Biol Blood Marrow Transplant 25 (2019) 2322–2329

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Reports

Worldwide Network for Blood and Marrow Transplantation Recommendations for Establishing a Hematopoietic Cell Transplantation Program, Part I: Minimum Requirements and Beyond

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Article history:
Received 27 February 2019
Accepted 1 May 2019

Key words:
Transplantation program requirements
Autologous versus allogeneic transplantation

A B S T R A C T

Hematopoietic cell transplantation (HCT) is a highly complex procedure that requires a dedicated multidisciplinary team to optimize safety. In addition, institutions may have different needs regarding indications based on regional disease prevalence or may have an interest in developing specialized services. Structured recommendations are not commonly available, however. The Transplant Center and Recipient Issues Standing Committee of the Worldwide Network for Blood and Marrow Transplantation (WBMT) organized a structured review of all pertinent elements for establishing a transplantation program. First, we solicited components from committee members and grouped them into domains (infrastructure, staff, cell processing laboratory, blood banking, laboratory, radiology, pharmacy, HLA testing, ancillary services, and quality). Subsequently, reviewers scored each element on a 7-point scale, ranging from an absolute requirement (score of 1) to not required (score of 7). An independent group of 5 experienced transplantation physicians reviewed the rankings. The minimum requirements for establishing any HCT program were identified among elements with mean score of $\leq$2.0, and specific elements for allogeneic and autologous HCT were identified. Mean scores of $>$2.0 to 4.0 were classified as preferred recommendation, and mean scores of $>$4.0 to $\leq$ 7.0 were considered ideal recommendations for advanced and complex types of transplantation. This structured set of recommendations guides the prioritization of minimum requirements to establish a transplantation program and set the stage for expansion and further development.

These guidelines were developed by WBMT and are published jointly in Hematology/Oncology and Stem Cell Therapy and Biology of Blood and Marrow Transplantation.

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INTRODUCTION

Considering the unique curative potential of hematopoietic cell transplantation (HCT) for many diseases and the considerable differences in activities worldwide, there is a global need to expand access, especially in regions with constrained

https://doi.org/10.1016/j.bbmt.2019.05.002

resources [1,2]. Now, after more than 60 years of progress, HCT has matured as a complex procedure requiring specialized care from expert professionals [3]. Safe and successful HCT requires cooperation of specialists from different fields of medicine. Program requirements differ depending on the type of transplant, indications for transplantation, availability of resources, and levels of complexity, and thus can vary substantially. When establishing a new HCT unit, prioritizing the required elements is often difficult.

The Worldwide Network for Blood and Marrow Transplantation (WBMT), a nongovernmental organization in an official relationship with the World Health Organization, works to expand access to HCT globally [4]. To fulfill its mission, the WBMT developed the annual HCT activity survey, which highlights differences worldwide [1,3-5]. Subsequently, the WBMT organized a series of workshops in different countries (Vietnam, Brazil, South Africa, Saudi Arabia, Morocco, and China) to analyze and promote the regional development of transplantation and provide a forum for practical approaches to clinical care.

Fundamental elements necessary for establishing a transplantation program were developed during these workshops; however, it became evident that these elements were highly dependent on the prevalence of diseases in different regions and on available resources [6-9]. These factors drive the types of transplantations needed locally and determine what is affordable or economically feasible [10].

The need for more structured guidelines delineating minimum requirements for establishing an HCT program is clear. In addition, as HCT programs expand, information on additional elements is needed for HCTs of greater complexity and risk, such as allogeneic HCT using unrelated or alternative donors.

In this report, we identify key elements for establishing and developing a new HCT program. Our recommendations are based on a structured assessment of program elements, which were reviewed by experienced transplantation physicians from different countries. After the various elements were analyzed and ranked, the recommendations were reviewed by a separate group of transplantation physicians with expertise in HCT, leading to the final recommendations presented herein.

METHODS

WBMT

The WBMT is a federation of societies formally created in 2007 by leaders from major HCT groups and donor registries worldwide. It evolved into a nongovernmental organization in a working relationship with the World Health Organization (WHO) and shares a mutual vision to combine efforts toward improving access and at a global level optimizing HCT, cellular therapies, and related fields. The WBMT includes 22 member societies and 7 standing committees, all with substantial interest in HCT and each with international reach and influence. The WBMT was incorporated in Bern, Switzerland as a nonprofit organization for educational, scientific, and philanthropic purposes under Swiss law. Elected officers and appointed committee leadership span the globe [11].

