Chapter 13

Hematopoietic Stem Cell Transplantation

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Note: Because of a lack of data to support differential management, in this chapter we do not distinguish classic dyskeratosis congenita versus other telomere biology disorders (for example Hoyeraal-Hreidarsson syndrome, Revesz syndrome, or aplastic anemia with very short peripheral blood cell telomere length, and/or with mutations in telomere biology genes). The comments are intended to apply generally to individuals with telomere biology disorders.

Introduction

Hematopoietic cell transplantation (HCT) can cure blood defects — bone marrow failure (BMF), myelodysplastic syndrome (MDS), and leukemia — in patients with dyskeratosis congenita (DC). However, HCT does not cure the other problems of DC. Early experience in HCT for DC was characterized by high morbidity and mortality, and raised concerns that conventional transplant regimens accelerated other disease manifestations in DC patients. HCT outcomes have improved in the past decade with advances in diagnosis, donor matching and supportive care, and prospective multi-center trials of reduced-intensity, disease-specific regimens.

History

Case reports in the 1980s and 1990s demonstrated that aplastic anemia (i.e., bone marrow failure) in DC could be cured with HCT [1-11] (reviewed in de la Fuente and Dokal [12]). However, the overall results in this era were dismal, with a 5-year overall survival of approximately 45%, and no long-term survivors of unrelated donor HCT [12, 13]. More than half of all patients died within 4 months of the HCT procedure, most often due to infections, graft failure, or graft versus host disease (GVHD) [12-15].

A striking increase in fatal lung and vascular complications was noted, attributed to both predisposition to pulmonary and endothelial disease in DC patients, and heightened sensitivity to cytotoxic chemotherapy and radiation used in the conditioning regimens [2, 7, 8, 12]. Other factors contributed to poor outcomes. The interval from onset of BMF to transplant was often years [6], and identification of DC sometimes went undiagnosed until after HCT, because the clinical syndrome was not recognized, and genetic or functional testing was unavailable [5].

With increased awareness, new diagnostic tests, and the application of lessons learned from reduced intensity conditioning (RIC) in the DNA repair disorder Fanconi anemia (FA) [16], HCT outcomes have improved for patients with DC in the past 15 years. In a retrospective study of data reported to the Center for International Blood and Marrow Transplantation Research (CIBMTR), the 5-year probability of overall survival for DC patients undergoing HCT from 2000-2009 was 65% [13]. Similarly, in retrospective reviews of DC transplants using RIC regimens after 2000, approximately two-thirds of patients were alive at 5 years, including survivors of unrelated donor and cord blood transplants [14, 15, 17]. The improvement has been attributed to reduction or elimination of alkylating agents (such as cyclophosphamide, busulfan, melphalan, thiotepa) and radiation in preparative regimens, and an increasing use of fludarabine- and antibody-based immunosuppressive conditioning [17-25].

Better outcomes are also the result of improved supportive care of transplant patients, expanded availability of alternative donors and umbilical cord blood grafts, and advances in molecular human leukocyte antigen (HLA) matching techniques. Disease-specific, prospective HCT trials are underway for DC patients [17, 26]. These aim to exploit the telomere maintenance and cellular replication defects in DC patients, and ask whether minimally toxic conditioning regimens will permit successful engraftment. One can anticipate that outcomes will continue to improve in HCT for DC, with new knowledge and coordinated efforts aimed at decreasing adverse effects, and increasing overall length and quality of life for patients.

Proceeding to HCT

Diagnosis

Patients with DC can present with highly variable signs and symptoms, from classic findings in children to isolated hematological abnormalities in adults. Establishing the diagnosis of DC as the cause of the patient's hematological problems has major

implications for how the transplant should be conducted. Therefore, a thorough investigation for DC should be conducted in all patients with BMF and MDS (and some patients with leukemia) who are being evaluated for HCT (see Chapter 3). With the availability of telomere length testing and BMF gene panels, it appears that there may be a growing number of patients diagnosed with telomere biology disorder (TBD) with or without an identified germline pathogenic variant.

It is also important to note that DC is not only a blood disorder, but rather, a systemic disorder that affects the entire vasculature and different organs including eyes, lungs, liver, and gut. The degree of systemic disease is variable among patients; it can be minimal in some patients even in adulthood and can be advanced in early life in other patients. This systemic aspect of the disease affects the transplant decision in two ways: (1) allogeneic HCT is curative for the blood disorder in DC/TBDs, but does not prevent or treat the progression of other systemic disease, and (2) if advanced, the systemic disease may significantly complicate or ultimately contraindicate HCT.

Timing of HCT

In general, the timing of HCT depends on several factors, including:

1. The nature of the patient's hematological problem and its severity
2. The degree of HLA match and the type of donor graft available to the patient
3. The patient's age
4. The patient's overall clinical condition including pulmonary and hepatic status
5. The transplant physician's recommendation
6. The parents' or patient's decision

Indeed, these six elements all come together with regards to the decision to proceed to allogeneic HCT. Here are two examples:

1. A 5-year-old patient with severe BMF, no other physical signs of clinical problems, and an HLA matched unrelated donor should proceed to HCT

2. A 22-year-old patient with moderate BMF, with pulmonary fibrosis, and no matched donors may not be recommended to proceed to HCT

The Age Factor

Over the years, several studies of allogeneic transplantation in non-malignant hematologic disorders have consistently shown that "younger is better" for HCT. Specifically, children younger than 10 years of age have a superior outcome than patients older than 10 [27-29]. It is also relatively accepted that the risks of progression of systemic disease increase with time. These two facts put together bring into the decision-making process a concept that has been used in the blood disorder thalassemia for a long time, that of "pre-emptive transplant." An illustrative and unanswered question is: should a child with DC who has a good donor go to transplant before the age of 10 years, regardless of bone marrow status and blood counts?

