor cells of all tissues. Multipotent stem cells, such as hematopoietic stem cells, have the capacity for self-renewal and can differentiate into more than one cell type in a particular tissue lineage. Because of their capacity for self-renewal, hematopoietic stem cells can repopulate the recipient’s marrow, which has been “emptied” by the administration of high-dose chemotherapy, either alone or combined with radiation.

4 Hematopoietic stem cells are rare cells, comprising less than 0.01% of all bone marrow cells. Isolation and quantitative measurement of hematopoietic stem cells are extremely difficult because of their rarity and their similar appearance to other cells. For these reasons, surrogate markers are used to measure the number of stem cells. CD34 is an antigen expressed on hematopoietic stem cells and other early progenitor cells. The number of cells expressing the CD34 antigen ($CD34^+$ cells) can be determined by flow cytometry and has become the standard method of measuring hematopoietic stem cell content.

Hematopoietic stem cells are found in the bone marrow, peripheral blood, and umbilical cord blood (UCB). Hematopoietic stem cells from the bone marrow are obtained by multiple aspirations from the anterior and posterior iliac crests while the donor is under general anesthesia. The procedure takes about 1 hour and yields 200 to 1,500 mL, depending on the size of the donor. In allogeneic bone marrow transplantation (BMT), the marrow stem cells are given to the recipient 12 to 24 hours after harvest. In autologous BMT, the marrow is frozen and stored until needed. After intravenous infusion, the marrow stem cells enter the systemic circulation and find their way to the bone marrow cavity, where they reseed and grow in the bone marrow microenvironment. Although the donor experiences local soreness for a few days, the procedure usually is well tolerated, with no delayed

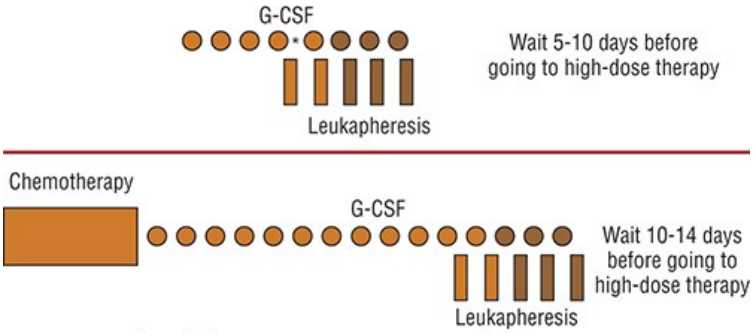
complications resulting from the marrow aspiration. The major risk of serving as a marrow donor is the risk of undergoing general anesthesia.

Hematopoietic stem cells in peripheral blood (peripheral blood stem cells [PBSCs]) are found in the mononuclear fraction of white blood cells (lymphocytes and monocytes) and are collected by a procedure called leukapheresis (or apheresis). This is an outpatient procedure that involves withdrawal of blood from a vein (through a specialized IV catheter), selective removal of mononuclear cells (containing the hematopoietic stem cells) by an apheresis machine, and reinfusion of the unneeded blood components back to the patient. During this process, about 10 to 15 L of blood is processed over several hours during each daily apheresis session. Most of the blood cells are returned to the donor, and each apheresis yields about 200 mL of cells. Leukapheresis is continued daily until a target number of $CD34^+$ cells (which include hematopoietic stem cells) are collected or until the collections are discontinued due to poor $CD34^+$ cell yield.

The number of hematopoietic stem cells that circulate in peripheral blood normally is too low for apheresis to be technically feasible. Without mobilization techniques, at least six apheresis are usually required to collect a sufficient number of PBSCs. Several methods have been used clinically to "mobilize" hematopoietic stem cells from the bone marrow into peripheral blood for use in HCT. Figure e163-2 shows representative schemas for mobilization and collection of PBSCs. The most commonly used mobilization method in both donor populations (healthy allogeneic donors and autologous donors) is the administration of the recombinant hematopoietic growth factor, granulocyte colony-stimulating factor (G-CSF [filgrastim]), usually at a dose of 10 μg/kg/day.[16–18] Chemotherapy followed by G-CSF in patients undergoing autologous HCT increases the number of PBSCs to a greater extent than growth factor alone. This approach is more expensive than single-agent G-CSF and is associated with more adverse drug reactions, but the number of apheresis is generally reduced, and the additional chemotherapy may further reduce tumor burden before transplant. However, these benefits have not translated into improved transplant outcomes, so this approach is generally not used.[16,17] Pegfilgrastim (pegylated filgrastim) has also been evaluated in the mobilization setting, either alone or after chemotherapy (6 and 12 mg doses). Its prolonged half-life of 33 hours allows for single-dose administration, increasing patient convenience. Studies of single agent pegfilgrastim are limited by small numbers and report varying degrees of success.[16,17] The combination of pegfilgrastim and chemotherapy mobilization results in similar $CD34^+$ cell collections and transplant-related outcomes to chemotherapy and G-CSF mobilization.[16,17]

FIGURE e163-2

Schema for collection of peripheral blood progenitor cells after hematopoietic growth factor administration (top) or after chemotherapy and hematopoietic growth factor administration (bottom). Symbols with darker shading represent procedures performed only if adequate numbers of $CD34^+$ cells have not been collected. (G-CSF, granulocyte colony-stimulating factor.) *Plerixafor initiated here and continued daily until sufficient cell collection (up to a maximum of 4 days).



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The first G-CSF biosimilar was introduced in Europe in 2008. Professional organizations were initially reluctant to recommend these agents for stem cell mobilization due to a paucity of safety and efficacy data. However, several prospective trials comparing biosimilar products to the reference product have been published. A meta-analysis summarized the results in over 1,800 subjects which included healthy donors and patients with hematologic malignancies who used biosimilar agents to collect PBSCs. Mobilization with biosimilars resulted in expected $CD34^+$ stem cell yields with similar posttransplant engraftment and adverse effects to G-CSF, which suggests that biosimilars are an acceptable option in mobilization, especially given their potential cost-savings.[18,19]

Plerixafor is a novel inhibitor of the CXCR4 chemokine receptor that is FDA-approved as a mobilizing agent in combination with G-CSF in autologous transplant candidates. When plerixafor is combined with G-CSF, higher $CD34^+$ cell yields, fewer apheresis sessions, increased likelihood of achieving $CD34^+$ target yields, and lower graft failure rates are observed compared to single-agent G-CSF.[16,17] Due to these advantages, the combination of plerixafor and G-CSF is routinely used to mobilize stem cells in autologous HCT patients.[18] However, because many patients can mobilize efficiently with G-CSF alone and plerixafor is expensive, transplant centers generally use a risk-adapted or preemptive approach to identify which patients are appropriate candidates for plerixafor. One approach is to give plerixafor to patients with certain characteristics that have been associated with a high risk of poor mobilization (ie, risk-adapted approach). These characteristics include older age, diagnosis of non-Hodgkin lymphoma (NHL), extensive chemotherapy history, previous radiation therapy, previous exposure to lenalidomide or purine analogs, previous mobilization failure, and low pre-apheresis circulating peripheral blood $CD34^+$ ($PBCD34^+$) cell counts.[20] However, these patient characteristics are not accurate predictors of poor mobilization outcomes and thus patients may be either over- or under-treated. Another approach is a preemptive strategy, which identifies poor mobilizers based on $PBCD34^+$ cell counts on day 4 or 5 of the G-CSF administration or on the first apheresis collection. Low numbers of $CD34^+$ cells after the G-CSF administration have been associated with mobilization failure. Patients who do not have a minimal number of $CD34^+$ cells receive plerixafor.[16–18] Many transplant centers use these preemptive approaches to guide their mobilization strategies, thereby limiting plerixafor use to patients who are not likely to obtain the target $CD34^+$ yield. These algorithms have been reported to improve initial mobilization rates while efficiently managing resources.[20] In 2023, the FDA approved a generic plerixafor product which could potentially offer significant cost savings. Early experience in MM and NHL patients has shown successful stem cell collections, engraftment, and full hematopoietic recovery with the generic product.[21]

A second CXCR4 inhibitor, motixafortide, was approved by the FDA in 2023. Motixafortide is indicated for mobilization in combination with G-CSF in patients with multiple myeloma. Compared to plerixafor, motixafortide has higher affinity for and longer receptor occupancy of CXCR4 resulting in extended clinical activity. A randomized, phase 3, placebo-controlled trial in myeloma patients undergoing mobilization demonstrated that administration of motixafortide and G-CSF successfully mobilized 92.5% of patients ($> 6 \times 10^6$ CD34+ cells per kg within two apheresis days) compared to 26.2% of patients receiving placebo + G-CSF. Of note, package labelling includes a triple-drug premedication regimen (H1 and H2 blockers and a leukotriene inhibitor) as well as an analgesic medication to prevent injection-related reactions and potential anaphylaxis.[22]

In about 20% to 30% of autologous transplant candidates, an optimal number of $CD34^+$ cells will not be obtained after the first attempt with G-CSF mobilization.[20] Several strategies for overcoming the obstacle of poor mobilization have been evaluated, including remobilization with the same or higher doses of the G-CSF, previously used mobilization regimen or a combination of chemotherapy and a hematopoietic growth factor, if chemotherapy is indicated.[20] Each of these remobilization strategies has been used with varying success. Unfortunately, these strategies are associated with failure rates that exceed 70%. Bone marrow harvest may be an option if other strategies fail.

Current guidelines recommend that plerixafor be used in remobilization regimens for patients failing primary mobilization attempts, regardless of whether it was used in the primary mobilization.[16–18] The use of plerixafor combined with chemotherapy and G-CSF may be a promising strategy, but further data are needed to better understand the appropriate use of this regimen. The selection of a secondary mobilization regimen should be based on patient-specific factors and clinician judgment.

The number of $CD34^+$ cells infused correlates significantly with the rate of neutrophil and platelet recovery after high-dose chemotherapy.[16,17] Rapid neutrophil recovery usually is observed in patients who receive at least 2×10^6 $CD34^+$ cells/kg (body weight of recipient). More rapid platelet recovery is observed when at least 5×10^6 $CD34^+$ cells/kg are transplanted compared with lower cell doses. As a result, current guidelines recommend 2×10^6 $CD34^+$ cells/kg as a minimum number to collect for autologous transplant, with an optimal target of 5×10^6 $CD34^+$ cells/kg.[18] The decision to use a collection yield of less than 2×10^6 $CD34^+$ cells/kg should be limited to those cases in which the potential benefit of an HCT outweighs the risks of infusing a suboptimal $CD34^+$ cell dose. If a second transplant (ie, tandem transplant) is planned, a minimum of 4×10^6 $CD34^+$ cells/kg may be collected and divided into two equal aliquots, one for each transplant.

5 The use of peripheral blood instead of bone marrow as a source of hematopoietic stem cells offers several clinical and economic advantages. For autologous transplant patients, the most clinically important advantage is that patients who receive mobilized PBSCs experience more rapid hematopoietic engraftment. Although engraftment of all lineages is more rapid when PBSCs are used, the most significant effect is observed with platelet recovery. Patients who receive mobilized PBSCs experience platelet recovery as much as 2 to 3 weeks earlier and require fewer platelet

transfusions than those who receive bone marrow stem cells. As a result, patients usually are discharged earlier from the hospital, so the overall cost of autologous HCT is reduced with the use of PBSCs. PBSCs may be less likely to be contaminated with malignant cells compared with marrow stem cells. Finally, because PBSCs are collected from the mononuclear cell fraction, a fraction that also contains immunocompetent cells (eg, natural killer [NK] cells and T lymphocytes), some investigators believe that infusion of PBSCs represents a form of "adoptive immunotherapy." In this model, NK cells and lymphocytes targeted against tumor cells help to kill residual tumor cells. As a result of these clinical and economic advantages, peripheral blood has replaced bone marrow as the source of stem cells in the autologous setting.

