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Quality of Care

Worldwide Network for Blood and Marrow Transplantation (WBMT) Recommendations Regarding Essential Medications Required To Establish An Early Stage Hematopoietic Cell Transplantation Program

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A B S T R A C T

Establishing a hematopoietic cell transplantation (HCT) program is complex. Planning is essential while establishing such a program to overcome the expected challenges. Authorities involved in HCT program establishment will

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need to coordinate the efforts between the different departments required to start up the program. One essential department is pharmacy and the medications required. To help facilitate this, the Worldwide Network for Blood and Marrow Transplantation organized a structured survey to address the essential medications required to start up an HCT program. A group of senior physicians and pharmacists prepared a list of the medications used at the different phases of transplantation. These drugs were then rated by a questionnaire using a scale of necessity based on the stage of development of the transplant program. The questionnaire was sent to 30 physicians, in different parts of the world, who have between 5 and 40 years of experience in autologous and/or allogeneic transplantation. This group of experts scored each medication on a 7-point scale, ranging from an absolute requirement (score of 1) to not required (score of 7). The results are presented here to help guide the prioritization of required medications.

Hematopoietic cell transplantation (HCT) is a complex, multidisciplinary procedure that requires collaboration between a number of hospital departments [1,2]. The pharmacy department plays an essential role in procuring and delivering the essential medications required for the smooth running of a transplant program. Different institutions will have different medication needs, depending on regional disease prevalence, the complexity of the transplantation program and the types of transplant delivered. The role of pharmacy becomes even more crucial with the global shortage of some of the essential medications. A structured supply chain is a key component of successful avoidance of drug interruptions and ensures safe and up-to-date transplant care. When establishing a transplantation program, identifying and prioritizing the essential medications needed is not an easy task, and will have an impact on drug approval and funding through the responsible health and insurance authorities [2]. The Worldwide Network for Blood and Marrow Transplantation (WBMT), a nongovernmental organization in an official relationship with the World Health Organization, works to promote transplantation globally [3]. An annual activity survey and a series of workshops were developed and organized by the WBMT to promote, analyze, and help transplantation activities worldwide [1,3-9]. Recently two seminal articles were published by the WBMT to address the requirements and provide guidance and recommendations for establishing a transplantation program including guidance for countries with limited resources [10,11]. This report describes the structured survey organized by the WBMT with the aim of delineating the essential medications needed to run an early-stage HCT program.

METHODS

First, we identified an expert group of physicians and pharmacists with no less than 5 years' experience in the field of HCT. This group prepared a list of the medications used in the different phases of transplant (Table 1). This list was built gradually after exchanging communications between the expert group members. A questionnaire was then constructed to rate these drugs on a scale of necessity (Table 2) based on the stage of development of the transplantation program (Table 3). The transplantation program stages were defined as stage I (program able to carry out 5 autologous HCT and 3 to 5 HLA-matched sibling HCT per year), stage II (program able to carry out 10 autologous HCT with the use of cryopreservation and 5 to 10 HLA-matched or -mismatched sibling HCT per year), and stage III (program able to carry out more than 10 autologous HCT with the use of cryopreservation and more than 10 allogeneic HCT per year using all types of alternate donor transplant with or without graft manipulation). This definition was based on the previously published WBMT recommendations to establish new transplantation programs [10,11].

The questionnaire was then sent to 30 physicians who had between 5 and 40 years of experience in autologous or allogeneic transplantation. They represented transplantation programs from distinct global regions (Europe, Africa, North and South America, Middle East, and Asia) and were directly involved in the development of new transplantation centers. Subsequently, the participants scored each medication on a 7-point scale, ranging from an absolute requirement (score of 1) to not required (score of 7). A drug was considered as the minimum or required, preferred, or ideal but not required, if voted as such by an arbitrary cut of ≥70% of participants.