The Hematologic Status

More than 80% of patients with classic DC will manifest BMF (defined as one or more peripheral cytopenias) by age 30 [30]. DC patients have a high risk of MDS (>500-fold over the general population) and acute leukemia (73-fold over the general population) [31].

Results of HCT are generally better for patients who are younger and for patients with BMF as compared to older patients or patients with MDS/AML. HCT is curative for BMF in DC, and in theory eliminates the risk of MDS or leukemia originating from the patient's blood cells. Lastly, the risk of graft failure is also higher in patients who have received a higher number of red blood cell or platelet transfusions.

These factors argue in favor of early intervention with HCT for DC patients manifesting hematologic defects, prior to significant transfusion exposure or evolution to MDS or leukemia. However, HCT is associated with a risk of transplant-related death of at least 15% and a risk of chronic GVHD of at least 10%. These risks are likely to be higher in DC

patients compared to other patients because of disease-associated co-morbidities such as lung and liver dysfunction, which adversely influence the HCT outcomes.

Indications for HCT

The following are considered absolute and relative indications for HCT in DC/TBD patients:

Absolute Indications

- **Severe cytopenias:** Defined as hemoglobin < 8 g/dL; absolute neutrophil count (ANC) < 500/mm^3; platelets < 20,000/mm^3; or requiring red blood cell or platelet transfusions to prevent significant symptoms of low hemoglobin or platelets. Immunosuppressive therapy used for idiopathic aplastic anemia will not cure BMF in patients with DC and should not be tried in this situation. Alternative treatments such as androgens or hematopoietic growth factors may be tried as temporizing measures, but for those without contraindications to HCT and with access to a suitable donor, it may be advisable to proceed to HCT without such a trial.
- **High-risk MDS and acute leukemia (that is, high-risk chromosomal abnormalities or marrow blast count >5%):** May require chemotherapy before HCT, depending on the practice of the transplant center.

Relative Indications

- **Moderate cytopenias:** If there is evidence of progression toward transfusion dependence, one may pursue HCT when a donor/graft with a suitable degree of HLA compatibility is available. Alternatively, it is reasonable to consider a trial of androgen therapy prior to proceeding with HCT.
- **Low-risk MDS (morphologic bone marrow dysplasia with no chromosomal abnormalities or with low-risk chromosomal abnormalities):** Depending on

donor availability, it may be favorable to proceed to HCT, given concerns for clonal evolution, rather than continue observation or trial androgen therapy.

Exclusions

In general, to undergo HCT, the patient must not have:

- Uncontrolled bacterial, fungal, or viral infection
- Severe organ dysfunction, such as lungs and liver
- An active pregnancy

Individual circumstances and specific conditioning regimens may permit consideration of HCT in patients with some of these conditions, and should be discussed with the transplant physician.

In summary, the decision on the timing of HCT timing for each DC patient is dependent on patient age, clinical condition, hematologic status, and donor availability, as well as the physician's and patient's assessment of relative risks and benefits.

Assessment and Planning for HCT

Referral to a Transplant Center

Because of disease-specific peri-transplant and long-term care considerations, and need for a tailored RIC regimen, patients should obtain a formal evaluation at a transplant center experienced in conducting HCT for DC. To determine the experience of a transplant center, the physician or patient may wish to ask the questions listed in Box 1. If a preferred transplant center is "out of network" for the patient's insurance, it may be possible to advocate for coverage of care through coordinated efforts of the patient, physician, and the expert transplant center. A similar approach is advised for international patients working with government or private health care insurance.

1. How many allogeneic DC transplants has your center performed? How many in children? How many in adults? How many have survived beyond one year?
2. How many unrelated donor transplants on DC patients has your center performed in the prior calendar year?
3. What specific regimen(s) does your center offer/recommend? (Obtain the doses of each therapy, graft types, and GVHD prophylaxis.) Is this regimen part of a trial?
4. What is your center's long-term follow-up plan for DC patients who undergo HCT?

Box 1. Transplant center interview questions. Adapted from "Fanconi Anemia: Guidelines for Diagnosis and Management"; 3rd edition, 2008; Chapter 10, Table 3; with permission from the Fanconi Anemia Research Fund.

There is no "standard" HCT regimen for DC that is used across centers; each transplant center may offer a different regimen for HCT, based on their own experience. Although this is not unusual in the practice of HCT, it can be unsettling for patients and families, who may be in the position of having to decide between complex medical regimens, usually without a medical background to guide them. In recent years there has been an effort to develop multi-institutional clinical studies employing consistent regimens for each HCT indication in DC (e.g., clinicaltrials.gov/ct2/show/NCT01659606) [26]. In the future, it is hoped that these types of coordinated efforts will yield more rapid advances in knowledge, which in turn will lead to more uniform standards of care among transplant centers.