Peripheral blood has also become the predominant source of hematopoietic stem cells in adults undergoing allogeneic HCT.[1] About two-thirds of allogeneic HCTs performed in adults currently come from PBSCs harvested from normal donors receiving G-CSF mobilization. G-CSF is generally well tolerated in the normal donor population. Short-term adverse drug reactions are similar to those seen in cancer patients receiving G-CSF (eg, bone pain, headache, fever, arthralgias, malaise). Although there are concerns about increased risk of acute myeloid leukemia (AML) in healthy subjects given G-CSF, no higher risk has been observed.[23] Up to 5% of healthy donors may mobilize poorly.[24] In such cases, reports of plerixafor used as salvage has shown benefit yielding improved CD34 collections with minimal gastrointestinal toxicity to the donor.[25]

Randomized controlled trials and meta-analyses have shown that the stem cell source can influence posttransplant outcomes in allogeneic HCT. Traditionally, matched-related PBSC transplants have been associated with a more rapid hematopoietic recovery and required fewer transfusions compared with patients receiving bone marrow.[26] The difference in the rate of engraftment may be related to the threefold higher numbers of $CD34^+$ cells infused in recipients of PBSC transplants. Although an increased risk of acute GVHD or transplant-related mortality in patients receiving allogeneic PBSC transplants has not been reported, a higher risk of chronic GVHD has been observed in many retrospective studies and meta-analyses.[26] The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) reported results from a trial that randomized 551 patients to allogeneic PBSC or bone marrow from matched unrelated donors.[27] Two years after transplant, no differences in overall survival, relapse, acute GVHD, or non-relapse mortality were observed. However, a higher incidence of chronic GVHD was reported in patients who received PBSC transplants. Most studies of the effect of stem cell source on transplant-related outcomes have focused on transplants following myeloablative conditioning. In a retrospective study of patients with hematologic malignancies who received reduced intensity unrelated donor transplants with either PBSCs or bone marrow, the CIBMTR reported that time-to-engraftment, risks of acute or chronic GVHD, relapse, nonrelapse mortality, and overall survival were not significantly different between the two groups. Subgroup analysis suggests that GVHD prophylaxis may impact survival in this patient population and warrants further evaluation.[28] The selection of the optimal source of hematopoietic stem cells for an individual patient should be based on the risk of relapse, chronic GVHD, graft failure, and donor preference.

Hematopoietic stem cells found in UCB are an attractive source for several reasons.[29] Because the stem cells are collected from placental blood, there is a low risk of transmissible infectious diseases, no risk to the mother or the baby, and the cells are immediately available. UCB initially was obtained from siblings, but now recipients of transplants from unrelated donors account for almost all patients who receive UCB transplants. More than 800,000 UCB units are available in more than 100 UCB banks, and more than 40,000 unrelated UCB transplants have been performed worldwide. However, cord blood use as a stem cell source is decreasing.[1] This decline in cord blood source is related to the increasing use of haplo-HCT and has been attributed to increasing costs, posttransplant infections, and the need for multiple cord blood units to increase stem cell dose.[29]

A major limitation of UCBT is the small volume of blood collected, usually 60 to 150 mL with resultant low numbers of $CD34^+$ cells. This has led to "pooling" two or more units of UCB for one recipient (referred to as double cord transplant). Despite increasing $CD34^+$ cell doses through use of double cord products, the time to engraftment following UCBT is longer compared to other cell sources. Additional interventions such as ex-vivo expansion of UCB stem cells prior to transplant have reported encouraging results but ongoing testing is needed to confirm long-term safety and efficacy.[29]

APPROACHES TO ERADICATE MALIGNANT CELLS

Conditioning Regimens

6 The purpose of the pretransplant conditioning regimen (also called the preparative regimen) depends on the type of transplant and the indication for its use. In the autologous setting, conditioning is used to eradicate malignant cells.[30] This is also the case in allogeneic HCT for malignant diseases,

but the conditioning regimen also serves a dual purpose to suppress the recipient's immune system to allow for donor cell engraftment. Conditioning regimens can be myeloablative, reduced intensity, or nonmyeloablative.[31] Myeloablative conditioning (MAC) regimens contain high doses of chemotherapy with or without radiation that would lead to life-threatening or fatal myelosuppression if hematopoietic stem cells were not infused. Patients undergoing autologous HCT receive only MAC regimens. Patients undergoing allogeneic HCT can receive MAC, reduced-intensity (RIC), or nonmyeloablative (NMA) conditioning regimens. RIC and NMA regimens consist of lower doses or different types of chemotherapy or lower doses of radiation than MAC regimens, resulting in less toxicity. Both were developed after the observation was made that some of the antitumor effect of the allogeneic transplant was mediated by a reaction between the donor's transplanted immune system and the recipient's cancer cells. This meant that high doses of chemotherapy, radiation, or both may not be needed in all patients. Because RIC or NMA conditioning regimens use lower doses of chemotherapy or radiation or less toxic drugs, older patients and those with comorbidities can be offered potentially curative allogeneic transplants. Table e163-1 lists chemotherapeutic agents frequently used in conditioning regimens, the doses used, and their dose-limiting toxicity in the transplant setting. Also listed are common regimens that include the agents listed.

TABLE e163-1

Dose-Limiting Nonhematologic Toxicities for Selected Chemotherapeutic Agents Included in Myeloablative Conditioning Regimens in Hematopoietic Cell Transplantation and Examples of Commonly Used Conditioning Regimens

Drug	Conventional Dose (mg)	HCT Dose (mg/m^2)	Dose-Limiting Toxicity	Commonly Used Regimens[a]
Busulfan (IV)	2 (PO)	300-780	Hepatic	BuCy, BuFlu
Carboplatin	400	2,000	Hepatic, renal	Carboplatin + E + Cy or Mel
Carmustine (BCNU)	200	1,200	Pulmonary, hepatic	BEAM, BEAC, CBV
Cyclophosphamide	1,000	7,500	Cardiomyopathy	CyTBI, FluCy + TBI
Etoposide	300-600	2,400	Mucositis	EtopTBI, BEAM, BEAC,
Melphalan (IV)	28-42 (PO)	140-200	Mucositis	Single agent melphalan, BEAM, FluMel ± TBI
Thiotepa	20-50	750	Mucositis, central nervous system	BCNU + Thiotepa
				Thiotepa + Bu + Cy
Fludarabine	125	125-240	Neurotoxicity	FluMel ± TBI, BuFlu, FluTBI

[a]Doses for regimens are given in the body of the text.

BCNU, carmustine; BEAC, BCNU, etoposide, cytarabine, cyclophosphamide; BEAM, BCNU, etoposide, cytarabine, melphalan; Bu, busulfan; CBV, cyclophosphamide, BCNU, etoposide; Cy, cyclophosphamide; E or V, etoposide or VP-16; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation.

Myeloablative Conditioning Regimens

MAC regimens usually include at least one anticancer drug with a relatively steep dose-response curve and myelosuppression as their dose-limiting toxicity, such as an alkylating agent. Cyclophosphamide, melphalan, busulfan, and carmustine are examples of chemotherapy agents commonly used in MAC regimens. They are combined with other agents that have additive or synergistic effects in specific types of cancers, or additional alkylating

agents may be used.

Total-body irradiation (TBI) is also used in some pretransplant conditioning regimens. In patients with malignant disease, the rationale of TBI is to eradicate malignant cells located in areas inaccessible to the systemic circulation and thus to the chemotherapeutic agents (eg, central nervous system and testicles). TBI also has significant immunosuppressive activity that prevents rejection of the donor cells (ie, graft rejection) and facilitates successful engraftment.[32] Historically, TBI doses in MAC regimens ranged from 10 to 16 Gy (1,000-1,600 rads or cGy), which is more than twice the lethal myelosuppressive dose of radiation for a normal person. TBI given at high doses is typically fractionated (split over 3-4 days, once or twice a day) rather than given as a single dose. Fractionated TBI has an improved therapeutic ratio compared with single-dose administration, that is, the destruction of more leukemic cells and marrow stem cells while sparing other normal tissues such as lungs, liver, eyes, and cartilage. The acute toxicities of TBI consist of fever, nausea, vomiting, diarrhea, dysphagia, anorexia, xerostomia, mucositis, erythema, rash, alopecia, fatigue, myelosuppression, and tender swelling of the parotid gland. Pneumonitis and sinusoidal obstruction syndrome can occur, but rates have declined with improved TBI delivery and supportive care measures. Long-term complications of TBI-containing regimens include cognitive deficiencies, pituitary dysfunction, cardiac dysfunction, hypothyroidism, cataract formation, growth retardation, osteopenia, carcinogenesis, permanent reproductive sterility, and secondary malignancies.[32]

Based on its immunomodulatory and antineoplastic effects, cyclophosphamide (60 mg/kg/day for 2 days) is commonly combined with TBI (CyTBI). Other chemotherapy agents have been used with TBI, including fludarabine and etoposide, but there is no evidence to suggest that any of these combinations are more effective than CyTBI. Due to the toxicities seen with high-dose TBI, chemotherapy-only regimens also have been developed and may be preferred depending on patient characteristics such as diagnosis, stage of disease, performance status, or age. For example, in patients with acute myeloid leukemia (AML), TBI conditioning regimens do not confer a survival advantage.[33] In contrast, patients with acute lymphoid leukemia (ALL) who received TBI-containing regimens had similar survival with improved relapse outcomes.[34] Many non-TBI regimens contain busulfan due to its activity against a variety of malignancies. Busulfan can either be given IV or orally, although IV administration is more common due to more consistent systemic exposure. The use of IV busulfan-containing regimens has been associated with improved survival compared to TBI-containing regimens in patients with myeloid malignancies.[35,36] Systemic exposure of busulfan has been shown to correlate with both efficacy and toxicity. At some transplant centers, plasma busulfan concentrations are monitored, and doses are adjusted to target busulfan exposure with improved patient outcomes.[35,36] However, variability between transplant centers make it difficult to interpret and compare the results. To overcome this barrier, an American Society for Transplantation and Cellular Therapy (ASTCT) committee recommends that busulfan plasma exposure units be standardized across institutions globally and reported as AUC in mg × h/L.[36] Examples of common regimens that use busulfan include busulfan and cyclophosphamide (BuCy) or busulfan and fludarabine (BuFlu).

Conditioning regimens used in autologous HCT are exclusively myeloablative and usually include at least one alkylating agent with other agents added that may have specific activity against the tumor type being treated.[30,37] TBI is not commonly used and is not included in the conditioning regimen in patients who have received prior radiotherapy. MAC regimens commonly used in patients with lymphoma include BEAM (BCNU [carmustine], etoposide, cytarabine, and melphalan), BEAC (BCNU, etoposide, cytarabine, cyclophosphamide), or CBV (cyclophosphamide, BCNU, and etoposide).[37] To reduce BCNU-related toxicities and due to periodic shortages of BCNU, substitute agents such as bendamustine are being evaluated in these lymphoma regimens. Rituximab was previously added in patients with CD20-positive lymphomas, but a recent CIBMTR registry study found no benefit in adding it to BEAM.[38] Single-agent melphalan (140-200 mg/m^2) is the standard conditioning regimen for patients undergoing autologous HCT for myeloma. The addition of other agents to melphalan has not been proven to be superior to melphalan alone.[30]

Reduced-Intensity and Nonmyeloablative Conditioning Regimens

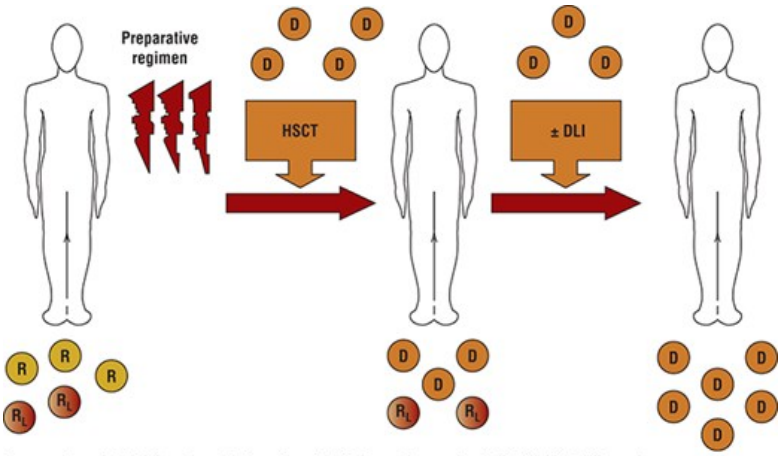
7 Donor T cells contribute to the tumor cell kill and prevention of relapse observed after allogeneic HCT, an effect referred to as the graft-versus-malignancy (GVM) effect. The GVM effect may be as important as the anticancer effect of the conditioning regimen. With the recognition of the importance of GVM in allogeneic HCT, the use of less intensive conditioning regimens has become increasingly common. These RIC regimens have shown to be less toxic but with adequate efficacy in many circumstances to increase the availability of HCT to populations previously excluded due to the risk of non-relapse mortality.[31]