This project was conducted under the auspices of the Transplant Center and Recipient Standing Committee, which recommends policies, programs, and actions pertaining to the performance of HCT and other cellular therapy procedures. This committee administers activities related to the WBMT Global Transplant Activity (GTA) reports and leads the review of proposals and deliberations when use of GTA data is requested with oversight and approval by the WBMT Board. It includes recommendations for technical processes and the conduct of individuals carrying out these procedures and practices, including twinning with experienced centers, hosting physicians, telemedicine, and information on HCT activity and HCT outcomes.

Identification of Raters and Reviewers

We identified volunteers for this project by polling the full committee. There were 2 groups of volunteers. The first group identified, categorized, and ranked the domains and requirements for both autologous and allogeneic HCT, and the second group reviewed these data and established a consensus. The 15 HCT physicians who participated (raters, n = 10; reviewers n = 5) had between 4 and 40 years of experience in autologous and/or allogeneic HCT procedures. They represented pediatric and adult programs, were mostly from academic centers, and were from distinct global regions (Austria, Brazil, France, Germany, India, Italy, Japan, Morocco, Saudi Arabia, and the United States). Raters and reviewers from Brazil, Germany, India, Saudi Arabia, and the United States were directly involved in the development of new transplantation centers.

Review Process

The first group of raters identified a wide variety of general requirements for HCT programs from all the WBMT workshops and from an initial survey to committee members. After substantial deliberation, items were categorized into domains for allogeneic HCT, autologous HCT, and requirements common to both types of HCT. Then each rater received a spreadsheet listing all the items to be ranked using a 7-point scoring system ranging from 1, absolutely required, to 7, not recommended (Table 1). The scores were summarized by mean and SD, and then domain elements were ranked. The group was convened on a conference call to discuss elements with discrepant scores. These discussions led to either clarification on how the item was described or recategorization to a separate tier.

The group categorized elements into 3 tiers: minimum, mean score of 1 to 2; preferred, mean score of >2 to 4; and ideal, mean score of >4 to ≤ 7. This 3-tier set guided priorities for development of an HCT program. The final list of recommendations was then sent to 5 reviewers via e-mail, who performed an independent evaluation. The external reviewers provided additional recommendations on ranking or expanding the explanation of each element. The interaction with external reviewers was all online.

RESULTS

The initial collection and review of all possible elements that could be used for the development and daily operations of a transplantation program yielded 102 elements for an allogeneic HCT program and 88 for an autologous HCT program. After review and reorganization, the final list yielded 94 and 77 elements, respectively (Tables 2 to 4). These elements were grouped into 13 domains: infrastructure, staff, cell processing laboratory, blood banking, HLA, laboratory, microbiology,

Table 1
Scoring of HCT Program Required Elements

Score	Description	Category	Level	Comments
1	Absolutely required	Minimum	I	A program cannot be implemented without this element
2	Required			A program needs to have this in place or at least planned in the first year of implementation
3	Important	Preferred	II	Important for further expansion of the program
4	Good			Not necessary but recommended
5	Important but not needed at early implementation	Ideal	III	Ideal element but not critical for the day-to-day operations
6	Might be beneficial in certain situations			Item that could be specific to a patient population or type of transplantation
7	Not recommended			Should not be considered a necessary element