Patient Assessment

Time and advanced planning are required to gather the information needed for a comprehensive pre-transplant evaluation. For DC patients, such an evaluation will involve the following elements:

Past Medical History

Because of the variability of DC clinical features, a thorough history is required to elicit factors that may complicate HCT. In particular, history should be obtained regarding infections, blood transfusion requirements, and use of prior therapies such as androgens and hematopoietic growth factors. Prenatal, birth, and developmental history, as well as neurologic, ophthalmologic, dental, gastrointestinal, pulmonary, hepatic, gynecologic/urologic, and oncologic conditions should be reviewed in detail. Prior surgeries and medical treatments, allergies, and current medications, including vitamins, supplements, and herbal therapies, should be detailed.

Family History

The family medical history is extremely important. Without exception, any family members being considered as potential HCT donors must undergo telomere length analysis and genetic testing (if the affected gene is known in the patient), to determine disease risk and suitability as a donor. It has been shown that family members who appear to be completely healthy and without any manifestations suggestive of DC may still carry a pathogenic germline genetic variant associated with DC, and may not be suitable HCT donors [32]. Moreover, in families with TBDs, short telomeres can be inherited independent of the genetic variant [33]; this raises the unanswered question of whether a well-matched unrelated donor is preferable to a fully matched related donor who does not carry the DC-associated gene variant but has short peripheral blood cell telomeres.

Social History

Behavioral, school, and work performance issues should be reviewed. Alcohol and tobacco use should be examined because of elevated risk of cancer, liver, and lung disease, both early on in the post-transplant period and long-term.

Physical Examination

Prior to HCT, the physician should systematically assess for physical abnormalities associated with DC that may alter the risk or plan of transplant therapy. The general examination should include particular attention to establishing a baseline for each organ system. This may include:

- Neurological imaging to screen for brain cysts, white matter changes, and calcifications
- Ophthalmological evaluation for retinal bleeding or exudate, and lacrimal duct obstruction
- Oropharyngeal inspection for precancerous lesions, general dental health, and infection risk
- Pulmonary function testing, with measurement of oxygen saturation diffusion capacity of the lung for carbon monoxide (DLCO), and imaging for pulmonary fibrosis or arteriovenous malformations
- Gastrointestinal status including liver function, and evaluation for evidence of cirrhosis, alimentary canal strictures, enteropathy, or gut bleeding
- Urogenital examination for urethral strictures or precancerous lesions
- Cutaneous inspection for baseline skin pigmentation and nail abnormalities, or precancerous skin lesions

The Donor Search

The compatibility of a patient and donor for HCT is determined primarily by their degree of donor/recipient HLA matching.

HLA antigens are encoded by several genetic loci (chromosomal regions), of which each individual has two copies or “alleles”. The loci of primary importance are HLA-A, HLA-B, and HLA-DRB1. A “6 out of 6 match” refers to a match at both alleles for all three of these loci. Two additional loci of importance for HCT are HLA-C and HLA-DQB1, and identity at all five of these genetic loci yields a “10 out of 10 match.” Donor/recipient

mismatches may or may not be acceptable for HCT, depending on several factors, including which specific HLA locus is mismatched and the type of donor or graft.

Determining whether the patient has a suitable donor is important for medical management decisions, even in the absence of an obvious short-term need for HCT. Therefore, it is essential that patients, siblings, and parents undergo HLA-typing as soon as the diagnosis of DC is made. A patient has a 25% chance of being HLA-identical to a full biological sibling. It is far less likely, but possible, for a parent to be a complete HLA match.

There is no given lower age limit for a potential sibling donor; infants can be used as sibling donors. However, because the number of cells transplanted per unit recipient weight correlates with success of engraftment, it may be difficult to use a sibling donor who is much smaller than the patient.

Generally speaking, a matched sibling is an ideal donor in that (1) there is a higher degree of shared genetic identity with the patient, which reduces the risk of GVHD; and (2) usually a sibling is readily available for donation, reducing the complexity and delays in transplant scheduling. The potential drawbacks of using sibling donors for HCT in patients with DC are (1) the sibling may be a silent carrier of the genetic variant causing the disease; and (2) the sibling may have inherited short telomeres, and hematopoietic stem cells may not be ideal for transplantation.

Because of these issues, all potential sibling donors should undergo a complete blood count, telomere length testing and genetic testing, whenever possible. When there is uncertainty, a bone marrow examination should be performed on the donor to assess for hypocellularity or dysplasia.

If a sibling donor is unavailable, searching for an unrelated donor involves comparing the patient's HLA typing to information stored in worldwide donor registries. A preliminary donor search can be performed by a transplant center within a few days and without cost to the patient. The availability of stored umbilical cord blood (UCB) units

that may be used for HCT is also determined this way. Again, it is essential that the availability of potential donors be determined as soon as the diagnosis of DC is made. In addition to family HLA typing, a preliminary search of existing registries for potential unrelated donors should be performed very early after diagnosis.