RESULTS

The drug list prepared by the expert group of physicians and pharmacists consisted of 65 medications. Each question of the survey was answered by the majority of participants (≥26/30). Table 4 summarizes the results. Medications voted for by ≥70% of participants as "minimum acceptable or required" medications for a stage I program comprised: chemotherapy and filgrastim for

Table 1
Medications for Use in Different Phases of Transplantation

Hematopoietic Stem Cell Mobilizer for Autologous PBSCT	Filgrastim. Chemotherapy + Filgrastim. Plerixafor
Mobilization of healthy donors for allogeneic PBSCT	Filgrastim
Chemotherapy for preparative regimens	Busulfan (oral), busulfan (IV), busulfan (IV) combined with TDM-guided dosing, carboplatin, carmustine (BCNU), cyclophosphamide, cytarabine, etoposide, fludarabine, melphalan, thiotepa
Seizure prophylaxis	Phenytoin, levetiracetam, benzodiazepine
Immunosuppression for GvHD prevention and treatment	Antithymocyte globulin (rabbit-derived), alemtuzumab (Campath), basiliximab, budesonide, cyclosporine, etanercept, extracorporeal photopheresis, infliximab, methotrexate, methylprednisolone, mycophenolate, prednisone, rituximab, sirolimus, tacrolimus
Nausea and vomiting	Dexamethasone, neurokinin antagonists, olanzapine, phenothiazines, 5-HT3 antagonists
Antimicrobials	Antibacterial: piperacillin/tazobactam, carbapenem, cefepime, ciprofloxacin, levofloxacin, tigecycline, vancomycin Antifungal: amphotericin B (conventional), amphotericin B (liposomal), echinocandin, fluconazole, isavuconazonium, posaconazole, voriconazole Antiviral: acyclovir, cidofovir, foscarnet, ganciclovir, letermovir, valacyclovir, valganciclovir PCP/PJP prophylaxis: bactrim, pentamidine
SOS prevention and management	Defibrotide, ursodiol
Other medication	IVIG, IV narcotics, PCA, TPN

GvHD indicates graft-versus host disease; IV, intravenous; IVIG, intravenous immunoglobulin; PCA, patient-controlled analgesia; PCP/PJP, pneumocystis carinii pneumonia/pneumocystis jirovecii pneumonia; SOS, sinusoidal obstruction syndrome; TPN, total parenteral nutrition.

Table 2
Scale of Necessity for Medications

Score	Description	Category	Level	Comments
1	Absolutely required	Minimum or required for this stage of program development	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 for this stage of program development	II	Important for further expansion of the program
4	Good			Not necessary but recommended
5	Important but not needed at early implementation	Ideal but not required for this stage of program development	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 3
stages of development of HCT program

	Stage I	Stage II	Stage III
Types of transplantation performed	■Autologous ■HLA-matched sib donors	Stage I + ■All MSD transplants including MMSD ■Autologous with cryopreserved products	Stage II + ■Haploidentical ■and/or MUD, MMUD ■and/or UCB ■and/or T-cell depleted
Number of HCT	5 Auto-HCT/year 3-5 Allo-HCT/year	10 Auto-HCT/year 5-10 Allo-HCT/year	>10 Auto-HCT/year >10 Allo-HCT/year

MMSD indicates mismatched sibling donor; MSD, matched sibling donor; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; UCB, umbilical cord blood; auto-HCT; autologous hematopoietic cell transplant; allo-HCT, allogeneic hematopoietic cell transplant.