Table 2
Minimum Requirements for Development of HCT Program by Transplant Type

Domain	Minimum Requirements	Allogeneic HCT Score, mean (SD)	Autologous HCT Score, mean (SD)
Infrastructure	Institution (or Hospital Leadership) support	1.7 (.67)	1.44 (.71)
	Cell processing laboratory (access to laboratory services for cell count, sterility assessment)	1.5 (.71)	1.67 (1.35)
	Tertiary care center*	2.60 (1.71)	2.11 (1.45)
	Intensive care unit (access to vasopressors, dialysis, positive-pressure or mechanical ventilatory support)	2.0 (1.49)	2.0 (1.84)
	Apheresis services (autologous HCT)	2.60 (1.26)	1.67 (1.14)
Staff	Medical director: hematologist/oncologist or immunologist	1.3 (.48)	1.44 (.82)
	Medical director, licensed hematologist with minimum 6 months training in a BMT unit (recommended: ability to establish relationship with an experienced HCT center)	1.5 (1.08)	1.44 (.82)
	Nurse with hematology-oncology experience or trained in handling chemotherapy and infection control	1.20 (.63)	1.33 (.79)
	Pharmacist with experience in handling chemotherapy	2.00 (1.41)	1.78 (1.03)
Cell processing laboratory	Cryopreservation procedures and storage capability (autologous HCT)	3.30 (1.57)	1.44 (.82)
Blood banking	Availability of blood and platelets	1.10 (.32)	1.11 (.47)
	Availability of leukocyte-reduced (or irradiated) blood products	1.30 (.48)	1.78 (.88)
HLA testing	Access to HLA typing laboratory (allogeneic HCT)	1.40 (.97)	—
Laboratory	Cell counter	1.00 (—)	1.00 (.32)
	Chemistry	1.20 (.63)	1.00 (.32)
	ABO blood typing	1.40 (1.26)	1.00 (.32)
	Immunohistochemistry	2.10 (.88)	1.89 (.95)
	CSA or tacrolimus level (allogeneic HCT)	1.30 (.48)	—
Microbiology	Basic bacterial and fungal cultures	1.30 (.48)	1.11 (.47)
	Serology for hepatitis, HIV, HSV, syphilis, and HTLV-1	1.10 (.32)	1.33 (.79)
Allogeneic HCT	CMV detection (antigenemia or PCR)	1.70 (.67)	2.67 (1.60)
Radiology	X-ray and CT scan	1.10 (.32)	1.33 (.63)
Pharmacy	Access to chemotherapy agents used in the conditioning regimen	1.00 (—)	1.33 (1.03)
	Antiemetics	1.20 (.42)	1.22 (.57)
	Broad-spectrum antibiotics	1.00 (—)	1.00 (.32)
	Antifungal agents for prophylaxis and/or treatment	1.10 (.32)	1.89 (1.06)
Allogeneic HCT	Agents for HSV prophylaxis and viral infection treatment (eg, acyclovir, ganciclovir)	1.10 (.32)	1.89 (1.16)
Allogeneic HCT	Agents for treatment of GVHD	1.40 (.70)	—
Allogeneic HCT	Availability of CNI with or without methotrexate for GVHD prophylaxis	1.10 (.32)	—
Interventional radiology	Placement of central line access	1.90 (1.29)	1.44 (.67)

* Added per recommendation of reviewers.
BMT indicates bone marrow transplantation; CSA, cyclosporine A; HSV, herpes simplex virus; HTLV-1, human T-cell leukemia/lymphoma virus type 1.

pathology, radiology, pharmacy, ancillary services, quality, and others.

Essential Requirements

Table 2 outlines all the elements that meet the criteria for essential requirements, including 20 elements common to the development of any HCT program plus 6 elements unique to allogeneic HCT and 3 elements unique to autologous HCT. Among the items of highest priority and thus considered essential elements (mean score $\leq$1.4) for the development of an HCT program with the greatest agreement across reviewers (SD $\leq$1.0) were the following:

- Institutional (or hospital leadership) support for development of an HCT program
- Leadership by a hematologist, oncologist or immunologist as a medical director
- Nursing staff trained in handling chemotherapy and infection control
- Availability of irradiated blood and platelets
- Laboratory services with blood cell counting, chemistry, microbiology testing for bacteria and fungi, and pretransplantation infectious disease markers
- Access to standard radiology and computed tomography (CT)
- Availability of chemotherapy, antiemetics, and broad-spectrum antibiotics.

In addition to these, highest-priority elements for developing an allogeneic program include the following:

- Access to an HLA-typing laboratory
- Ability to monitor calcineurin inhibitor (CNI) levels
- Availability of antiviral and antifungal agents for treatment
- Agents to prevent and treat graft-versus-host disease (GVHD).

Corresponding elements in autologous and allogeneic program include availability of interventional radiology expertise for insertion of indwelling central venous catheters.