A formal unrelated donor search involves determining the willingness, compatibility, and suitability of one or more adult individuals to donate blood or bone marrow to a specific patient. Because it involves blood tests including high resolution HLA typing of potential donors, there are costs to the patient or insurance. The process of identifying a suitable donor can take anywhere from several weeks to months. Once a donor has been identified and the decision is made to proceed with HCT, it may still take several weeks to schedule the donor collection and complete the necessary pre-transplant evaluation and testing. Therefore, early planning is required to prevent delays in HCT.

In some cases, a haploidentical matched donor, a donor who matches at half of the tested HLA loci, may be considered. This is typically a parent or close relative. This type of stem cell donor has the advantage of being readily available and may be considered for patients with very challenging unrelated donor searches who have few unrelated donors with acceptable HLA matches. As a related donor they must also be screened similarly to a sibling donor as above. The potential drawbacks of using haploidentical donors is increased risk of GVHD and potentially slower return of a normal immune system after HCT. To prevent graft versus host disease, these stem cells require additional manipulation and treatments discussed later in this section like *ex vivo* T depletion or post-transplant cyclophosphamide. At the time of this writing experience with the use of haploidentical donors in DC is very limited [34, 35].

The Graft

The graft is the blood or bone marrow product containing the hematopoietic stem cells obtained from the donor for infusion into the patient. Various types of graft can be used:

1. **Bone marrow (BM).** Liquid bone marrow, similar in appearance and consistency to blood, is typically removed from the pelvic bones of donors via needle aspiration. The donor is typically put under general anesthesia for this procedure. The amount removed is dependent on the size of the patient, but ranges from 300–1200 milliliters (10–40 fluid ounces). The BM is filtered and may be further manipulated based on the donor and recipient ABO blood types and recipient size.
2. **Peripheral blood stem cells (PBSC).** Granulocyte colony stimulating factor (GCSF) is given to the donor to mobilize hematopoietic stem cells from the marrow into the peripheral blood. The donor undergoes pheresis, which entails: (1) collection of blood via intravenous catheters, (2) separation and harvesting of white blood cells (which contain the mobilized stem cells), and (3) return of the remaining blood components to the donor. The donor is awake for the procedure, which may require multiple sessions over a few days. PBSC have the potential advantage of improved engraftment compared to bone marrow, but may be associated with higher risk of GVHD.
3. **Umbilical cord blood (UCB) cells.** UCB is rich in hematopoietic stem cells. It is collected from the umbilical cord and placenta immediately after birth, HLA typed, and frozen at specialized blood banks. These banks serve as repositories for UCB units to be dispensed as needed for patients requiring this graft source. The potential advantages of using cord blood for transplantation are that it is readily available, and there is a decreased risk of GVHD. Therefore, less than perfect HLA matching at HLA-A, -B, and -DRB1 is acceptable. In the United States, it is estimated that UCB units mismatched at one or two HLA loci are available for almost all patients younger than 20 years of age and for more than 80% of patients 20 years of age or older [36]. The disadvantage of UCB is that the volume of the product (and therefore the stem cell “dose”) is fixed and may be insufficient. In this case, infusion of more than one UCB unit (a double UCB transplant) may be required. When obtained from a public bank, one cannot obtain more stem cells from the same donor. There may also be a higher risk of

graft failure and certain post-transplant viral infections with UCB transplants because of fewer mature immune cells (T lymphocytes) in cord blood.

The choice of a BM, PBSC, or UCB graft for a given patient will depend on several factors including:

1. Urgency of HCT
2. Degree of HLA match for a family donor versus unrelated donor versus UCB donor unit(s)
3. Regimen-specific or transplant center requirement or preference
4. Donor preference (BM versus PBSC donation)
5. Clinical considerations, most notably patient age and history of infections
6. Donor/graft-specific considerations (for example, the age, parity, and cytomegalovirus (CMV) status of the donor, or the cell count of the available UCB unit[s])

Conditioning Regimen

The conditioning regimen (also known as preparative or cytoreductive regimen) is the process by which the patient is treated with chemotherapy, radiation, and/or immunosuppressive drugs to allow engraftment of the donor hematopoietic stem cells. The “intensity” of a conditioning regimen refers to how aggressively the combination of agents depletes the blood-forming and immune cells of the patient. A higher intensity conditioning regimen more reliably enables engraftment of donor cells, but also causes increased toxicity and side effects. An ideal conditioning regimen would subject the patient to the least toxic agents (or no agents at all), and would achieve full replacement of the patient’s blood and immune cells, as well as eradication of any dysplastic clones or leukemia cells.

Based on historical evidence showing an unacceptable rate of toxicity and death, fully myeloablative regimens consisting of high dosages of radiation or alkylating agents should not be used to treat patients with DC. Although higher intensity conditioning

regimens may be warranted to eradicate MDS or leukemia, the focus of current trials is to decrease short- and long-term complications by minimizing conditioning intensity as much as possible for DC patients with BMF. An open question is whether patients with MDS/leukemia should be treated with chemotherapy before HCT, or whether they should proceed directly to HCT, as has been described in FA [37].

Relatively few agents are used in reduced intensity regimens for DC, but the combinations and dosages can vary significantly between transplant centers. The major classes of agents, as well as their typical dosages and range of toxic effects are listed in Table 1. At the time of this writing, there is no standard or “consensus” conditioning regimen for patients with DC, and therefore the physician and patient should give detailed consideration to the different regimens being offered at the centers where the patient is being evaluated for HCT. It is also important to note that given the high variability in symptoms and complications affecting different individuals with DC, it is unlikely that there will be one ideal regimen for all patients.