RIC regimens contain ≥30% lower doses of chemotherapy or radiation, or less toxic agents, and were developed to take advantage of the GVM effect

but with a lower risk of regimen-related toxicity than that of MAC regimens.[31] The major advantage of RIC is that potentially curative transplants can be offered to patients who typically would not be considered for allogeneic HCT because of their unacceptably high risk of transplant-related complications due to increased age or moderately compromised organ function. The use of RIC regimens has steadily increased in patients aged 50 years and older.[1] In addition, because of the lower rate of toxicity, allogeneic HCT with RIC can be offered to patients who have relapsed after traditional myeloablative autologous or allogeneic transplants, provided they are healthy enough to tolerate a second transplant. Because RIC regimens may not be completely myeloablative, host hematopoiesis can persist and lead to mixed chimerism (ie, blood cells from both donor and recipient are present) (see Fig. e163-3).[39] Several studies have reported significant correlations between donor T-cell chimerism levels and the risk of graft rejection, GVHD, and relapse. For example, a low percentage of donor T and NK cells present on day 14 has been associated with graft rejection, but high T-cell donor chimerism on day 28 has been associated with acute GVHD. Achievement of full donor chimerism was associated with better GVM effect and longer progression-free survival. These data suggest that monitoring donor chimerism after transplant may allow early interventions to prevent graft rejection or relapse.[39]

FIGURE e163-3

Schema for nonmyeloablative transplantation for hematologic malignancy. Recipients (R) receive a reduced-intensity conditioning regimen and an allogeneic hematopoietic cell transplant (HCT). Initially, mixed chimerism is present with the coexistence of donor (D) cells and recipient-derived normal and leukemia/lymphoma (R_L) cells. Donor-derived T cells mediate a graft-versus-host hematopoietic effect that eradicates residual recipient-derived normal and malignant hematopoietic cells. Donor lymphocyte infusions (DLIs) can be administered to enhance graft-versus-malignancy effects.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Several RIC regimens that vary in their cytotoxic, myelosuppressive, and immunosuppressive activity have been developed.[31] Most regimens include fludarabine (125-240 mg/m^2) because of its potent immunosuppressive activity, combined with either low-dose TBI (at doses up to 8 Gy [800 rad]) or an alkylating agent, such as cyclophosphamide (2-3.6 g/m^2 or 120-200 mg/kg), busulfan (less than 9 mg/kg [or intravenous equivalent]), or melphalan (less than 140 mg/m^2). ATG or alemtuzumab is sometimes given for additional immunosuppression, and other purine analogs (eg, pentostatin or clofarabine) are sometimes used instead of fludarabine. Many of these regimens are myeloablative but are defined as RIC because of the lower doses of chemotherapy and the reduced toxicity associated with these regimens as compared to MAC regimens.[31]

Some RIC regimens are considered nonmyeloablative because they result in little to no myelosuppression and do not require hematopoietic cell support for recovery of hematopoiesis. NMA regimens are associated with little regimen-related toxicity but are similar to other RIC regimens in that they are sufficiently immunosuppressive to allow for full engraftment of donor immune effector cells. Over the last two decades, transplant-related mortality and overall survival outcomes have continued to improve with nonmyeloablative transplants, further supporting their use in older patients with high comorbidity burden.[40] Two of the most common NMA regimens are fludarabine (25 mg/m^2/day for 3-5 days) combined with cyclophosphamide (60 mg/kg/day × 2 days) plus TBI (less than or equal to 2 Gy [200 rad]), or fludarabine plus TBI. Although these regimens are clearly nonmyeloablative, the distinction may be more difficult with other regimens as definitions remain somewhat arbitrary.

Transplant-related outcomes, such as nonrelapse mortality, relapse rate, and overall and progression-free survival, vary depending on the specific regimen, disease type and status (eg, advanced disease, and residual disease) at the time of transplant, donor type, and patient age, performance status, and comorbidities. In general, regimen-related toxicity and nonrelapse mortality are lower than that of historical or concurrent control participants receiving MAC regimens in these nonrandomized comparisons.[31] This is remarkable considering the older age and higher prevalence of comorbidities in patients receiving RIC transplants. Of concern, however, has been an increased rate of relapse in patients receiving RIC regimens in some comparisons, resulting in similar overall survival. This finding depends on the RIC regimen, and patient and disease characteristics. Randomized trials comparing MAC versus RIC regimens to date have included primarily patients with AML or myelodysplastic syndrome (MDS). Results have been mixed with nonrelapse mortality, relapse and overall survival, most likely due to the heterogeneity of patient populations (eg, age, diagnosis, cytogenetic risk) and regimens used.[31] The BMT CTN conducted a large randomized trial comparing RIC versus MAC in patients with high-risk AML or MDS, and long-term follow-up results have been reported.[41] Eligibility criteria included age less than or equal to 65, disease in complete remission and minimal comorbidities. This trial was halted early because a significantly lower relapse rate in the MAC arm of the study was observed. With a longer follow-up, patients who received MAC had significantly longer overall survival at 4 years versus the RIC recipients; the survival benefit was primarily observed in AML patients. Patients who received MAC had higher treatment-related mortality, but this was offset by the significantly lower relapse rate.[41] The investigators concluded that the results support the use of MAC for patients who are less than 60 years of age with high-risk AML or MDS.[41]

Posttransplant Therapy

Relapse of primary disease remains the most common cause of death for both allogeneic and autologous HCT patients. As a result, much research has been directed at both preventing and treating posttransplant relapse or progression of disease.[42–44] Posttransplant therapy can be categorized either as “maintenance (or consolidation) therapy” or “salvage therapy.” Maintenance/consolidation therapy is used to prevent relapse, whereas salvage therapy is given to treat active relapse. Methods to identify relapsed disease for many hematologic malignancies have become quite sensitive, and disease can often be detected at the molecular level (ie, minimal residual disease) and used to direct posttransplant therapy. Several posttransplant therapies have been evaluated both in the maintenance and salvage settings, including immunotherapy, conventional chemotherapy, and targeted therapy. The ideal posttransplant therapy should be clinically effective, well-tolerated, and should not worsen other recognized posttransplant complications such as cytopenias, infections, or GVHD.[44] Relapse after autologous transplant can often be treated with standard doses of chemotherapy, a second autologous transplant, chimeric antigen receptor (CAR) T-cell therapy, or an allogeneic transplant, depending on the diagnosis, disease status, side effects, response, and duration of response to the first transplant. Treatment options for most patients who relapse after allogeneic HCT are more limited, and the prognosis is generally poor. Disease-specific chemotherapy and immunotherapy can be considered for some patients. A second allogeneic HCT may be considered but is associated with a mortality rate of up to 45%.[43]

Immunotherapy

The rationale for posttransplant immunotherapy after allogeneic HCT is based on the GVM effect. To take advantage of the GVM effect in patients who relapse after allogeneic HCT, immunosuppressive therapy being used for GVHD is withdrawn as quickly as possible without inducing a serious GVHD flare. In rare cases, this is enough to reinduce a remission, but further therapy is usually required. This is not a viable option in patients with active GVHD.

A commonly used form of posttransplant immunotherapy is donor lymphocyte infusion (DLI).[45] Lymphocytes are collected from the same donor who provided hematopoietic stem cells for the original allogeneic transplant, thus limiting this option to patients with available donors. They can be given as therapeutic (given in the relapse setting), preemptive (given if minimal disease is detected following HCT), or prophylactic (given in patients at high-risk for relapse) therapy, although the role of the latter two remains unclear. Response to DLI is disease specific and is more effective with lower malignancy burden; in lymphoid malignancies, better results are seen in indolent lymphomas compared to aggressive lymphomas, myeloid malignancies have shown intermediate results.[45] More than 80% of patients with CML who are in cytogenetic or molecular relapse respond to DLI. The response rate of patients in more advanced phases is about 15% to 30%. Although the time-to-response is delayed (median, 3-4 months), patients often have a durable molecular remission to DLI. Response rates to DLI of patients with AML and MDS are generally lower (15%-30%) than the rates of patients with CML. Posttransplant DLI has little benefit in patients with relapsed ALL, which may be related to the rapid proliferation of acute leukemia during the often prolonged time-to-response after DLI. Patients with relapsed AML after HCT are more likely to achieve a complete response to DLI if they had a longer remission period after transplant and have some GVHD after the DLI; low tumor burden, remission at the time of DLI, and good-risk cytogenetics have also been shown to be favorable characteristics. Administration of induction chemotherapy or therapeutic agents such as 5-

azacitidine before DLI administration may improve the antitumor activity of DLI in patients with AML or other rapidly proliferating malignancies.[45]

The most serious complications of DLI are pancytopenia and GVHD, and DLI is not usually given to patients with active GVHD. The cytopenias generally are transient and can be treated with hematopoietic growth factors. Some patients may have a more prolonged course of aplasia with the associated risk of infection, bleeding, and anemia, and these patients may benefit from another infusion of donor hematopoietic stem cells.

Chimeric antigen receptor (CAR) T-cell therapy is another option in patients with lymphoid malignancies, such as non-Hodgkin lymphoma, B-cell lineage ALL, or multiple myeloma, who relapse after HCT. The use of these therapies is discussed in the respective disease-specific chapters.

Monoclonal Antibodies

Although rituximab is a mainstay in the treatment of non-Hodgkin lymphomas, its use as maintenance therapy in the posttransplant setting for these patients has not been associated with a consistent benefit. Routine use of rituximab maintenance is not recommended in diffuse large B-cell lymphoma, but it is recommended for high-risk follicular lymphoma and mantle cell lymphoma.[42] Rituximab may be useful in combination with other active agents for salvage therapy of posttransplant relapse.

Brentuximab vedotin (anti-CD30 antibody conjugated to monomethyl auristatin E, a microtubule-disrupting agent) was evaluated as maintenance therapy in a randomized placebo-controlled study in patients with Hodgkin lymphoma after autologous HCT.[42,46] Progression-free survival at 5 years was significantly improved in patients randomized to brentuximab. Consistent benefit was seen across all subgroups that were analyzed, but the benefit of brentuximab was more pronounced in patients at higher risk for relapse. The most frequent adverse drug reactions in the brentuximab group were peripheral sensory neuropathy and neutropenia. These results led to the FDA approval of brentuximab administration after autologous HCT and has been increasingly adopted into clinical practice. Other monoclonal antibody agents being evaluated for use as maintenance therapy after HCT in Hodgkin lymphoma are the anti-programmed cell death-1 (anti-PD-1) checkpoint inhibitors, pembrolizumab, and nivolumab.[42]

Chemotherapy or Targeted Therapy

Tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, and nilotinib, are used to prevent and treat relapse after allogeneic HCT in patients with CML and Philadelphia chromosome–positive (Ph+) ALL.[42,47] In patients with CML who experience hematologic relapse (presence of leukemic blasts in blood or bone marrow) after allogeneic HCT, imatinib can induce complete hematologic responses (disappearance of leukemic blasts) and complete cytogenetic responses (disappearance of cytogenetic markers of disease) in most patients. Similar outcomes in patients with Ph+ ALL have been reported. TKIs may be given soon after transplant to prevent relapse.[42,47] Patients with Ph+ ALL and CML without evidence of disease after transplant who are treated with TKIs to prevent relapse appear to have sustained cytogenetic remissions (without evidence of cytogenetic markers of disease). TKIs are generally well tolerated after transplant. Commonly reported adverse drug reactions include neutropenia, thrombocytopenia, liver function abnormalities, edema, and muscle pain, which may require dosage reductions or discontinuation. Large comparative studies will be required to define the benefit of TKIs after transplant and the optimal dosing, timing, and duration of therapy.