Preferred Requirements

Table 3 outlines all elements that meet the criteria of preferred requirements, including the largest number of items (n = 53). Among the common elements for the development of any HCT program include added infrastructure, with government support for activating or registering units, additional staff, focus on quality, accreditation, availability of a series of ancillary services, and more specialized laboratory tests and radiologic services.

Ideal Requirements

Table 4 outlines 19 ideal elements for an HCT program. These elements define further extension of the infrastructure, additional staff, cell processing laboratory capabilities, and other services to accommodate more complex types of transplantations and extension of procedures to maximize safety for higher-risk transplantations.

Review of Requirements

Reviewers recommended additional details on blood product requirements, including the availability of leukocyte-reduced and irradiated blood products. Requirement for access to a tertiary care center, defined as a center of specialized medical care, was ranked as a preferred element; however, reviewers revised this item to be considered an essential requirement, to allow patients to be receive care at hospitals with the maximum concentrated services and available capabilities to address post-HCT emergencies, such as neutropenic fever or acute bleeding. Among laboratory services, the reviewers stressed that access to services off-site is also an acceptable alternative. Access to infection control services and an office for financial services were deleted. The requirement for a minimum number of transplantations per year was removed, because it is already part of most accreditation procedures, an expected natural evolution for an established HCT program. Blood banking criteria were revised to blood banking accredited by the AABB or equivalent, allowing centers a broader range of international accrediting agencies.

DISCUSSION

Minimum requirement guidelines for establishing either an autologous or allogeneic HCT program can help prioritize elements within key domains for initiating a program. An organized and stepwise approach to establishing an HCT program is important to make sure all elements are in place, facilitating future expansion and maximizing both patient and donor safety. Programs embarking on allogeneic HCT face greater challenges owing to the complexity and extended duration of patient risks. The set of requirements presented here can aid the strategic development of programs to optimize the utilization of resources.

Once an HCT program is established, it evolves, and its focus may change. This natural progression leads to increased capacity to offer HCT to a larger number of patients, leading to the need for additional resources and involving increased complexity of care. In addition, as the adoption of newer transplantation modalities may require implementation of additional elements to mitigate risks. For example, haploidentical donor allogeneic HCT requires HLA typing for assessment of donor-specific antibodies, which is rarely needed in an HLA-matched donor HCT.

Essential Requirements

Proper leadership, a dedicated multidisciplinary (especially pharmacist) team, and support within the institution is essential for implementation of a successful HCT program. Other fundamental requirements include access to critical care services (and multispecialty consultants) as well as emergency services, because a variety of life-threatening complications can quickly develop in HCT, regardless of type. The availability of apheresis services, onsite or offsite, is essential for autologous HCT. As new programs plan, they should consider establishing a relationship early with an experienced HCT center within the region or remotely (eg, telemedicine or a “twinning” partnership arrangement) to provide experienced advice in the nuances of HCT procedures. To encourage these relationships with established transplantation centers, the group required that a medical director be a hematologist, oncologist, or immunologist and receive at least 6 months of training focused on HCT.

A feature traditionally considered a minimum requirement for cell processing laboratories is access to a controlled-rate freezing system for optimal stem cell viability. However, this requirement has been debated, given the costs and constraints of cryopreservation systems. Some centers avoid cryopreservation by shortening the period from collection using brief conditioning and then infusion [12]. This could be considered as an alternative in some situations. However, for certain indications, such as multiple myeloma, a second autologous HCT is sometimes planned for a later, second salvage HCT. This cannot be done without appropriate long-term graft cryopreservation.

Laboratory ancillary services must provide procedures required for daily clinical decisions, including complete blood counts, serum chemistry, and tests for diagnosis of bacterial and fungal infections.

Routine blood banking services are needed, as well as the availability of leuko-reduced and irradiated products to avoid the risk of transfusion associated GVHD in severely immunosuppressed HCT recipients. All blood products must meet minimum standards according to international blood bank societies. The AABB is widely known globally, but one regional group, the Africa Society for Blood Transfusion, has collaborated with other international groups to develop a stepwise approach for the preparation and availability of blood products [13].

Basic radiology services with standard X-ray and CT are essential. Availability of basic imaging and CT at the HCT center is critical to facilitate routine clinical decisions.