Table 1. Conditioning agents.

Radiation	Physically damages DNA and thereby kills and/or prevents division and growth of patient cells
	Very effective in destroying host blood and immune cells in preparation for donor stem cell engraftment
	Toxic effects are not specific to blood and immune cells: there are dosage-related toxic effects on all organs/tissues that are exposed
	Usually delivered to the whole body (TBI=total body irradiation); sometimes dose is focused on lymphoid organs (TLI=total lymphoid irradiation)
	Myeloablative dose is 1350-1400 cGy (centigray) total in several fractions
	Reduced intensity doses are approximately 200-400 cGy.
Alkylating Agents (examples include cyclophosphamide, busulfan, melphalan, and thiotepa)	Chemically modify and damage DNA, thereby killing and/or preventing division and growth of cells
	Very effective in destroying host blood and immune cells in preparation for donor stem cell engraftment
	Toxic effects are not specific to blood and immune cells: there are dosage-related toxic effects on multiple organs
	High-dosage ranges: cyclophosphamide 120-200 mg/kg total; busulfan 12.8-16 mg/kg total; melphalan 140-180 mg/m2 total
	Reduced intensity dosages: cyclophosphamide 20-50 mg/kg total; busulfan 0.8-3.2 mg/kg total; melphalan 70 mg/m2 total
Fludarabine Phosphate	Interferes with DNA synthesis and thereby kills and/or prevents division and growth of patient cells
	Very effective in destroying host blood and immune cells in preparation for donor stem cell engraftment
	Toxic effects are largely limited to blood and immune cells, because the intravenously administered drug has limited penetration into other tissues

	Major component of reduced intensity conditioning regimens
	Dosage is typically 120 – 200 mg/m^2 total
Antibodies	Bind to and promote the destruction and clearance of hematopoietic and immune cells
	Long-lasting and powerful immunosuppressive agents; can destroy not only the donor immune cells, but depending on dosage and schedule, can deplete the immune cells in the graft can create serum sickness-like reactions in the short-term; other toxic effects are limited to hematopoietic and immune cells
	a. Anti-thymocyte globulin: produced from different sources (horse or rabbit immune globulin raised against human immune cells; or rabbit immune globulin raised against human lymphocyte cell lines)
	i. Long track record of use in HCT ii. Limited by heterogeneity of formulations and lack of availability of particular formulations in different parts of the world
	b. Anti-CD52 antibody (alemtuzumab): humanized monoclonal antibody causes rapid, profound and sustained lymphocyte depletion
	c. Rapid, profound and sustained lymphocyte depletion
	d. May be associated with increased risk of viral reactivations/infections post-transplant
	e. May be associated with decreased risk of GVHD

Graft Versus Host Disease Prophylaxis and Treatment

All patients undergoing allogeneic HCT are at risk of GVHD, which occurs when the immune cells in the donor graft recognize the patient's tissues as "foreign", and cause

inflammation and cell destruction. The two phases of GVHD — acute and chronic — are characterized by different symptoms (Table 2).

Table 2. Manifestations of GVHD. From "Fanconi Anemia: Guidelines for Diagnosis and Management"; 3rd edition, 2008; Chapter 10, Table 8; with permission from the Fanconi Anemia Research Fund.

Acute GVHD	a. Skin (maculopapular rash to generalized erythroderma to desquamation and bullae)
	b. Liver (hyperbilirubinemia)
	c. Gastrointestinal system (secretory diarrhea, abdominal pain, ileus, hemorrhage, nausea/vomiting)
	d. Ocular (photophobia, hemorrhagic conjunctivitis, pseudomembrane formation, and lagophthalmos)
Chronic GVHD	a. Skin (lichen planus, scleroderma, maculopapular rash, hyperkeratosis, hair and nail loss)
	b. Liver (cholestasis, absent bile duct syndrome, cirrhosis, portal hypertension, hepatic failure)
	c. Gastrointestinal system (dysphagia, failure to thrive, aperistalsis, malabsorption syndrome)
	d. Lung: obliterative bronchiolitis (restrictive/obstructive airway disease)
	e. Sicca syndrome (keratoconjunctivitis sicca with burning, photophobia, irritation, pain; oral dryness, pain, lichenoid lesions, gingival atrophy, dental caries)
	f. Vaginitis, vaginal dryness/strictures
	g. Pancytopenia; eosinophilia
	h. Serositis (pleural, pericardial, joint effusions)
	i. Myofasciitis

GVHD is a major cause of morbidity and death after HCT, and the risks of GVHD are higher in unrelated or haploidentical donor PBSC or BM transplants compared to sibling

donor or UCB transplants. Chronic GVHD is of particular concern as it targets tissues that are often already affected in DC patients, and so may accelerate liver or lung failure, malignancy, or other disorders. Several strategies are used to decrease the risk of GVHD, some of which may be preferable in DC patients:

1. **Calcineurin inhibitors:** Cyclosporine A (CSA) and tacrolimus (FK506) are immunosuppressive agents that diminish the response of immune cells to foreign antigens, and are mainstays of GVHD prophylaxis. CSA or FK506 is used for several months after HCT, typically in combination with one or more other GVHD prophylactic strategies described below. The side effects and toxicity profiles of calcineurin inhibitors make them suitable for use in HCT regimens for DC patients.
2. **Methotrexate (MTX):** MTX is given for several doses in the days immediately following graft infusion. Because it inhibits DNA synthesis, it destroys donor immune cells that otherwise divide rapidly in response to the patient's "foreign" antigens. MTX effects are not specific to immune cells. It may cause mucositis, pulmonary fibrosis, and other cytotoxicity, so it is preferable to avoid using it as GVHD prophylaxis in DC patients.
3. **Mycophenolate mofetil (MMF):** MMF also inhibits immune cells in the donor graft but without significant toxicity to other cell types. It is given for several weeks after HCT. The side effects and toxicity profiles make MMF suitable for use in DC patients.
4. **Graft modification**
    a. ***Ex vivo* T cell depletion:** Reduction of T cells in the donor graft significantly reduces the risk of GVHD without exposing the patient to pharmacological toxicity. This may be accomplished by specifically removing T cells from the graft (e.g., "alpha/beta T cell depletion"), or enriching stem cells from graft ("CD34+ selection") in the laboratory prior to infusion into the patient. T cell reduction may permit a shorter duration or elimination of GVHD prophylaxis. T cell depleted grafts have been used

successfully in DC patients [34, 38]. The main risks of T cell depletion are graft failure and an increased susceptibility to viral infections. T cell depletion is not available at all transplant centers.

b. ***In vivo* T cell depletion:** Anti-thymocyte globulin (ATG), alemtuzumab, or other anti-lymphocyte antibodies given as part of the conditioning regimen may persist in the patient after infusion of the graft and so effectively result in T cell depletion. This may be used as a strategy in the setting of haploidentical stem cell transplant in some patients to avoid the use of cyclophosphamide. The degree of GVHD protection afforded by this strategy is difficult to measure and is likely to be highly variable between patients. Like ex vivo T cell depletion, major risks may include increased graft failure and viral infections.
c. **Post-transplant cyclophosphamide:** In the setting of haploidentical stem cell transplant cyclophosphamide (Cytoxan) can be given for several doses after the stem cell infusion to destroy donor immune cells that otherwise divide rapidly in response to the patient's "foreign" antigens. Cyclophosphamide is an alkylating chemotherapy that causes DNA damage that is not specific to immune cells. It may cause mucositis, pulmonary fibrosis, and other cytotoxicity, so doses must be reduced in patients with DC. Experience with using this approach is limited at the time of this writing and largely based on experience in other chemo-sensitive diseases [39, 40].

Despite preventive measures, patients may still develop GVHD, ranging in severity from limited skin involvement to life-threatening multi-organ failure. Corticosteroids such as methylprednisolone are first-line therapy for GVHD, and adequate control may require long-term immunosuppression. In DC patients with GVHD, consideration should be given early on to strategies that minimize cumulative exposure to high-dose, systemic corticosteroids, to reduce additive effects on musculoskeletal, endocrine, and other organ systems (see also Chapter 22).

Transplant Care Timeline

The timeline of HCT for DC patients can be broken down to 4 periods:

1. Conditioning/preparative therapy
2. Graft infusion and supportive care until engraftment
3. Post-HCT care
4. Long-term care (Table 3)

Patients are usually hospitalized from the period of conditioning through engraftment, approximately 4-6 weeks, followed by outpatient post-HCT care over the subsequent 9-12 months.

Conditioning/Preparative Therapy

Prior to or upon admission, a central venous catheter is placed to enable routine blood sampling and supportive care during the HCT procedure. In the 7-10 days prior to graft infusion, the patient is hospitalized and the conditioning regimen is administered. During this period, depending on the regimen, patients may experience immediate side effects such as nausea, vomiting, fever and fatigue. Medications to control these symptoms and prevent infections are administered. GVHD prophylaxis may begin during this time.

Graft Infusion and Supportive Care Until Engraftment

The day of the graft infusion is termed “day 0.” Hydration and medications to prevent infusion reactions are administered. The graft is administered intravenously, similar to a blood transfusion. As donor cells circulate in the blood stream, they respond to cues that guide them to the bone marrow to establish a new hematopoietic, and subsequently, immune system. Blood counts — including white blood cells, red blood cells and platelets — fall in the days that follow due to the effects of the conditioning regimen. Transfusions of red blood cells and platelets are usually required. For white

blood cells, a medication called granulocyte-colony stimulating factor (G-CSF) to encourage efficient growth of new monocytes and neutrophils from the donor stem cells may be provided. Pain management for oral mucosal breakdown (mucositis) and nutritional support are usually required during this phase of HCT; however, with some RIC regimens used for DC, the severity of these symptoms is decreased.