Table 4
Medication Score as Voted for by ≥70% of Expert Group

	Required (Score 1 and 2) With Votes Above 70%	Preferred (Score 3 and 4) With Votes Above 70%	Ideal (Score > 4) With Votes Above 70%
Stage I program	Mobilization: -Chemotherapy and filgrastim for autologous PBSCT mobilization -Filgrastim for autologous PBSCT mobilization -Filgrastim for allogeneic PBSCT mobilization Conditioning: -Cyclophosphamide -Cytarabine -Melphalan -Fludarabine Seizures prophylaxis: -Benzodiazepine GvHD prophylaxis: -Cyclosporine -Methotrexate -Methylprednisolone -Prednisone -Dexamethasone Antimicrobials: -Piperacillin/Tazobactam -Cefepime -Ciprofloxacin -Vancomycin -Fluconazole -Acyclovir -Ganciclovir -Bactrim Supportive: -IV narcotics -5-HT3 antagonists	Mobilization: none Conditioning: -Oral busulfan -Intravenous busulfan -Carboplatin -Carmustine -Etoposide Seizures prophylaxis: -Phenytoin -Levetiracetam GvHD prophylaxis: -Tacrolimus -Mycophenolate -Rituximab Antimicrobials: -Carbapenem -Levofloxacin -Tigecycline -Amphotericin B (liposomal) -Echinocandin -Voriconazole -Posaconazole -Valganciclovir -Foscarnet -Valacyclovir -Pentamidine Supportive: -Phenothiazines -Neurokinin antagonists -Ursodiol -IVIG -TPN -PCA	Mobilization: -Plerixafor for autologous PBSCT mobilization Conditioning: -Intravenous busulfan with TDM Seizures prophylaxis: none GvHD prophylaxis: -Antithymocyte globulin rabbit -Budesonide -Sirolimus -Etanercept -Alemtuzumab -Basiliximab -Extracorporeal photopheresis -Infliximab Antimicrobials: -Amphotericin B (conventional) -Isavuconazonium -Cidofovir -Letermovir Supportive: -Defibrotide -Olanzapine

TDM indicates therapeutic drug monitoring.

autologous peripheral blood stem cell transplantation (PBSCT) mobilization, filgrastim for autologous PBSCT mobilization, filgrastim for allogeneic PBSCT mobilization, cyclophosphamide, cytarabine, melphalan, fludarabine, benzodiazepine, cyclosporine, methotrexate, methylprednisolone, prednisone, dexamethasone, 5-hydroxytryptamine receptor antagonists, piperacillin/tazobactam, cefepime, ciprofloxacin, vancomycin, fluconazole, acyclovir, ganciclovir, Bactrim, and intravenous narcotics.

Medications voted for by ≥ 70% of participants as "preferred to have available but not required" medications for a

Table 5
Suggested Transplant Procedure (Stage I Program) for Prevalent Diseases Driven By This Survey's Results

Disease/HCT	Conditioning	GvHD Prophylaxis	GvHD Treatment	Antimicrobials	Antiemetics
SAA	Flu/Cy	MTX/Csa	Prednisone	-Piperacillin/tazobactam -Cefepime -Ciprofloxacin -Vancomycin -Fluconazole -Acyclovir -Ganciclovir -Bactrim	-5-HT3 antagonists -Steroids
AML	Flu/Mel Flu/Cy Preferably: Bu/Cy	MTX/Csa	Prednisone	-Piperacillin/tazobactam -Cefepime -Ciprofloxacin -Vancomycin -Fluconazole -Acyclovir -Ganciclovir -Bactrim	-5-HT3 antagonists -Steroids
ALL	Cy/TBI	MTX/Csa	Prednisone	-Piperacillin/tazobactam -Cefepime -Ciprofloxacin -Vancomycin -Fluconazole -Acyclovir -Ganciclovir -Bactrim	-5-HT3 antagonists -Steroids
Lymphoma auto-HCT	Melphalan Preferably: BEAM or CBV	Na	Na	-Piperacillin/tazobactam -Cefepime -Ciprofloxacin -Vancomycin -Fluconazole -Acyclovir -Ganciclovir -Bactrim	-5-HT3 antagonists -Steroids
Myeloma auto-HCT	Melphalan	Na	Na	-Piperacillin/tazobactam -Cefepime -Ciprofloxacin -Vancomycin -Fluconazole -Acyclovir -Ganciclovir -Bactrim	-5-HT3 antagonists -Steroids

ALL indicates acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; BEAM: BCNU, etoposide, Ara−C, and melphalan; Bu/Cy, busulfan and cyclophosphamide; CBV, cyclophosphamide, BCNU, and etoposide; Cy/TBI, cyclophosphamide/total body irradiation; Flu/Cy, fludarabine/cyclophosphamide; Flu/Mel, fludarabine/cyclophosphamide; MTX/Csa, methotrexate/cyclosporine A; NA, not applicable; SAA, severe aplastic anemia.

stage I program comprised: oral or intravenous busulfan, carboplatin, carmustine, etoposide, phenytoin, Levetiracetam, tacrolimus, mycophenolate, rituximab, phenothiazines, neurokinin antagonists, carbapenem, levofloxacin, tigecycline, amphotericin B (liposomal), echinocandin, voriconazole, posaconazole, valganciclovir, foscarnet, valacyclovir, pentamidine, ursodiol, intravenous immunoglobulin, total parenteral nutrition, and patient-controlled anesthesia.