Unique to the allogeneic HCT setting is the need for access to HLA typing for searching and verifying anti-HLA antibodies. HLA testing and verification of antibodies can be part of blood banking services and, like blood banking, can be performed in reference laboratories. It is important that the laboratory responsible for HLA typing follow guidelines from the American Society of Histocompatibility and Immunogenetics and the European Federation for Immunogenetics for testing and for reporting results.

In addition, in the allogeneic HCT setting, viral monitoring for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) must be available with rapid turnaround. Depending on the prevalence of other viral infections in certain regions, access to testing other viruses (eg, viral hepatitis) will also determine the scope of this requirement. Pretransplantation testing to assess patient eligibility must include serology for previous exposure to CMV, EBV, hepatitis B and C virus, HIV, and human T cell leukemia/lymphoma virus type I, and syphilis. The same serology must be available for testing of potential allogeneic donors.

Table 3
Preferred Requirements for Development of an HCT Program

Domain	Preferred Requirements	Allogeneic HCT Score, mean (SD)	Autologous HCT Score, mean (SD)
Infrastructure	Apheresis suite	2.60 (1.26)	1.67 (1.35)
	Cryopreservation cell storage warehouse	3.30 (1.57)	2.78 (2.01)
	Dedicated transplantation unit	2.90 (1.37)	3.78 (1.65)
	Government support for development or registering new programs	2.30 (1.06)	2.89 (1.52)
	HEPA-filtered units	2.90 (1.37)	4.00 (1.79)
	Outpatient clinic for transplantation recipients	2.10 (.88)	3.11 (1.25)
	Operating room with availability for elective bone marrow harvesting (allogeneic HCT)	2.50 (1.08)	4.33 (2.04)
	Private patient rooms	2.20 (1.32)	3.22 (1.03)
	Transplantation rooms in hematology/oncology wards	2.20 (1.40)	2.22 (1.70)
Staff	Additional physicians: hematologist/oncologist	1.70 (.95)	2.44 (1.62)
	BMT program quality management professional (for accreditation)	4.30 (.95)	3.89 (1.65)
	Cell processing lab director, MD/PhD or PhD with HCT laboratory experience	2.00 (.82)	2.33 (1.43)
	Dedicated professional responsible for coordination of care: PBSC pheresis and bone marrow harvest, including training personnel, scheduling, and performing the procedure	2.50 (1.35)	2.56 (1.57)
	Social worker	4.10 (.74)	4.00 (1.84)
	Physician to oversee related donor workup who is not directly involved with the recipient's workup (allogeneic HCT)	3.90 (1.10)	–
Cell processing laboratory	Capabilities for minimum graft manipulation: RBC reduction, $CD34^+$ cell enumeration	2.20 (1.40)	–
	Cryopreservation procedures and storage space	2.00 (1.40)	1.44 (.82)
Blood banking	Accreditation from the AABB or equivalent	3.20 (.79)	3.22 (1.66)
HLA Testing	Access for consultation with immunogenetic professional to assist in donor or cord blood selection (allogeneic HCT)	3.40 (.97)	–
	Access to trained professional in performing unrelated donor searches	3.10 (1.20)	–
	Capabilities to test for anti-HLA antibodies	3.30 (1.64)	–
Laboratory	Immunoglobulin level	2.30 (1.42)	3.44 (2.33)
	Chimerism analysis (allogeneic HCT	2.60 (.97)	–
Microbiology	CMV detection (antigenemia or PCR) (autologous HCT)	1.70 (.67)	2.67 (1.60)
	Availability for testing for different viruses, including molecular testing (PCR)	2.80 (1.14)	3.67 (1.40)
Pharmacy	Patient-controlled analgesia	3.30 (1.25)	3.33 (2.31)
	Total parenteral nutrition	2.70 (1.06)	4.00 (1.37)
	Ganciclovir for treatment of viral infection (autologous HCT)	1.30 (.48)	3.33 (1.89)
Pathology	Flow cytometry	2.00 (.94)	2.56 (.95)
	PCR for disease markers (allogeneic HCT)	3.70 (1.49)	4.44 (1.57)
Radiology	Magnetic resonance imaging	2.60 (.84)	2.67 (1.43)
Interventional radiology	Placement of central line and assistance with other procedures, including lumbar puncture, thoracentesis, paracentesis, and image-guided biopsy, among others	2.20 (1.62	2.56 (1.89)
Ancillary services (consults)	Hematopathologists	1.90 (.99)	2.22 (1.41)
	Infectious diseases	2.30 (1.25)	2.78 (1.84)
	Gastroenterology and endoscopies services	2.00 (1.15)	3.89 (2.27)
	Pulmonary and endoscopies services	2.20 (1.03)	3.22 (1.85)
	Critical care services or intensivists	1.70 (.95)	2.22 (1.25)
	Radiation oncology	2.20 (1.03)	3.00 (1.83)
	Ophthalmology (cGVHD) (allogeneic HCT)	2.90 (1.20)	–
	Gynecologist (cGVHD) (allogeneic HCT)	4.00 (1.49)	–
	Neurology (allogeneic HCT)	3.20 (1.23)	–
Quality	Accreditation with local, regional, or international BMT quality entities	3.00 (1.56)	3.22 (1.73)
	Collection of demographic and outcome data according to international standardized forms	3.40 (1.07)	3.44 (1.66)
	Data sharing with local, regional, or international outcomes registries	3.60 (1.51)	3.78 (2.01)
	Development of a quality program	3.40 (1.26)	3.44 (1.85)
	Development of a relationship with an established transplant program for at least the first year of implementation	2.00 (.94)	2.44 (1.55)
	Development of standard operating procedures for the HCT program that are available to the whole team	2.50 (1.51)	2.89 (1.78)
Other	Participation and training program for junior faculty in transplantation	4.00 (1.56)	3.11 (1.55)