In the subsequent weeks, patients are monitored closely for signs of complications such as infections, organ dysfunction, metabolic disturbances, vascular leak, and acute GVHD. Medications for GVHD and infection prophylaxis continue to be administered. The conditioning regimen can damage endothelial cells which line blood vessels throughout the body [41]. In some cases damaged endothelial cells accumulate, blocking blood flow through the liver causing veno-occlusive disease (VOD) [42]. Symptoms include abdominal pain, particularly in the location of the liver, weight gain/fluid retention, and jaundice (increased bilirubin on liver blood labs). Damaged endothelial cells can additionally block small blood vessels called capillaries in organs such as the kidneys, small bowel and lungs — consuming platelets, activating a portion of the immune system called complement, and shearing red blood cells trying to pass. This latter constellation is called transplant-associated thrombotic microangiopathy (TA-TMA) [43]. Signs/symptoms can include high blood pressure, anemia, thrombocytopenia, acute renal insufficiency, and mental status changes, among others. Both VOD and TA-TMA have targeted therapies should they be needed.

Neutrophil engraftment is defined as recovery of ANC to ≥ 500 cells/mm^3 for three days, and usually occurs between days 14 and 35 after graft infusion. Timing of neutrophil engraftment is associated with the stem cell donor source, cell dose, and occurrence of any complications that may delay hematopoiesis. Each cell type has a unique timeframe for development from stem cell differentiation to maturity and release into circulation. Because of these differences, red blood cell and platelet transfusion dependence may continue even after neutrophil engraftment. Unfortunately, some patients experience graft failure after HCT, either through active rejection of the donor cells by the patient's immune system or loss of the graft related to active infection or problems in the bone

marrow niche, or stem cell home [44]. Efforts to avoid graft failure include optimal HLA-matching, providing adequate stem cell dose, adequately targeting the patient's immune system during conditioning, and screening for circulating anti-HLA antibodies in the patient before HCT. Graft failure can occur early or late after transplant, with late or secondary graft failure arising after neutrophil engraftment had previously been demonstrated. In some cases, a patient's own stem cells can recover providing a safety net of hematopoiesis. However, in the majority, graft failure is accompanied by neutropenia and requires new or additional stem cells for recovery and survival.

Post-HCT Care

Patients are discharged from the hospital after neutrophil engraftment if: (1) there are no signs of infection or significant organ dysfunction, (2) they are able to maintain adequate hydration, nutrition and symptom control, and (3) an appropriate outpatient care management plan is in place. To reduce the risk of infections, patients are restricted from social contacts for 6-12 months after HCT, including work/school and participation in crowded indoor functions. The first 100 days after transplant are considered the highest risk time period for HCT-related complications. Patients may need to relocate temporarily to be in close proximity to a transplant center. Clinic visits are typically multiple times per week to administer medications and/or transfusions, and to assess for infection, graft function, GVHD, medication toxicity, metabolic derangements, and other post-HCT complications. If the patient is doing well after this period, the central venous catheter may be removed, and clinic visits may decrease in frequency. If the patient has traveled to a transplant center for HCT, care may be transitioned to providers closer to the patient's home, depending on several factors.

Immunosuppressive medications to prevent GVHD and infection prophylaxis are usually reduced or eliminated after 6-9 months, depending on the regimen, the patient's clinical status, and the transplant center's practice. In an ideal scenario, by one-year post-HCT, the patient will have discontinued almost all transplant-related medications, will be independent of transfusions, and resumed normal activities at home, school, or work. At

this time re-immunization can also start, as the transplant process will cause most patients to lose the protective effect of their previous immunizations.

The timing for discontinuation of immunosuppression to prevent GVHD, infectious prophylaxis, and re-immunization rely on knowledge of immune recovery after HCT [45]. Most lymphocytes live for a week to a few months. Therefore, donor lymphocytes present in the graft that may recognize the patient's body as foreign and cause GVHD, if adequately controlled, will have died by 6 months after HCT. This allows for discontinuation of immunosuppression. At the same time, the donor stem cells in the patient's bone marrow give rise to a new immune system, with specific cell populations recovering at different times following HCT [46]. Innate immune cells, early responders to infection and tissue damage, such as neutrophils and natural killer (NK) cells recover fastest, providing protection from some bacteria and fungi. Lymphocytes, including the B cells which produce protective antibodies and T cells that both instruct B cells and respond to innate immune signals to help eliminate infection or damaged/abnormal patient cells, are slower to recover. T and B cells are particularly important for response to viral infections. T cell development is particularly time consuming [47], as precursor T cells must travel from the bone marrow to an organ in the chest called the thymus. In the thymus, these developing T cells are educated on "self" versus "foreign" before being allowed to circulate to prevent autoimmunity. Many T cell populations take 9-12 months to reach normal numbers in circulation. Recovery timing may vary based on HCT conditioning regimen and immunosuppression approach to prevent or treat GVHD. Adequate response to immunizations requires both T and B cells, hence the typical re-immunization initiation between 6-12 months post-HCT [48]. Live-attenuated vaccines are often delayed until 2 years after HCT to prevent possible vaccine-mediated infection [49].

The transplant physician or hematologist coordinating the patient's care should continue comprehensive surveillance for DC-related complications in the immediate post-transplant period. Several reports have documented the overlap of chronic GVHD symptoms and non-hematological manifestations of DC [50-52], including oral mucosal,

skin, and hair changes, musculoskeletal abnormalities, and lung disease. In some cases of presumed idiopathic aplastic anemia, these manifestations have led to a diagnosis of DC in the months to years following HCT. Awareness and careful evaluation are required to discern between HCT-related complications that may require aggressive interventions such as corticosteroids, versus the natural progression of DC.