Medications voted for by $\geq$ 70% of participants as "ideal, but not preferred nor required" in a stage I program comprised the following: plerixafor for autologous PBSCT mobilization, intravenous busulfan with therapeutic drug monitoring, rabbit antithymocyte globulin, budesonide, sirolimus, etanercept, alemtuzumab, basiliximab, extracorporeal photopheresis, infliximab, olanzapine, amphotericin B (conventional), isavuconazonium, cidofovir, letermovir, and defibrotide.

DISCUSSION

Transplant programs are developed using an organized stepwise approach, usually starting with autologous and a small number of allogeneic transplants. Establishing a transplant unit is a challenging task especially in countries with limited resources. As the procedure is complex, so too is the infrastructure involved and consists of multiple disciplines. One essential discipline is pharmacy. Ensuring a constant supply of essential medications is of utmost importance for transplant success. The WBMT works to promote and facilitate transplant activities worldwide. This current project aimed to identify essential medications needed to start a stage I transplant program defined as a program planned to carry out approximately 5 autologous and 3 matched sibling donor transplants per year. A list of 65 frequently used transplant associated medications was collected by a group of experts, this list was sent to 30 transplant experts. Of the 65 medications, 22 were identified (by $\geq$ 70% of the survey participants) as required to run a stage I program, while 27 were labeled as 'preferred to have available but not required' and 16 medications were labeled as ideal to have in a stage I program. Obviously, this list does not encompass all the medications or pharmaceuticals used in transplantation (antibiotics, proton pump inhibitors, anti-tuberculosis medications, anti-hypertensive, new drugs approved for GvHD, etc.). However, we think the paper and the discussion are comprehensive enough to safely plan and implement a stage I program. Of note, the list prepared by the group of experts missed newly approved medications in transplant (like ibrutinib and ruxolitinib), probably as a result of long standing practice bias. Transplant medications are expensive and constitute around 8-39% of the total

transplant cost. Antimicrobials, growth factors and immunosuppressive agents are the major contributors [12-14]. A list of the essential pharmaceuticals will help new program leaders to allocate the budget appropriately depending on the country's constraints and economic status. From a public health perspective, this will help planners to negotiate with health authorities, insurance agencies and payers to develop informed policies. Another important issue that underscores the importance of identifying the essential medications early in the planning process is ensuring their availability and reliable supply. In some countries, busulfan, and parenteral cyclosporine among other drugs, are not available and importing these may be difficult due to logistics (licensing, approval, supplier, manufacturer interest, limited usage etc.). We recommend to identify critical drugs early during the planning process and to pay every effort to make sure supply is not interrupted through mutual agreements with health care authorities and manufacturers as well as agreements with well-established/collaborating international programs. We also recommend to have a backup internal policy in place in case critical drugs are interrupted.

The surveyed senior physicians, after reviewing the survey results, felt that amphotericin or voriconazole, carmustine and etoposide (for lymphoma conditioning) were required medications even for an early stage program, however, as a group these medications were voted as preferred but not required.

CONCLUSION

We have provided a list of fundamental drugs necessary to establish an early-stage HCT program. Table 5 provides the authors' opinion on how to conduct transplantation for prevalent diseases in an early-stage program based on the survey's results. This list is based on the opinion of an expert group from the WBMT based on existing practices in centers worldwide. The group is aware that many drugs are used in some countries but not others (treosulfan, amsacrine, pyrimethamine, etc.), new medications and biosimilars are getting approval in different countries, and essential medications may differ by country depending on the prevalence of specific diseases. However, the list is flexible and can be modified (without compromising the patients' safety) on the basis of specific local practices, economic situation, availability and approval of new drugs, availability of therapeutically-equivalent drugs, and disease prevalence in specific countries.

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SUPPLEMENTARY MATERIALS

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