Several agents designed to target specific pathways in AML are also being evaluated for posttransplant maintenance. One such target is the tyrosine kinase FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD).[42,48] AML patients positive for FLT3-ITD mutations have been found to have shorter remission times and higher relapse rates than those without these mutations. FLT3 inhibitors, tyrosine kinase inhibitors (TKIs), have been evaluated in several different studies in the setting of posttransplant maintenance.[42,48] First-generation TKIs include sorafenib and midostaurin. Based on a nonrandomized comparison, the Acute Leukemia Working Party of the European Bone Marrow Transplantation (EBMT) Association recommends sorafenib as maintenance therapy after allogeneic HCT.[48] Midostaurin, gilteritinib, and quizartinib are also being evaluated, especially in the setting of minimal residual disease post HCT.[42,44]

Based on their activity in AML and MDS, hypomethylating agents (HMAs) such as 5-azacitidine and decitabine have been evaluated in the posttransplant setting to prevent relapse in these populations but with mixed results.[42,44] Additional studies are ongoing to determine the role of these agents as post-HCT maintenance therapies.

Posttransplant therapy is also being evaluated in patients with multiple myeloma. Lenalidomide has been shown to prolong progression-free survival compared with patients receiving placebo and is now considered standard of care unless contraindicated.[42,49] Unfortunately, a small but significant

increased risk of second primary cancers has been reported in the lenalidomide-treated patients. Patients should be informed of this potential safety issue when treatment with lenalidomide after autologous HCT is considered. Bortezomib, a proteasome inhibitor delivered either intravenously or subcutaneously, can be considered for maintenance therapy after autologous HCT. Although some studies suggest bortezomib increases progression-free survival, no prospective randomized trials have been conducted. Its use should be reserved for patients with poor tolerance to lenalidomide, renal insufficiency, high-risk cytogenetics, or history of other cancers.[42] Another proteasome inhibitor, the oral agent ixazomib, has also been reported to improve progression-free survival when used as a post-HCT maintenance therapy.[42] Other agents currently being explored include carfilzomib, daratumumab, and elotuzumab.

TRANSPLANT-RELATED COMPLICATIONS

Although many patients with cancer treated with high-dose chemotherapy and autologous or allogeneic HCT experience long-term survival and cure of their disease, this modality is associated with many serious and potentially life-threatening complications. Despite the availability of improved broad-spectrum anti-infective agents, immunosuppressive drugs, and hematopoietic growth factors, the transplant-related mortality rate after allogeneic HCT with HLA-matched sibling and unrelated donors is 20% to 30%. The mortality rate is generally lower with RIC regimens and higher when alternative donors are used. Causes of nonrelapse mortality include regimen-related toxicity, infection, GVHD, or immunosuppression. The risk of transplant-related mortality after autologous HCT generally is less than 5%, depending on the patient population and conditioning regimen. The mortality rate is lower with autologous transplants because of the lack of GVHD and associated complications of immunosuppression. Transplant-related mortality in autologous HCT usually is caused by regimen-related toxicity or infection.

Table e163-1 lists the dose-limiting nonhematologic toxicities for several drugs that are commonly included in MAC regimens. These toxicities may be uncommon or rare with the administration of conventional doses of specific drugs. When these agents are given in high doses, the toxicities seen with conventional doses (eg, mucositis, enteritis, nausea, vomiting, and hematuria) can be more frequent or severe. Several unusual and severe manifestations of HCT regimen-related toxicities are discussed in this section.

Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), formerly known as hepatic venoocclusive disease (VOD), occurs as a result of chemotherapy-induced damage to the sinusoidal endothelial cells of the liver, which leads to release of proinflammatory cytokines and further damage to the endothelium. Gaps develop between the endothelial cells, which allow cellular debris to accumulate and cause the sinusoids to narrow and eventually become occluded. In addition, injury to the endothelial cells produces fibrin deposition and clot formation, further narrowing the sinusoids.[50,51] These histologic changes can lead to obstruction of sinusoidal flow, reduced hepatic venous outflow, portal hypertension, and hepatic failure. Clinical signs of SOS include fluid retention (resulting in sudden weight gain and ascites), hepatomegaly (sometimes painful), and hyperbilirubinemia or jaundice. The diagnosis of SOS is based on the revised EBMT criteria which considers the presentation of symptoms and length of time from transplant.[51] SOS occurs within the first 3 weeks after transplant in “classical SOS” or later than 3 weeks in “late-onset SOS,” and the incidence of SOS ranges from 5% to 20% in most published series. Severe SOS is fatal in 50% to 75% of cases. Factors reported to increase the risk of SOS include use of TBI-containing conditioning regimens (dose-dependent), use of sirolimus for the prevention of GVHD, increased systemic exposure to busulfan, oral administration of busulfan, individual variability in cyclophosphamide metabolism, chronic viral hepatitis, and elevated liver function test results before transplant. Pretransplant exposure to either gemtuzumab ozogamicin or inotuzumab ozogamicin have been implicated in the development of SOS in patients undergoing allogeneic HCT, especially when given within a few months of transplant.[50,51]

Ursodiol is the only agent that can reduce the risk of SOS in patients undergoing MAC allogeneic transplants and reduce the risk of transplant-related mortality and GVHD.[51] Defibrotide, a polydisperse oligonucleotide with fibrinolytic properties, can be considered for SOS prophylaxis in patients at high risk of SOS.[51] However, data supporting this approach is conflicting. In a prospective randomized phase 3 study of defibrotide prophylaxis compared to controls in a pediatric population, SOS incidence was reduced in the treatment arm.[52] However, in a more recent randomized multicenter, phase 3 trial including a more heterogenous population of adults and pediatric HCT recipients, there was no benefit to using defibrotide prophylactically as compared with best supportive care.[53]

Treatment of SOS is generally supportive, including fluid and electrolyte management, platelet transfusions, paracentesis, and pain management.[51] Hepato- and nephrotoxic drugs should be avoided. Mild-to-moderate disease generally resolves without specific therapy. Defibrotide was FDA-

approved based on prospective clinical trials in patients with SOS with advanced multi-organ dysfunction that showed improved response rates and lower mortality as compared with historical controls.[54] Adverse effects were not distinguishable from those commonly reported in this patient population. Post-hoc analysis showed that earlier initiation of defibrotide treatment was associated with significantly higher posttransplant day 100 survival rates.[55] Future research should focus on identification of biomarkers that predict SOS onset.

Pulmonary Complications

Pulmonary complications after HCT can be categorized as infectious and noninfectious (see Chapter e48). Noninfectious complications can be caused by direct damage to the pulmonary tissue by chemotherapy or radiation used in the conditioning regimen, immune effects of the graft, or other causes not clearly understood. Early complications include diffuse alveolar hemorrhage, periengraftment respiratory distress syndrome, and idiopathic interstitial pneumonitis.[56] Diffuse alveolar hemorrhage is characterized by dyspnea, hypoxia, dry cough, and fever; chest radiography usually shows diffuse infiltrates in an alveolar pattern. It occurs in 5% to 12% of HCT patients with mortality rates reported as high as 60% to 100%. Diffuse alveolar hemorrhage is diagnosed by examination of bronchoalveolar lavage fluid via bronchoscopy, which reveals progressively bloodier fluid with each instilled aliquot and negative findings on microbiologic analysis. Although the condition can be life-threatening or fatal, prompt treatment with high doses of corticosteroids (methylprednisolone 500-1,000 mg daily for five days) is sometimes beneficial.[56]

Periengraftment respiratory distress syndrome is characterized by fever, erythrodermatous skin rash, and noncardiogenic pulmonary edema and can occur during neutrophil recovery after HCT.[56] The incidence of engraftment syndrome is not known because of the lack of uniform diagnostic criteria, although some series report that 5% to 10% of patients who receive autologous HCT develop the syndrome. This syndrome can progress to life-threatening respiratory failure with or without multiple organ failure. Treatment consists of methylprednisolone 1 to 2 mg/kg/day for 3 days, followed by a rapid taper.

Idiopathic interstitial pneumonitis (also called idiopathic pneumonia syndrome) is defined as widespread alveolar injury in the absence of active lower respiratory tract infection, cardiac or renal dysfunction, or iatrogenic-induced circulatory overload after HCT.[56] Patients with idiopathic interstitial pneumonitis are clinically indistinguishable from patients with interstitial pneumonitis related to infection. Idiopathic interstitial pneumonitis is postulated to have a multifactorial etiology, including toxic effects of MAC regimens, immunologic cell-mediated injury, inflammatory cytokine-induced lung damage, and occult pulmonary infections. The risk is similar in recipients of autologous or allogeneic HCT but appears to be higher in patients who are conditioned with a TBI-containing regimen or who have acute GVHD. A mortality rate as high as 80% has been reported, and treatment consists of supportive care and broad-spectrum antimicrobial therapy; the efficacy of corticosteroids has not been consistently reported.

Late pulmonary complications cover a wide spectrum of disorders and include both obstructive and restrictive lung diseases.[56,57] The most common disorders are cryptogenic organizing pneumonia (COP; previously known as bronchiolitis obliterans with organizing pneumonia [BOOP]) and bronchiolitis obliterans syndrome (BOS). COP is an interstitial and airspace disease with symptoms that mimic classic pneumonia, but biopsy reveals chronic alveolar inflammation and extensive granulation of the alveolar ducts and small airways.[56] COP is generally responsive to prednisone 1 mg/kg/day with an extended taper over several months. BOS is thought to result from chronic GVHD affecting the lungs and is generally irreversible with mortality rates as high as 40%.[56,57] Therapy consists of oral corticosteroids, which are about 50% effective, often in combination with the triple-therapy inhaled fluticasone, azithromycin, and montelukast (FAM). Extracorporeal photopheresis, belumosudil, and ruxolitinib may also provide benefit.[56–59]

Graft Failure

Initial engraftment of hematopoietic cells after MAC regimens usually occurs in the first 2 to 4 weeks after transplant. Engraftment is evidenced by rising peripheral blood counts and the presence of hematopoietic precursor cells in the marrow; it is defined as an absolute neutrophil count of greater than 500 cells/mm^3 (0.5×10^9/L) and a platelet count of greater than 20,000 cells/mm^3 (20×10^9/L) on the first day of 7 consecutive days without a platelet transfusion. In allogeneic HCT, the presence of donor cells (ie, chimerism) is confirmed by PCR-based analysis of polymorphic DNA sequences of cells from the bone marrow and peripheral T cells. Full chimerism is defined as greater than 95% of cells of donor origin. In most patients, engraftment is sustained with complete recovery of hematopoiesis.[39]

However, graft failure (loss of bone marrow function with resulting loss in peripheral blood counts) can occur after both allogeneic and autologous

HCT.[60,61] It can be the result of heavy pretreatment with chemotherapy or radiation therapy (or both); infusion of insufficient numbers of hematopoietic stem cells; viral infection; recurrence of primary hematologic malignancy; drug reaction (eg, ganciclovir); development of a secondary myelodysplasia; or in the allogeneic setting, an immunologic reaction between the donor and recipient caused by inadequate immunosuppression of the recipient (ie, graft rejection). Two syndromes have been observed. Whereas early graft failure occurs when the rate of hematopoietic recovery is delayed greater than 28 days after transplant (later after UCBT) or does not occur at all (primary graft failure or delayed engraftment), late graft failure is characterized by a decline in peripheral blood counts after initial engraftment (secondary graft failure).[39] With widespread use of PBSCs and posttransplant growth factors, primary graft failure is rare after autologous and HLA-matched allogeneic HCT but is not uncommon after UCBT. Graft failure that occurs after allogeneic HCT, characterized by regrowth of immunocompetent recipient cells and a simultaneous loss of donor cells, is referred to as *graft rejection*. Graft rejection occurs rarely after HLA-matched allogeneic HCT. An increased risk of graft rejection has been observed in recipients of hematopoietic stem cells from HLA-mismatched donors, recipients of T cell–depleted marrow, and patients with severe aplastic anemia or other nonmalignant disorders. In a large retrospective analysis of over 20,000 patients undergoing myeloablative allogeneic HCT, the incidence of primary graft failure was 5.5%.[61] In this analysis, risk factors for primary graft failure included bone marrow (vs peripheral blood) grafts, RIC regimens, diagnosis of a myeloproliferative disorder, HLA-mismatched transplants, ABO incompatibility, and BuCy conditioning (compared with other MAC regimens).