Long-Term Care

Optimal care of all patients who have undergone HCT requires lifelong regular and comprehensive evaluation; late effects of the conditioning agents and immunosuppressive medications used in HCT, and complications, such as GVHD and infections, demand ongoing surveillance. There is increased concern for significant post-HCT sequelae in patients with DC given the nature of the underlying disease. Notably, HCT only addresses the hematopoietic and immune complications of DC. All other cell types of the body remain with short telomere lengths and associated risks. While there are concerns that transplant toxicity may expedite complications such as pulmonary fibrosis or development of malignancies, data to support or refute such concerns are lacking. Certainly HCT would not be expected to improve pulmonary outcomes, and pulmonary complications remain a predominant cause of late post-HCT mortality [15, 51].

DC patients should undergo regular, comprehensive multi-disciplinary evaluations with appropriate targeted testing in the years following HCT [53]. Late effects of alkylating agents and radiation include malignancy, fertility problems, and endocrine defects, to which DC patients are predisposed. Chronic GVHD and prolonged use of corticosteroids or other immunosuppressive therapies may exacerbate bone disease and magnify risk of malignancy in DC. Lung complications of HCT may decrease pulmonary reserve and accelerate respiratory decline in these patients. HCT late effects and their overlap with DC are listed in Table 3.

Table 3. Overlap between manifestations of DC and HCT late effects.

	DC	HCT Late Effects
Hematology	Bone marrow failure, iron overload	Iron overload
Dermatology	Reticular pigmentation changes, skin thickening, nail changes	Chronic GVHD: rash, skin thickening and tightening, nail changes
Ophthalmology	Tear duct obstruction, loss of eyelashes	Ocular GVHD and dry eyes, cataracts
Oral	Leukoplakia, dental problems	Oral GVHD, dental problems
Endocrine	Skeletal defects, short stature, hypogonadism	Thyroid defects, growth hormone deficiency, fertility problems, hypogonadism, metabolic syndrome
Pulmonary	Fibrosis, arteriovenous malformations	Fibrosis, emphysema, pulmonary infections, idiopathic pneumonia syndrome, chronic GVHD
Gastroenterology	Esophageal stenosis, enteropathy, enterocolitis, cirrhosis, portal hypertension	Sequelae of gut GVHD, infectious colitis
Neurology, Psychiatry, Social	Development and psychiatric disorders, quality of life issues	Neurocognitive defects, post-traumatic stress disorder, anxiety, depression, social restrictions, quality of life issues
Oncology	MDS/leukemia, squamous cell cancers of head/neck/mucosal surfaces	Secondary MDS/leukemia, skin, and other cancers

With HCT survival improving for DC patients, deliberate attention must be given to coordinating and facilitating ongoing multi-disciplinary care, preventing long-term complications, and optimizing quality of life. Patient encounters should include

counseling on a healthy lifestyle and avoidance of harmful habits such as smoking and excessive alcohol consumption, which may accelerate lung and liver disease. Similarly, patients should avoid the DNA damage conferred by ultraviolet radiation of unprotected sun exposure on the skin already prone to squamous cell carcinoma development. Human papillomavirus vaccination is encouraged given the contributions of this virus to head and neck squamous cell carcinoma. Ideally, to anticipate problems and intervene appropriately, post-HCT and long-term care of DC patients should be coordinated by a provider or combination of providers knowledgeable about both DC-related complications and the late effects of HCT. At minimum, post-HCT DC patients should undergo annual pulmonary function testing, blood test of liver function, and comprehensive exams for cancerous or pre-cancerous lesions (complete skin exam by a dermatologist, oral/head/neck exams by dentistry and ENT, and anorectal/vaginal exams by an internist, urologist, and/or gynecologist). Vascular malformations of the lung, liver, or gastrointestinal tract may also be present and require attention.

Challenges and Opportunities

In 2022, through multi-center efforts, disease-specific approaches, and coordinated long-term multi-disciplinary care, improvements are being realized in HCT outcomes for patients with DC, demonstrating it to be an effective and feasible curative strategy for BMF. Ongoing challenges include tailoring HCT regimens for high-risk patients, such as those with allo-sensitization as they will have a higher risk of graft rejection, and those with significant DC-associated co-morbidities who may not tolerate RIC. As recognizing the diagnosis of an underlying TBD increases in adults with MDS and leukemia, who suffer high treatment-related mortality from conventional HCT approaches [54, 55], there is also a pressing need for pre-emptive strategies and/or trials of alternative conditioning agents. To this end, in the last several years, gene therapy has advanced in several non-malignant conditions. Genetic modification, replacement or repair of blood cells using viral transduction, CRISPR/Cas9 and/or base editing can be seen on the horizon for DC. The successful demonstration of safety and efficacy using autologous

gene therapy would drive pre-emptive strategies to prevent MDS/leukemia in DC, albeit with the risk that residual uncorrected cells might transform. Advances will also be needed to reach organs and tissues other than the blood affected in DC patients. Alongside genetic approaches, novel conditioning agents such as antibodies against CD45 or CD117 are being developed to avoid non-targeted cellular cytotoxicity, which could be of particular benefit in DC/TBD patients. One can expect trials of all of the above strategies in the coming years, in hopes of fundamentally changing the experience and outcomes of hematologic complications in DC/TBD.

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