cGVHD indicates chronic graft-versus-host disease.

Table 4
Ideal Requirements for Development of an HCT Program

Domain	Ideal Requirements	Allogeneic HCT Score, mean (SD)	Autologous HCT Score, mean (SD)
Infrastructure	Structure for outpatient transplantation: infusion room open daily with staffing	3.20 (1.87)	3.33 (1.58)
Staff	Access to a donor search coordinator	4.20 (1.48)	–
	Clinical coordinator for organization of pretransplantation testing and scheduling	4.00 (1.25)	5.00 (1.79)
	Data manager responsible to data capture and reporting	4.60 (.84)	4.11 (1.64)
	Dietitian	4.30 (1.34)	4.11 (1.64)
	Financial services professional	4.40 (1.51)	4.67 (2.10)
	Psychologist for pretransplantation evaluation	5.50 (1.18)	5.22 (2.31)
Cell processing laboratory	Capabilities for more than minimum graft manipulation, such as T cell depletion or $CD34^+$ cell selection	4.40 (0.84)	–
Laboratory	Busulfan PK, either local or as a send-out	4.40 (1.71)	–
Microbiology	Galactomannan assay	4.50 (1.90)	4.67 (1.69)
Pharmacy	Access to ATG	4.00 (1.05)	6.89 (.32)
	Defibrotide	4.60 (1.71)	–
Pathology autologous HCT	PCR for disease markers	3.70 (1.49)	4.44 (1.57)
Radiology	Nuclear medicine	4.20 (1.32)	4.33 (1.97)
	PET/CT scan	3.80 (.79)	4.11 (2.00)
Ancillary services	Psychiatrist	4.40 (.97)	–
Other	Access to extracorporeal photopheresis	5.00 (1.63)	–
	Clinical research coordinators for development or participation in clinical trials	5.30 (1.63)	5.11 (2.07)

PK indicates pharmacokinetics; ATG, antithymocyte globulin; PET, positron emission tomography.

Polypharmacy is a common scenario in transplant recipients. Pharmacists are an important asset to a program and for information on drug interactions, drug levels, and oversight of the use and availability of necessary drugs [14]. Medications used in HCT are expensive and often require prolonged use over weeks to months to minimize complications. Drugs used for infection prophylaxis and treatment (including antibiotics, antifungals, and antivirals); GVHD prophylaxis with CNIs, methotrexate, or mycophenolate mofetil regimens; and corticosteroids and a range of other immunosuppressant agents are all required, particularly for allogeneic HCT. Chemotherapeutic agents used for conditioning and associated antiemetic agents are also important. Access and availability of certain drugs for prolonged treatmentperiods are important considerations.