The long-term prognosis of patients with persistent graft failure is poor. Despite supportive care and treatment with hematopoietic growth factors, death may result from infection or bleeding. In some patients with an allogeneic donor, a second infusion of stem cells can be attempted. While this can be a viable alternative for some patients, many are not physically able to undergo a second transplant. Of those that do, nonrelapse mortality is high, despite the use of NMA regimens.[60] Hematopoietic growth factors usually are given after transplant to patients who receive autologous HCT, based on several benefits associated with their use including fewer antibiotic days and decreased length of stay. Decreasing resource utilization after transplant (total antibiotic days and length of stay) can help justify the cost of growth factors in this patient population. Growth factors can be initiated the day of, the day after, or as late as 7 days after the infusion of stem cells and are continued until neutrophil recovery to greater than an arbitrary number of neutrophils (500-1,000 cells/mm^3 [0.5 − 1.0 × 10^9/L]). Pegfilgrastim appears to be equally efficacious to G-CSF in this setting.

Hematopoietic growth factors also accelerate the rate of neutrophil recovery in patients undergoing allogeneic HCT. However, G-CSF has not been shown to reduce infection rates, antibiotic days or length of stay in this population. The decision to use G-CSF preemptively may be reserved for patients who are at risk for delayed neutrophil recovery (eg, UCBT or those receiving PTCy). If allogeneic HCT patients develop graft failure, G-CSF can be given based on data that supports its use in this situation.[60]

Results of studies to improve platelet recovery posttransplant with thrombopoietin and interleukin-11 (IL-11) have been disappointing. Several case studies and case series have described the use of eltrombopag, an oral thrombopoietin receptor agonist, in allogeneic HCT patients with persistent thrombocytopenia posttransplant.[60] Although additional data are needed, the response rates have been promising. Platelet transfusions remain the standard of care in patients with thrombocytopenia below a given threshold (eg, 10,000 cells/mm^3 [10 × 10^9/L]) and in patients with significant bleeding.

Anemia may be problematic in the posttransplant setting, especially in patients receiving allogeneic HCT. The etiology is unclear and most likely is multifactorial. Although erythropoiesis-stimulating agents may reduce the need for red blood cell transfusions, its use in cancer patients is associated with an increased risk of adverse events and is limited by FDA warnings and restrictions.

Graft-Versus-Host Disease

GVHD is caused by immunocompetent allogeneic donor T cells reacting against recipient/host antigens on the surface of antigen-presenting cells (APCs). In that setting, donor T cells recognize unmatched major or minor histocompatibility antigens of the host as genetically foreign, become activated, proliferate, and attack recipient tissue, thereby producing the clinical syndrome of GVHD.

Two different clinical syndromes of GVHD (acute and chronic) are recognized, each with two subcategories. Classic acute GVHD occurs within 100 days after transplant or DLI while persistent, recurrent or late-onset acute GVHD occurs beyond 100 days after transplant, withdrawal of immunosuppression or DLI.[62] Both subcategories of acute GVHD occur in the absence of chronic GVHD. Classic chronic GVHD usually occurs after day 100, with only clinical manifestations that can be attributed to chronic GVHD. Chronic GVHD may occur after the resolution of acute GVHD or de novo (no prior acute GVHD). Acute and chronic overlap syndrome is a newly defined entity in which features of both acute and chronic GVHD appear

together. Chronic GVHD usually develops before the resolution of acute GVHD (also called progressive onset). The clinical manifestations of GVHD are distinct. Whereas acute GVHD usually is limited to the gastrointestinal tract, skin, and liver, signs and symptoms of chronic GVHD resemble an autoimmune disorder and can affect many organ systems.

A “hyperacute” form of GVHD may occur in patients with multiple HLA mismatches and in patients who receive T cell–replete transplants without adequate GVHD prophylaxis, especially after MAC regimens.[62] Descriptions of hyperacute GVHD vary but usually include fever, generalized erythroderma, desquamation, and edema. More severe forms with accompanying organ failure have been seen in haploidentical donors. Hyperacute GVHD typically occurs about 1 week after transplant before engraftment of neutrophils. The response rate to first-line therapy appears to be lower in patients with hyperacute GVHD compared with patients who develop GVHD later after transplant, but no difference in survival has been observed.

Acute Graft-Versus-Host Disease

The pathophysiology of acute GVHD is a complex inflammatory cascade of innate immune cells (such as neutrophils, macrophages, and monocytes), cytokines, and chemokines.[63,64] The conditioning regimen damages gastrointestinal tissue, weakening the cellular barriers and destroying cells. This permits bacterial translocation from the intestinal lumen into circulation. Invading bacteria release molecules such as lipopolysaccharide, which stimulate neutrophil, monocytes, and dendritic cells. Simultaneously, damaged gastrointestinal cells release additional substances which further enhance inflammation. When the innate immune cells arrive to the site of damage, they act to kill the bacteria by releasing reactive oxygen species (ROS), which adds further damage to recipient GI tissue. Neutrophils and both donor and recipient dendritic cells, also called APCs, activate donor T cells.

Damage to the intestinal mucosa stimulates the secretion of inflammatory cytokines such as IL-1, IL-6 and tumor necrosis factor-α (TNF-α). These cytokines upregulate MHC gene products and host APCs. Activated donor T cells also secrete cytokines such as IL-2 and interferon-γ, contributing to the recruitment of macrophages and alteration of target cells in the gastrointestinal tract and skin so that they are more susceptible to damage. Multiple cytotoxic effector cells (T cells and macrophages) are generated and contribute to target tissue injury by secreting more inflammatory cytokines that cause target cell apoptosis. The term “cytokine storm” is sometimes used to describe the critical role of inflammatory cytokines in this process.

Three general approaches have been used to prevent GVHD in humans. The first is to reduce host tissue damage with the use of RIC regimens. The second and most widely used approach is to modulate donor T cells by reducing T-cell numbers (T-cell depletion), activation (most immunosuppressive agents), or proliferation (antiproliferative agents). The third approach is to block inflammatory stimulation and effectors (eg, TNF-α inhibition, IL-1 receptor blockade).

The principal target organs in acute GVHD are the skin, liver, and gastrointestinal tract.[62] Acute GVHD is classified into four grades, depending on the number of organs involved and the degree of involvement of each organ. Diagnostic criteria from the Mount Sinai Acute GVHD International Consortium (MAGIC) group are outlined in Table e163-2.[65] Grade I disease involves only the skin. Grades II through IV involve the skin and the liver, gastrointestinal tract, or both. Acute skin GVHD usually is manifested as a generalized maculopapular rash that initially involves the face, ears, palms, soles, and upper trunk. The skin rash can spread to the rest of the body and, if untreated or refractory to treatment, will progress to bullae formation and desquamation similar to a burn injury. Gastrointestinal GVHD presents as secretory diarrhea but may progress to abdominal pain or cramping and ileus; hemorrhage may also occur. GVHD of the upper intestinal tract appears as persistent nausea, vomiting, anorexia, and dyspepsia. The diagnosis of gastrointestinal GVHD should be made by biopsy of the intestinal tract (stomach, duodenum, or rectum). Hepatic GVHD usually is asymptomatic, consisting of hyperbilirubinemia and elevated alkaline phosphatase levels; increases in serum transaminases occur less consistently. The diagnosis can be made by biopsy, if possible. Electronic tools or algorithm-driven mobile applications (Apps), such as the ASTCT Practice Guidelines Mobile App, can be easily and freely downloaded on mobile devices to aid in a more accurate assessment and grading of acute GVHD.

TABLE e163-2

Consensus Grading of Acute Graft-Versus-Host Disease

Organ/Extent of Involvement			
	Skin	**Liver**	**Intestinal Tract**
Stage			
1	Rash on <25% of skin[a]	Bilirubin 2-3 mg/dL (34.2-51.3 µmol/L)[b]	Diarrhea >500-999 mL/day[c] or 3-4 episodes/day; persistent anorexia, nausea, or vomiting[d]
2	Rash on 25%-50% of skin	Bilirubin 3.1-6 mg/dL (51.3-102.6 µmol/L)	Diarrhea >1,000-1,500 mL/day or 5-7 episodes/day
3	Rash on >50% of skin	Bilirubin 6.1-15 mg/dL (102.6-256.5 µmol/L)	Diarrhea >1,500 mL/day or >7 episodes/day
4	Generalized erythroderma with bulla formation and desquamation (5% of body surface area)	Bilirubin >15 mg/dL (256.5 µmol/L)	Severe abdominal pain with or without ileus or grossly bloody stools (regardless of stool volume)
Grade			
0	None	None	None
I	Stage 1-2	None	None
II	Stage 3	and/or Stage 1	and/or Stage 1
III[e]	—	Stage 2-3	and/or Stage 2-3
IV[f]	Stage 4	or Stage 4	or Stage 4

[a]Use the "rule of nines" to determine body surface area involvement.

[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.

[d]Persistent nausea with histologic evidence of graft-versus-host disease in the stomach or duodenum.

[e]Grade 0-3 skin may also be present but overall grade driven by liver or GI involvement.

[f]Grade IV may include lesser organ involvement but with extreme decrease in performance status.

Data from Reference 65.

The overall incidence of moderate-to-severe (grades II-IV) acute GVHD varies widely depending on patient- and transplant-related characteristics. The incidence of GVHD is related to the degree of histocompatibility, number of T cells in the graft, donor and recipient age and gender, intensity of the conditioning regimen, source of hematopoietic cells (bone marrow versus peripheral blood), and prophylactic regimen. The most severe acute GVHD is

observed in allogeneic HCT with non-HLA-identical donors. In this setting, the incidence of grades II to IV acute GVHD can exceed 50% despite aggressive GVHD prophylaxis. Severe acute GVHD is a major cause of mortality, and the risk of death increases as the grade of GVHD increases. This risk is further increased if initial therapy is not effective.

Multiorgan acute GVHD and the drugs given to prevent or treat the disease are associated with delayed immunologic recovery and increased susceptibility to infections. Infection is often the primary cause of death in patients with GVHD. Patients with GVHD treated with an immunosuppressive regimen should receive prophylactic antiviral, antibacterial, and antifungal therapies and be monitored routinely for the occurrence of these infections.

As outcomes from acute GVHD can be potentially life-threatening, identifying which patients will have poor outcomes would be beneficial. This has led to an interest in identifying GVHD biomarkers, defined by the Food and Drug Administration (FDA) as "an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions." In this setting, biomarkers for acute GVHD are now designated as one of four types: diagnostic (identifies acute GVHD at early onset; distinguishes it from similar disease presentations), prognostic (determines risk and severity of acute GVHD), predictive (provides insight into how a patient may respond to a specific therapy), or response to treatment (helps to monitor response once therapy has been started).[66] While several biomarkers have been discovered and continue to be studied, two have been successfully tested and validated in several studies: stimulation 2 (ST2) and regenerating islet-derived 3-alpha (REG3α). Either can be used individually or together; both fall under all four biomarker subtypes. Presence or absence of these markers can be used to guide or support the care of acute GVHD in transplant recipients.

Prevention of Acute Graft-Versus-Host Disease

9 Because treatment of established acute GVHD often is unsatisfactory, aggressive preventive measures usually are taken. The most common strategy used to prevent acute GVHD is to block the activation of T cells by administration of immunosuppressive agents.[63,64] Several immunosuppressive agents have been used, including methotrexate (MTX), cyclosporine (CSA), tacrolimus (TAC), sirolimus, mycophenolate mofetil (MMF), PTCy, ATG, abatacept, corticosteroids, and monoclonal antibodies directed at T cells. Table e163-3 shows the doses, toxicities, and monitoring of immunosuppressive agents used to prevent or treat GVHD.[67–74] Most GVHD prophylaxis regimens combine immunosuppressive agents that affect different stages of T-cell activation. The most commonly used GVHD prophylaxis regimens are CSA or TAC with MTX; both combinations are considered equivalent. Another strategy is removing or depleting most T cells from donor bone marrow ex vivo before transplant by physical separation or by treatment with monoclonal antibodies directed at T cells.