Additional laboratory tests for allogeneic HCT include monitoring drug levels, particularly those of CNIs (cyclosporine or tacrolimus). Monitoring is critical for routine clinical care of transplant recipients, as drugs must be within therapeutic range to minimize toxicity and avoid breakthrough of GVHD. Like other laboratory tests, availability of testing and rapid turnaround of drug levels are imperative to maximize clinical utility.

Autologous HCT is mainly done using mobilized peripheral blood stem cells (PBSCs), and thus programs that begin with autologous HCT must have an available leukapheresis service for stem cell collection. Allogeneic HCT programs may at first choose only one type of stem cell collection to contain costs and develop focused expertise.

More specialized radiology services, including interventional radiology for insertion of central line access, are preferred but not critical, because these procedures can be performed by others. However, placement of central venous access catheters is among the minimum requirements, so practitioners with expertise in performing this intervention should be available for both autologous and allogeneic HCT. Although not encouraged and rarely needed, donors may also require central line placement for PBSC collection via leukapheresis. Having this expertise available is critical to minimize the risks for donors.

Although it is not part of the minimum requirements, quality management processes should be considered at the very start of an HCT program. As centers expand their services and/or perform higher-risk procedures or newer approaches (eg, cellular therapies and immunotherapies), increasing emphasis should be placed on quality management and accreditation [10]. These services require specially trained professional staff, not only to record and oversee results in their own programs, but also to share with relevant international or regional registries. This can help develop standards of practice in line with accreditation requirements and ensure team compliance with recognized performance standards. One important component related to standards of practice is related to establishing an appropriate plan of care for HCT survivors to screen and educate for late effects after transplantation.

In addition, in the earliest stages of development, programs should establish ongoing training for junior faculty and nursing staff. This is important in forward-thinking programs. Simple growth or evolution into increasingly complex procedures also demands planning, including consideration of data reporting and participation in clinical trials—all of which require skilled clinical coordinators dedicated to research.

Reporting of activities through national or international societies is an essential part of any HCT program. This should be performed in each center using unique and confidential identifiers for each patient.

Preferred Requirements

As programs grow or embark on more complex approaches, there is the need, irrespective of HCT type, for additional trained staff, as well as highly experienced program leaders and other clinical consultants whose subspecialties can support the expanding program. Access to these consultants and off-hour emergency services is critical. It is also advised, resources permitting, to have independent, private patient rooms in a dedicated transplant unit space (within or close to hematology-oncology units) with high-efficiency particulate air (HEPA)- filtered air reaching each room. Of note, practices

vary [15], and many centers perform allogeneic HCTs in non-HEPA-filtered rooms or even in an outpatient setting [12,15], although the latter is often reserved for reduced-intensity conditioned HCT.

The outpatient clinic is important, as even HCT itself can be performed in this setting, but this requires a dedicated infusion room that must be staffed by those capable of handling transplant recipients and skilled in recognizing presentations and complications requiring immediate attention and consultation from more specialized services.

As more complex HCT procedures are conducted, cell processing laboratories, particularly in the allogeneic HCT setting, need to develop expanded capabilities for higher-level processing techniques beyond minimal graft manipulation (eg, T cell depletion or $CD34^+$ cell selection). Conventional HCT procedures can be performed just with the graft processing needed for ABO incompatibilities and appropriate quality assurance.

Support staff become increasingly valuable, particularly dedicated personnel to coordinate bone marrow harvests and/or apheresis activities as well as pre- and post-HCT scheduling and testing. A social worker can also be important to support the myriad of personal and social stressors affecting patients and their families.

Finally, at this preferred tier, governmental support is important for more complex program development, registration of new programs and support for data collection and reporting. Regardless of the model, HCT programs need to stress continuing process improvement.

Once a center has experience performing several transplantations, a plan for accreditation by international bodies and a clinical follow-up plan need to be in place. The importance of accreditation depends on the region. In certain countries, the ability to continue performing HCT is constrained by insurance contracts (as in the United States) or by registration to perform HCT with the government healthcare system (as in the European Union). Participation in clinical trials may also depend on whether the center is accredited by national or international agencies, such as the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE). For other centers, working through the accreditation process is important to standardize all the processes associated with HCT and improve quality. However, given the demanding nature of formal accreditation, the timing and necessity for approval need to be balanced with the cost and time investment for establishing an HCT program. A commitment to work toward accreditation should be part of the aspirational goals of any new program.

Another important activity is the development of a process to monitor and understand HCT outcomes. This is done by registering data from all HCTs with national or international outcomes databases. These data collection processes can directly support program quality improvement. Outcome registries have harmonized the types of data and time points required to understand transplantation outcomes. Participation in these registries is another invaluable activity that has an impact not only locally, but also within the overall transplantation community.

Ideal Recommendations

Ideal but less critical program activities are usually associated with centers performing more advanced procedures that require highly technical support services, such as access to extracorporeal photopheresis techniques requiring expensive equipment and supplies, as well as professionally trained staff. Access to a pharmacokinetics laboratory for safe administration of busulfan is also included. Offsite testing also can be considered an ideal activity.

At this level, quality management and improvement activities are automatically incorporated into accreditation and are an important objective for the sustained quality of an HCT program. Clinical protocols and management algorithms for commonly observed complications can standardize practices and minimize risks to individual patients. Accreditation standards also highlight procedures for communication and coordination of care. The importance of monitoring and reporting transplantation outcomes requires understanding the variables to be captured and setting up a plan to collect and store these data for reporting and analysis. In an ideal setting, a data manager responsible for data capture and reporting is important for any HCT program, as is a quality management professional to oversee the accreditation process. New programs ideally should plan ahead for both these components in the early startup stages.

For greater depth, an HCT program ideally should have a multidisciplinary staff, including a dietitian as well as a psychologist for pretransplantation evaluation, and even a financial advisory professional to plan for payer coverage and define the out-of-pocket expenses for the patient and family. Donor search coordinators and clinical coordinators for organizing all pretransplantation activities become even more important to allogeneic programs. As programs expand and as resources permit, in many centers, one staff member performs multiple roles, particularly at the coordinator level.

Some of these suggestions—particularly for the essential, minimum requirements—have not necessarily been tested in prospective studies. They are recommended based on existing practices in numerous centers worldwide. Thus, there may be alternative approaches to facilitate transplantation that can be considered safe if the broad principles are followed in terms of having suitably trained personnel in a tertiary health care setting. It should be appreciated that staff in areas with scarce resources may identify alternative approaches that are adapted to specific local challenges or reach out to existing structures and organizations. For example, over the last several years, FACT and JACIE in collaboration with the Latin American Group for Blood and Marrow Transplantation have been developing and piloting a stepwise process for centers in the region [16,17]. The 6th edition of the FACT-JACIE standards were broken down into 3 levels to make them more approachable for centers in resource-restricted environments. Level 1 was focused on safety and basic quality structures. Level 2 was aimed at making the quality system operational, whereas level 3 is considered equivalent to full accreditation. In terms of capacity building, a series of joint FACT-JACIE Spanish-language webinars designed to explain fundamental concepts of quality management were provided to professionals in the region. In November 2018, the first pilot inspection was performed, at a center in Argentina. Several more onsite assessments will be performed during 2019, after which the accreditation bodies will review the feasibility and effectiveness of the process for future planning. For centers in World Health Organization-defined low- and middle-income countries, such initiatives have the potential to complement the recommendations presented here.

In conclusion, there is clear demand from the growing low- and middle-income country transplantation community for ways to maximize quality and safety in the delivery of HCT. A phased approach using guidelines and incremental standards

can assist centers in further developing their program activities in a focused and cost-effective matter. HCT specialists in better-resourced countries also have much to learn from their colleagues in other regions in terms of HCT practices adapted to function in conditions of constrained resources. For all, irrespective of location, recognizing the difficulty in implementing even the minimum required elements, and the safety margins required for a successful HCT program, is necessary to refine these recommendations.

ACKNOWLEDGMENTS

The authors thank Carol Doleysh for assistance in organizing the data and Jennifer Motl for editorial support, which was funded by the Medical College of Wisconsin in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The authors also acknowledge Eoin McGrath, JACIE Operations Manager, for reviewing and providing input on the manuscript.

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