TABLE e163-3

Immunosuppression for the Prevention and Treatment of GVHD

Agent	Dose	Drug Monitoring
Prevention		
Tacrolimus (TAC)[67]	0.02-0.03 mg/kg/day (IBW) IV beginning 1-3 days before transplant; change to PO when able to tolerate	Check blood levels ~72 hours after start and then 2-3 times/week until stable (trough blood levels, 5-15 μg/L [6.2-18.6 nmol/L]); serum creatinine for renal toxicity; CBC for hematologic toxicity; CMP, CBC, haptoglobin for TMA; blood pressure for hypertension; BMP for electrolyte abnormalities
Cyclosporine (CSA)[67]	3-5 mg/kg/day (IBW) IV beginning 1-3 days before transplant; change to PO when able to tolerate	Check blood levels ~72 hours after start and then 2-3 times/week until stable (trough blood levels, 150-450 mcg/L [125-374 nmol/L]); serum creatinine for renal toxicity; CBC for hematologic toxicity; CMP, CBC, haptoglobin for TMA; blood pressure for hypertension; BMP for electrolyte abnormalities
Sirolimus[68]	Loading dose 12 mg PO on day +1 followed by 4 mg	Check serum levels ~24 hours after start and then 2-3 times/week until stable (trough serum levels, 3-12 ng/mL [3-13 nmol/L]); serum creatinine for renal toxicity; CBC for hematologic toxicity;

	PO daily starting on day +2	LFTs for liver toxicity
Methotrexate (MTX)[67,68]	15 mg/m^2 IV on day +1 followed by 10 mg/m^2 IV on days +3, 6, and 11 or 5 mg/m^2 IV on days +1, 3, 6, and 11	Monitor for toxicity: mucositis; LFTs for hepatic dysfunction; serum creatinine for renal impairment; fluid retention; and CBC for hematologic toxicity; methotrexate levels are not routinely monitored unless the patient develops renal dysfunction or third spacing; doses may be omitted if severe mucositis or hepatotoxicity develops; leucovorin may be administered to reduce toxicity
Mycophenolate mofetil (MMF)[67,68]	15 mg/kg/dose IV twice daily (maximum dose, 3 g/day) beginning on day 0; change to PO when able to tolerate	Monitor for toxicity: CBC for neutropenia; severe GI symptoms may occur; therapeutic drug monitoring can be considered (more routine in pediatric population)
Cyclophosphamide (Cy)[68]	50 mg/kg/day (IBW) IV on days +3 and +4	Monitor for toxicity: BMP for renal impairment or SIADH; LFTs for hepatic toxicity (including SOS); urinalysis for hemorrhagic cystitis; vital signs and possible cardiac workup for pericarditis (only for symptomatic patients). Mesna must be administered around cyclophosphamide administration to prevent hemorrhagic cystitis
Rabbit ATG[68,69]	2.5-6 mg/kg/day IV beginning 3 days before transplant	Monitor for toxicity: infusion reactions, frequent vital signs during infusion, fever, rash, cardiovascular and GI dysfunction, anaphylaxis; serum sickness
Alemtuzumab[68]	10-20 mg/day IV daily beginning 4-5 days before transplant	Monitor for toxicity: fever, chills, infection, and anaphylaxis
Abatacept[68]	10 mg/kg/dose (ABW, maximum dose, 1 gram) IV on days −1, +5, +14, +28	Monitor for hypertension, fever, infections (CMV, EBV, other), CBC for hematologic cytopenias
Treatment		
Methylprednisolone[a,b] or Prednisone[a,b,18,70]	0.5-2 mg/kg/day	Monitor for toxicity: glucose for hyperglycemia, blood pressure for hypertension; labile mood; bone osteopenia, avascular bone necrosis; impaired wound healing; adrenal insufficiency
Ruxolitinib[b 18,71,72]	Acute GVHD: 5 mg PO BID with option to increase to 10 mg PO twice daily after 3 days in the absence of cytopenia Chronic GVHD: 10 mg PO BID	Monitor CBC for anemia, thrombocytopenia, and neutropenia; infections such as CMV

Mycophenolate mofetil (MMF)[18,70]	1.5-2 g PO daily in divided doses	As above
Sirolimus[18,70]	1-2 mg/day; then adjust based on levels	As above
Infliximab[18,73]	10 mg/kg/week for at least four doses (ABW)	Monitor for infections; anaphylaxis (rare)
Etanercept[18,73]	0.4 mg/kg/dose (maximum dose, 25 mg) SQ twice weekly for 8 weeks (ABW)	Monitor for infections; local injection site reactions; generally well tolerated
Rabbit ATG[18,70]	0.5 mg/kg for first dose followed by 1-1.5 mg/kg for subsequent doses	As above
Belumosudil[18,74]	200 mg PO daily	Monitor for upper respiratory infections; diarrhea, nausea; edema, hypertension; increased LFTs
Ibrutinib[c][18,75]	420 mg PO daily	Monitor for fatigue; diarrhea; bleeding, bruising

ABW, actual body weight; ATG, anti-thymocyte globulin; BID, twice daily; BMP, basic metabolic panel; CBC, complete blood count; CMP, complete metabolic panel; CMV, cytomegalovirus; EBV, Epstein-Barr Virus; ECP, extra-corporal photopheresis; GI, gastrointestinal; IBW, ideal body weight; IV, intravenous; LFT, liver function test; PO, orally; SC, subcutaneous; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy.

[a]Considered first-line therapy for both acute and chronic GVHD (initial dose varies per indication).

[b]Treatment for both acute and chronic GVHD.

[c]Treatment for only chronic GVHD.

The combination of a calcineurin inhibitor (either CSA or TAC) with MTX is considered the standard immunosuppressive regimen for the prevention of acute GVHD in a MAC regimen. PTCy in combination with TAC and MMF is the standard of care when using a RIC regimen.[94] Intravenous CSA or TAC is usually started a few days before or on the day of transplant. Patients are converted to oral formulations when they can be tolerated. CSA or TAC is usually given at full doses until days 50 to 100, gradually tapered in the absence of GVHD and discontinued by day 180. MTX is given IV on days 1, 3, 6, and 11 after transplant. Elimination of one or more MTX doses may be associated with an increased risk of GVHD. However, toxicities such as severe mucositis, delayed engraftment, hepatotoxicity, or the development of conditions that may prolong MTX systemic exposure (eg, renal failure or third spacing) are common reasons to omit the day 11 dose of MTX. For patients who have delayed MTX elimination or experience significant MTX toxicity, monitoring of MTX levels with leucovorin rescue may be warranted.

Despite standard prophylaxis with CSA or TAC and MTX, grade II to IV acute GVHD still occurs in 30% to 50% undergoing allogeneic HCT.[63] In search of less toxic agents and more effective combinations, other prophylactic regimens have been evaluated. Sirolimus, an mTOR inhibitor, has theoretical advantages when used as GVHD prophylaxis. This agent has been reported to promote immune tolerance through generation of regulatory T cells, has antiviral properties (CMV and Epstein-Barr virus), and has antitumor activity against some hematologic malignancies.[68] Several studies have shown encouraging results with sirolimus when combined with a calcineurin inhibitor (TAC or CSA) in the prevention of acute GVHD, and many clinicians believe that the combination of TAC and sirolimus is less toxic and more efficacious than CSA and sirolimus. A meta-analysis of sirolimus-based GVHD prophylaxis showed that when compared to TAC and either MTX or MMF, sirolimus-based regimens significantly decreased the incidence of grade II-IV acute GVHD (relative risk 0.65). However, the incidence of grade III to IV acute and chronic GVHD was similar, and no significant differences in event-free

or overall survival were observed. An analysis of the sirolimus toxicity showed a significantly higher risk of SOS.[76] Because of the association observed with SOS, sirolimus should not be used in patients who are at increased risk for SOS due to baseline characteristics or their HCT conditioning regimen.

Other MTX-sparing strategies have been evaluated for GVHD prophylaxis. Mycophenolate mofetil (MMF) through its metabolite, mycophenolic acid, inhibits lymphocyte proliferation and is synergistic with calcineurin inhibitors. MMF, combined with either CSA or TAC, is a reasonable alternative to MTX when toxicity is a concern, although anti-GVHD activity may be inferior. In recipients of UCBT, MMF is often used to prevent delayed engraftment associated with MTX.[67,70]

PTCy is another GVHD prophylaxis strategy used for acute GVHD prevention and is given either as a single agent, in combination with sirolimus, or in combination with two other agents (sirolimus or TAC, plus MMF).[68] Initially established in the setting of haplo-HCT, PTCy is now being used in matched related, unrelated, and mismatched unrelated HCTs.[77,78] Its immunosuppressive activity is related to its antiproliferative effects on rapidly dividing alloreactive T cells. Hematopoietic stem cells have high levels of aldehyde dehydrogenase, which spares them from the antiproliferative activity of cyclophosphamide. The use of PTCy, combined with other immunosuppressive agents such as MMF and a calcineurin inhibitor, is an effective immunosuppressive regimen. In a phase II multicenter trial (BMT CTN 1203), 273 patients undergoing allogeneic HCT with RIC were randomized to PTCy, TAC, and MMF and two other GVHD prophylaxis regimens; each of the three regimens was compared to a concurrent nonrandomized prospective cohort of 224 patients receiving standard GVHD prophylaxis with TAC and MTX.[79] When compared to the control group, the PTCy combination had a higher 1-year GVHD-free, relapse-free survival (primary endpoint) and lower risk of grade III-IV acute GVHD and chronic GVHD requiring intervention. Disease relapse and survival rates were similar.[79] Given the positive results shown with the PTCy combination, a multicenter phase III trial i (BMT CTN 1703) was recently conducted validating the benefit with this triple therapy over the historic standard in patients undergoing a matched-related, matched-unreleated, or mismatched unrelated donor RIC transplant.[95] GVHD-free, relapse-free survival at 1 year was found to be superior in the PTCy-treatment arm at 52.7% compared with 34.9% in the standard arm. Overall survival, relapse, and other endpoints were similar between both arms.

Abatacept, a recombinant fusion protein that blocks the costimulatory CD28-CD80/86 interaction and inhibits T cell proliferation, is the first FDA-approved agent for the prevention of GVHD. FDA approval was based on a phase II trial in which patients were placed into one of two strata based on whether they were recipients of HLA-matched or mismatched unrelated donor HCT.[80] Patients undergoing matched unrelated donor HCT were randomized to receive standard GVHD prophylaxis (calcineurin inhibitor and MTX) with abatacept or placebo. Patients undergoing HLA-mismatched unrelated donor HCT received a calcineurin inhibitor, MTX, and abatacept and were compared to a CIBMTR control group of patients who received standard GVHD prophylaxis with a calcineurin inhibitor and MTX. In patients undergoing HLA-matched related donor HCT, the incidence of grades III and IV acute GVHD was lower in the patients receiving the abatacept combination, but the difference was not statistically significant. However, the risk of grades III and IV acute GVHD was significantly lower in patients undergoing HLA-mismatched unrelated donor HCT. No significant difference in the risk of chronic GVHD between groups was observed with either strata.[80] Other agents such as bortezomib and tocilizumab have been studied in GVHD prevention, but only limited efficacy has been observed and their use is not recommended outside of a clinical trial.[68]

Another strategy to prevent acute GVHD is to reduce the number of donor T cells in the stem cell donation. In vivo T-cell depletion may be incorporated into conditioning regimens with agents such as ATG. Results from randomized trials show that ATG decreases the incidence of chronic GVHD without increasing the risk of relapse or nonrelapse mortality; a reduction in acute GVHD was not consistently reported.[68,69] Results from these trials are difficult to compare due to the heterogeneity in ATG products, dosage and schedule, donor, conditioning, and other agents used for GVHD prophylaxis. Most of these studies were unable to demonstrate significant differences in overall survival, despite the lower incidence of chronic GVHD.[68] Based on the results of these studies, the EBMT suggest that rabbit ATG should be used in patients undergoing matched unrelated donor HCT and in patients undergoing matched related donor HCT who are at high risk for GVHD.[70] These recommendations have not been widely adopted in the United States.

Treatment of Acute Graft-Versus-Host Disease

10 Patients with mild skin-only acute GVHD (grade I) can be treated with topical corticosteroid preparations and counseled on the appropriate use of sunscreen. If a patient develops grades II to IV GVHD, prophylactic agents are continued, and single agent, high-dose corticosteroids in the form of IV methylprednisolone or oral prednisone are given.[18,70,73,81] The usual dosage is 0.5 to 2 mg/kg/day given in two divided doses; higher dosages have not

been shown to be more efficacious. About 25% to 40% of patients with established acute GVHD respond to high-dose corticosteroids. If the patient responds, the corticosteroid dose is tapered gradually, depending on response. In patients who experience a flare in GVHD during the taper phase, therapy consists of increasing the corticosteroid dose and then tapering more slowly. Steroid-sparing options such as sirolimus have also been evaluated and may provide an effective steroid-free therapy in select patients with lower risk acute GVHD (defined by biomarker assessment).[73] Oral beclomethasone dipropionate, a topically active corticosteroid, has been shown to reduce the frequency of gastrointestinal GVHD relapses when continued after prednisone taper.[70,82] Administration of beclomethasone has been associated with improved survival at 200 days and 1 year after transplant. Budesonide, another nonabsorbable corticosteroid, has also been evaluated in uncontrolled studies and may also reduce the need for sustained use of high-dose systemic corticosteroid administration.[70,82]

GVHD-associated mortality is strongly correlated to response to initial treatment with corticosteroids and ranges from about 25% in patients who had a complete response to about 80% in patients who had no response or progressive disease. The mortality rate of patients with steroid-refractory acute GVHD is high: 50% at 6 months and less than 30% at 2 years.[81] Criteria and indications for initiating secondary therapy for steroid-refractory acute GVHD are not well defined. Although different centers may have varying criteria, in general, if the manifestations of acute GVHD in any organ worsen over 3 days of corticosteroid treatment or symptoms do not improve by 7 days, the patient likely will not respond to corticosteroids, and secondary therapy should be considered.[73] Several therapies have been evaluated in steroid-refractory acute GVHD. Ruxolitinib is an oral FDA-approved therapy for steroid-refractory acute GVHD that inhibits both Janus kinase (JAK) 1 and JAK 2 tyrosine kinases that have been found to be associated with acute GVHD pathogenesis. When given in steroid-refractory patients, ruxolitinib not only improves the overall response rate but also allows steroid doses to be reduced significantly in many patients.[71,73,82] Other options for second-line therapy consist of continuation of corticosteroids with the addition of one or more of the following: ATG, tocilizumab, mycophenolate mofetil, sirolimus, infliximab, etanercept, alemtuzumab, or pentostatin.[18,70,73] One approach that has shown benefit in this setting is extracorporeal photopheresis (ECP). During this procedure, the patient's blood is exposed extracorporeally to 8-methoxypsoralen followed by ultraviolet A radiation and then returned to the patient. This process results in suppression of T-cell reactivity and induction of regulatory T cells. Clinical results have been positive, especially in patients with skin GVHD.[83] The choice of a second-line regimen for acute GVHD should be based on the risk of potential toxicities, interactions with other agents, convenience, and cost.

Chronic Graft-Versus-Host Disease

Chronic GVHD is the major determinant of late transplant-related morbidity and mortality in allogeneic transplant recipients. The pathophysiology of chronic GVHD appears to involve defects in immune tolerance combined with adaptive immune responses targeting autoantigens. This produces chronic tissue inflammation and damage, often resulting in fibrosis.[84,85] A three-phase model based on murine and human data has been proposed to explain the pathophysiology of chronic GVHD: tissue injury and inflammation secondary to a variety of insults (eg, conditioning regimen toxicity, infection, acute GVHD, sun exposure) (phase 1), chronic inflammation and dysregulated B-cell and T-cell immunity (phase 2), and tissue repair with fibrosis (phase 3).[85] Specific cellular and cytokine activity during these processes have become therapeutic targets for which pharmacologic agents are being evaluated and used in the prevention and treatment of chronic GVHD.

The incidence of chronic GVHD ranges from 30% to 70% and is increasing due to the increased use of alternative (mismatched and unrelated) donors, transplantation of older patients, and longer survival of transplant recipients. The risk of chronic GVHD increases with a previous history of acute GVHD, increasing donor and recipient age, patients who receive transplants from HLA-nonidentical donors and in patients who receive PBSC transplants versus BMT (especially with higher $CD34^+$ cell doses).[85] Prophylaxis of chronic GVHD includes similar strategies used to prevent acute GVHD such as in vivo T-cell depletion with ATG or PTCy.[84,86]

Unlike the acute form, chronic GVHD can affect many different organs and tissues including the skin, mouth, eyes, genitalia, GI tract, liver, lung, and joints.[85] The National Institutes of Health (NIH) Consensus Development Project developed standardized criteria for the diagnosis of chronic GVHD and proposed a clinical scoring system for the evaluation of patients with chronic GVHD based on the extent of organ damage and degree of functional impairment.[87] The Working Group recommends that the diagnosis of chronic GVHD be made with the presence of at least one diagnostic clinical sign of chronic GVHD (eg, poikiloderma or esophageal web) or a distinctive manifestation (eg, keratoconjunctivitis sicca) confirmed by biopsy or other test (eg, Schirmer test). In addition, the NIH Working Group recommends documenting all specific manifestations (acute and chronic) when establishing a diagnosis.[87]

The clinical scoring system categorizes chronic GVHD into mild, moderate, and severe, based on the scoring of individually involved organ systems.[87] Mild chronic GVHD involves only one or two organs or sites (except the lung) with no clinically significant functional impairment (no more than mild involvement in any one organ). Moderate chronic GVHD involves at least one organ or site with clinically significant but no major disability (at least moderate involvement), three or more organs or sites with no clinically significant functional impairment (no more than mild involvement), or mild lung involvement. Severe chronic GVHD indicates major disability caused by chronic GVHD (at least one organ with severe involvement) or at least moderate lung involvement.

Patients with mild skin-only chronic GVHD can be treated with topical steroid preparations; lower potency steroids are preferred for the face, axillae, and groin, whereas more potent preparations can be used for other areas. Topical calcineurin inhibitor products such as TAC and pimecrolimus have also been used with some success.[18,88] Mild-to-moderate involvement of the mouth can also be managed with local therapy including rinsing with oral solutions of high potency steroids such as dexamethasone, budesonide, or clobetasol.[18,88] Artificial tears are usually recommended for mild ocular involvement; moderate-to-severe disease requires CSA or steroid eye drops or punctal occlusion.[88]

Initial treatment of patients with moderate or severe chronic GVHD consists of prednisone 0.5 to 1 mg/kg/day with or without either sirolimus or a calcineurin inhibitor.[18,86] Although sirolimus and calcineurin inhibitors do not clearly improve the response rates to prednisone, they are often used to reduce toxicities of prolonged steroid therapy by enabling the use of lower prednisone doses, especially in patients who may be at high risk for prednisone-related complications. The addition of other agents such as MMF to first-line treatment with prednisone has not been shown to be beneficial.[84,86] Tapering of prednisone dosing is generally initiated after 1 to 2 weeks if signs and symptoms have improved or stabilized. The tapering schedule varies by institution. Unfortunately, patients with chronic GVHD may require many lines of therapy and often continue prolonged immunosuppressive treatment for several years from the initial diagnosis.[86]

In addition to treatment specifically for chronic GVHD, ancillary therapies and supportive care should be recommended to lessen the symptoms of chronic GVHD.[88,89] Patients should be educated on the avoidance of sun exposure and the use of sunscreens to reduce skin injury and exacerbation of GVHD skin lesions. Nonsclerotic skin lesions without erosions or ulcerations may respond well to emollients in addition to topical steroids. Patients should be advised to maintain good oral hygiene with routine dental care. Saliva substitutes can be given for mild dry mouth symptoms. Physical therapy is recommended to reduce functional loss from steroid myopathy, joint contractures, and deconditioning.[88]

About one-third of patients respond to initial systemic steroid therapy; those who do not respond have a poor prognosis. Steroid-refractory chronic GVHD is defined as progression on 1 mg/kg/day for 2 weeks, stable disease on greater than or equal to 0.5 mg/kg/day of prednisone for 4 to 8 weeks, or inability to taper prednisone to less than 0.5 mg/kg/day due to a flare in symptoms. Patients with steroid-refractory disease require additional therapy to control progression and reduce systemic steroid exposure. Uncontrolled trials have investigated several therapies in this setting with varying degrees of success. No consensus has been reached regarding the optimal choice for salvage therapy.[18,84–86,89,90] When choosing initial salvage therapy, clinicians should consider agents with documented activity and an adequate safety profile as well as agents that are steroid sparing. To date, three agents have received FDA approval for the treatment of steroid-refractory chronic GVHD: ibrutinib, belumosudil, and ruxolitinib.[91] Several other agents have reported activity in refractory chronic GVHD including extracorporeal photophoresis, sirolimus, methotrexate, bortezomib, rituximab, low-dose interleukin-2, imatinib, and others.[18,84–86,89,90] Some appear to be more effective in treating specific organ systems better than others. In general, ineffective therapies should be discontinued prior to starting a new agent, except for steroid therapy, which is usually continued. Clinicians are encouraged to enroll patients with steroid-refractory chronic GVHD in clinical trials when available.

Monitoring for long-term drug toxicities and infectious complications is critical during prolonged immunosuppression. Infection is the primary cause of death in patients with chronic GVHD, and antimicrobial prophylaxis is an important component of the care of patients being treated for chronic GVHD. Patients should receive oral trimethoprim–sulfamethoxazole, penicillin, an antifungal azole agent, and acyclovir to prevent infections commonly seen in immunocompromised patients. Routine monitoring for CMV reactivation should be performed. Some HCT centers also administer intravenous immunoglobulin to patients with low serum immunoglobulin G levels. Patients who remain on long-term steroids should be monitored for chronic corticosteroid toxicities, including osteoporosis, cataracts, hypertension, myopathies, and diabetes mellitus. Other chronic GVHD therapies have their own toxicity profiles and patients should be counseled and monitored accordingly.

Infection

Patients undergoing high-dose chemotherapy with autologous or allogeneic HCT are severely immunocompromised and therefore are at high risk for bacterial, fungal, and viral infections. Management of these infections is discussed in detail in Chapters 144 and 145.

Late Complications

With the success of HCT, the number of long-term survivors has grown. Many survivors experience delayed complications of transplantation and treatments used to prevent or treat those complications, including restrictive and obstructive pulmonary disease, bone and joint disease (including osteoporosis and avascular necrosis), cataract formation, endocrine dysfunction (including sterility and thyroid dysfunction), impaired growth and development, infections, cardiovascular disease, chronic renal and hepatic dysfunction, and secondary malignancies.[92,93] These effects are more frequent after allogeneic compared with autologous HCT and among allogeneic HCT patients, those with chronic GVHD tend to have a higher prevalence of multiple health conditions than those without chronic GVHD.[92,93] Physical recovery tends to occur earlier than psychological or work recovery. Full recovery usually takes several years, and about two-thirds of patients are without major limitations by 5 years. Both allogeneic and autologous HCT are associated with a several-fold increase in the risk of premature death; relative mortality decreased with time but remained significantly elevated even 10 years after transplant. The leading cause of death is relapse of primary disease in both allogeneic and autologous HCT patients. Allogeneic HCT patients also continue to die from complications of chronic GVHD while autologous HCT patients more frequently developed secondary malignancies.[92,93] Long-term monitoring of HCT patients is required, both by transplant clinicians and primary care providers who are knowledgeable in the care of these patients, to screen for, prevent and treat late complications when such interventions are available. To assist healthcare professionals providing care to HCT survivors, the CIBMTR (in partnership with leading transplant organizations) published posttransplant care recommendations for adult and pediatric autologous and allogeneic HCT recipients on their Website (www.cibmtr.org/posttransplant).

CONCLUSION

HCT offers prolonged disease-free survival, and cure in some cases, for patients with a variety of malignant and non-malignant diseases. These positive results are related to advances in preparative regimens, mobilization strategies, and posttransplant maintenance therapies. With allogeneic HCT, we have learned how to select the best donor and hematopoietic cell source given the recipient's HLA typing, diagnosis and disease status and risk for graft failure and GVHD. Ongoing research will determine best practices in the prevention and treatment of posttransplant complications such as GVHD. With increasing success of HCT, additional research should focus late complications seen in long-term HCT survivors.

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
APC	antigen-presenting cell
ASTCT	American Society for Transplantation and Cellular Therapy
ATG	anti-thymocyte globulin
BMT	bone marrow transplantation
BOS	bronchiolitis obliterans syndrome
CAR	chimeric antigen receptor
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	chronic myeloid leukemia

CMV	cytomegalovirus
COP	cryptogenic organizing pneumonia
CSA	cyclosporine
CTN	Clinical Trials Network
DLI	donor lymphocyte infusion
EBMT	European Society for Blood and Marrow Transplantation
G-CSF	granulocyte colony-stimulating factor; filgrastim
GM-CSF	granulocyte-macrophage colony-stimulating factor; sargramostim
GVHD	graft-versus-host disease
GVM	graft-versus-malignancy (effect)
Haplo-HCT	haploidentical allogeneic transplant
HLA	human leukocyte antigen
HMA	hypomethylating agent
HCT	hematopoietic cell transplantation
MAC	myeloablative conditioning
MDS	myelodysplastic syndrome
MMF	mycophenolate mofetil
MHC	major histocompatibility complex
MTX	methotrexate
NIH	National Institutes of Health
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
NMA	nonmyloablative (conditioning)
NMDP	National Marrow Donor Program
PCR	polymerase chain reaction
Ph+	Philadelphia chromosome–positive

PBSC	peripheral blood stem cell
PTCy	posttransplant cyclophosphamide
RIC	reduced-intensity conditioning
SOS	sinusoidal obstruction syndrome
TAC	tacrolimus
TBI	total-body irradiation
TKI	tyrosine kinase inhibitor
TNF-α	tumor necrosis factor-α
TKI	tyrosine kinase inhibitor
UCB	umbilical cord blood
UCBT	umbilical cord blood transplant
VOD	venoocclusive disease

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is *false* concerning the rationale for hematopoietic cell transplantation?

   A. In some cases, the administration of high doses of chemotherapy can overcome resistance mechanisms that have developed in tumor cells, thereby increasing the likelihood of cure.

   B. Many chemotherapy agents demonstrate a steep dose-response curve with increased anticancer activity at higher doses.

   C. Infusion of hematopoietic stem cells acts as a “rescue” from severe hematopoietic toxicity caused by high-dose chemotherapy.

   D. Immune-mediated effects play a significant role in the anticancer activity of autologous hematopoietic stem cell transplants.

2. Which of the following mobilization regimens would be most appropriate for a 67-year-old man with non-Hodgkin lymphoma in complete remission who has an extensive chemotherapy history?

   A. G-CSF 10 μg/kg twice daily for 5 days followed by GM-CSF 250 $\mu g/m^2$/day for 5 days

   B. Cyclophosphamide plus etoposide followed by G-CSF 5 μg/kg/day

   C. No mobilization is necessary because of the high concentration of $CD34^+$ cells in the peripheral blood

   D. G-CSF 10 μg/kg daily with plerixafor 24 mg daily starting on the evening of the fourth day of G-CSF

3. All of the following are advantages of peripheral blood over bone marrow as a source of allogeneic hematopoietic stem cells *except*

A. More rapid engraftment

B. Fewer transfusions

C. Reduced incidence of chronic graft-versus-host disease

D. Higher numbers of $CD34^+$ cells infused

4. LT is a 19-year-old woman with acute lymphocytic leukemia in second complete remission. Her 25-year-old brother is an 8/8 HLA antigen match, and the patient is scheduled to receive a myeloablative allogeneic hematopoietic cell transplant. Which of the following conditioning regimens would be an appropriate choice?

A. Cyclophosphamide (120 mg/kg) and total-body irradiation (12 Gy [1200 rad])

B. Cyclophosphamide (120 mg/kg) and fludarabine (125 mg/m^2)

C. Fludarabine (125 mg/m^2) and TBI (2 Gy [200 rad])

D. Cyclophosphamide (120 mg/kg) and busulfan (8 mg/kg)

5. All of the following are advantages of reduced-intensity regimens compared to myeloablative regimens *except*

A. Improved overall survival

B. Lower transplant-related mortality

C. Broader inclusion criteria

D. Can be used in second transplants

6. JH is a 35-year-old woman with acute myelogenous leukemia (AML) who is day +24 post BuCy and 8/8 HLA-matched unrelated donor transplant with increasing bilirubin, maculopapular skin rash over the trunk and back, and intractable nausea and vomiting. She has no hepatomegaly, and her weight has remained stable over her transplant course. Her current medications include tacrolimus, voriconazole, acyclovir, trimethoprim/sulfamethoxazole, ursodiol, magnesium supplements, and as-needed lorazepam. Her medication regimen has been stable and no new agents have been introduced. She is afebrile and is engrafting with a white blood count of 2,100/mm^3 (2.1×10^9/L) and a platelet count of 54,000/mm^3 (54×10^9/L). What is the most likely diagnosis?

A. Sinusoidal obstructive syndrome

B. Acute graft-versus-host disease

C. Drug hypersensitivity reaction

D. Acute infectious cholecystitis

7. For the case in question #7, what is the most appropriate therapeutic management?

A. Discontinue the trimethoprim/sulfamethoxazole to see if rash resolves and recommend a topical steroid cream

B. Begin broad-spectrum antibiotics

C. Biopsy the liver and consider defibrotide therapy

D. Start prednisone 1 mg/kg/day

8. Which agent is FDA approved for treatment of steroid-refractory acute graft-versus-host disease?

A. Ruxolitinib

B. Etanercept

C. Infliximab

D. Ibrutinib

9. Which of the following statements about stem cell sources is true?

A. UCB has a higher risk of GVHD but a low risk of graft failure

B. Bone marrow as a stem cell source has been correlated with an increase in risk of acute GVHD with an associated decrease in overall survival

C. PBSC used as a stem cell source is associated with more rapid platelet engraftment

D. All stem cell sources are considered equal; there is no benefit to using one stem cell source over another

10. Which of the following posttransplant prophylaxis therapies would be the most appropriate for a 42-year-old patient with BCR-ABL–positive ALL who is at high risk of relapse after myeloablative allogeneic transplant?

A. Donor lymphocyte infusion

B. Dasatinib

C. Rituximab

D. 5-Azacitidine

11. TB is a 57-year-old man with AML who is 19 days post-myeloablative matched related donor peripheral blood stem cell transplant. On examination, it is noted that TB complains of right upper quadrant pain and his abdomen is tight and distended. His laboratory values indicate that he is neutropenic and thrombocytopenic. His complete metabolic panel is normal except for elevated bilirubin and liver enzymes. His nurse also reports that TB has gained 7 kg since his admission. What is the most likely diagnosis for TB?

A. Graft-versus-host disease

B. Pancreatitis

C. Sinusoidal obstructive syndrome

D. Infection

12. Which of the following statements about *acute* GVHD is considered true?

A. The number of T-cells within the stem cell source correlates with the risk for GVHD.

B. The mortality rate directly attributable to GVHD exceeds 80%.

C. The age of the donor and recipient does not impact the risk of GVHD.

D. Biomarkers are commonly used to predict who will develop GVHD.

13. Which of the following drug regimens would be the most appropriate for GVHD prophylaxis?

A. Methylprednisolone 2 mg/kg/day

B. Cyclosporine, methotrexate, and methylprednisolone

C. Tacrolimus and methotrexate

D. Posttransplant cyclosporine

14. Which of the following statements about chronic GVHD is true?

A. It primarily affects the skin, liver, and GI tract.

B. The incidence of chronic GVHD is decreasing because of alternative donors.

C. The initial treatment of chronic GVHD is mycophenolate mofetil.

D. A previous history of acute GVHD increases the risk for chronic GVHD.

15. HS is a 48-year-old man who was just diagnosed with severe chronic GVHD of the skin. His physician would like to initiate therapy immediately. Which of the following choices would be the most appropriate for initial therapy for chronic GVHD?

A. Prednisone 1 mg/kg/day

B. Clobetasol cream

C. Prednisone 0.5 mg/kg/day with mycophenolate

D. Mycophenolate mofetil.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** D is false because there are no "immune-mediated effects" in autologous HCT. Anti-cancer effects in this setting is based only on the effects of the conditioning regimen. In addition, because the stem cells being used are from the recipient, there is no HLA disparity to cause stimulation of the immune system. All of the other distractors are true. This is discussed in the "Introduction" and "Conditioning Regimens" sections.

2. **D.** D is the correct answer based on patient-specific characteristics (older age, non-Hodgkin lymphoma diagnosis, extensive chemotherapy history), he is at risk for not collecting the minimum number of $CD34^+$ cells. For initial mobilization regimens, plerixafor with G-CSF was associated with higher $CD34^+$ cell yields, fewer apheresis sessions, increased likelihood of achieving $CD34^+$ target yields. Use of combination colony stimulating factors (G-CSF with GM-CSF) or G-CSF combined with chemotherapy are commonly used if a patient has already failed a previous mobilization attempt.

3. **C.** Peripheral blood stem cells are associated with an increased incidence of chronic GVHD when compared to bone marrow. Peripheral blood stems cells are associated with rapid engraftment, fewer platelet transfusions and a higher number of $CD34^+$ cells as discussed in the "Hematopoietic Stem Cells" section.

4. **A.** A is correct because this is the only myeloablative regimen listed (per the question) based on the doses given. The other answers are either reduced intensity or nonmyeloablative. This is discussed in the "Conditioning Regimen" section.

5. **A.** A is correct because studies to date have not consistently demonstrated an increase in overall survival. Although lower nonrelapse mortality has been reported, this is offset in many studies by an increase in relapse rates with reduced-intensity conditioning (compared to myeloablative). Because of the lower incidence of nonrelapse mortality, older patients and those with comorbidities can be transplanted with RIC regimens, thereby broadening inclusion criteria for transplant. In select patients who have relapsed post-HCT, RIC regimens can also be used in second transplants. This is discussed in the "Conditioning Regimen" section

6. **B.** The patient has symptoms associated with acute GVHD. Maculopapular rash over the trunk and back as well as nausea and vomiting are commonly associated with acute GVHD. Hepatic SOS is not correct because the patient does not have hepatomegaly and her weight has remained stable indicating she does not have significant abdominal ascites. This is not likely infectious as her WBC is within a normal range and the patient is afebrile. Drug-induced hypersensitivity can be ruled out because the rash is contained to the trunk and the back, as well as no new drugs have been

introduced into JH's regimen.

7. **D** Since this is likely acute GVHD with organ involvement, the patient should be started in systemic steroids as described in the "Graft-Versus-Host Disease" section.

8. **A.** Of all of the agents listed, only ruxolitinib has received approval for steroid-refractory acute GVHD as described in the "Graft-Versus-Host Disease" section.

9. **B.** B is correct because GVHD is more frequent in patients who are not HLA matched and as the degree of mismatching increases, so does the risk for GVHD. Graft rejection is also correlated with HLA mismatching. Only class I and II HLA antigens are important for allogeneic transplant donors. The most important antigens include those that are listed in D) but also include HLA-C. This is discussed in the "Histocompatibility Testing and Donor Selection" section.

10. **B.** Dasatinib, a tyrosine kinase inhibitor, would be the most appropriate therapy after a transplant in a patient with BCR-ABL positive ALL who is at high risk of relapse. A is not correct because DLI's have not shown to be effective in patients with ALL. Rituximab and 5-azacitidine are used in patients with NHL and AML, respectively.

11. **C.** C is correct as the patients have all of the classic symptoms of SOS as described in the "Sinusoidal Obstruction Syndrome" section.

12. **A.** Increased numbers of T-cells within the graft can increase the risk of GVHD. B is not correct because 20% of deaths after transplant are attributable to GVHD. C is not correct because the older the age of the donor and recipient so does increase the risk of GVHD. Finally, D is not correct because the use of biomarkers to predict GVHD is an area of ongoing investigation and should only be used within the setting of a clinical trial.

13. **C.** Tacrolimus and methotrexate are still commonly used agents in the prevention of GVHD. A is not correct, methylprednisolone at 2 mg/kg/day is a common agent used to treat, not prevent, GVHD. B is not correct because the three drug combination of cyclosporine, methotrexate and steroids has not shown to be more effective than tacrolimus and methotrexate. Finally, single agent cyclosporine was shown to be not as effective as the combination of methotrexate and cyclosporine.

14. **D.** As described in the GVHD section, the risk of chronic GVHD increases if the patient has a history of acute GVHD. Unlike acute GVHD which primarily affects the skin, liver and GI tract, chronic GVHD may affect any organ system. Finally, initial therapy for moderate or severe GVHD is systemic steroids.

15. **A.** A is correct as prednisone 1 mg/kg/day is the treatment of choice for severe chronic GVHD. Topical therapies are not sufficient for this severity of disease and additional medications added to prednisone have not been shown to provide benefit. ECP can be effective in the treatment of skin chronic GVHD but only used in steroid-refractory disease. This is discussed in the "Chronic Graft-Versus-Host Disease" section.