Biol Blood Marrow Transplant 21 (2015) 2052–2060

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Report

Suitability Criteria for Adult Related Donors: A Consensus Statement from the Worldwide Network for Blood and Marrow Transplantation Standing Committee on Donor Issues

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Article history:
Received 12 July 2015
Accepted 5 August 2015

Key Words:
Related stem cell donor
Suitability criteria

A B S T R A C T

The number of allogeneic hematopoietic stem cell (HSC) transplants performed globally each year continues to increase. Advances in HLA typing, better supportive care, and administration of reduced-intensity conditioning regimens allow treatment of older patients with older sibling donors. Pretransplant donor assessment and testing are very important processes affecting the quality and safety of donation. For unrelated HSC donors detailed recommendations for health assessment have been published, allowing donation only if they are unrestrictedly healthy. Eligibility criteria for related donors are less strict and vary significantly between centers. In situations where a family donor does not meet the suitability criteria for unrelated donors, involved physicians often struggle with the decision whether the matched relative is suitable for donation or not. On behalf of the Worldwide Network for Blood and Marrow Transplantation Standing Committee on

Financial disclosure: See Acknowledgments on page 2059.
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http://dx.doi.org/10.1016/j.bbmt.2015.08.009

Donor Issues, we intended to develop a consensus document with recommendations for donor workup and final clearance of family donors who would not be able to serve as unrelated donors because of their age or pre-existing diseases. This article covers different topics intending to support decision-making, with the goal of minimizing medical risk to the donor and protection of the recipient from transmissible diseases.

INTRODUCTION

Over the last years the total number of allogeneic hematopoietic stem cell transplantations (HSCTs) performed annually has exceeded 30,000 a year. The observed continuous annual increase of around 10% is mainly because of a rise in allogeneic HSCT from unrelated stem cell donors (URDs) [1,2]. In 2013 the proportion of URDs was 53% in centers reporting to the European Group for Blood and Marrow Transplantation (EBMT) [3], and the stem cell source preferably used was granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSCs) in 73% of HSCTs [2]. Furthermore, the number of donor lymphocyte infusions has also been increasing. Advances in HLA typing, the use of new immunosuppressive protocols, better supportive care, and the administration of reduced-intensity conditioning regimens contribute to the increased frequency of HSCT and allow treatment of older patients whose related donors usually are also older [4,5].

Pretransplant donor assessment and testing are very important issues affecting the quality and safety of donation. Several international regulatory bodies (eg, European Directives for Donation of Tissues and Cellular Therapy Products, US Food and Drug Administration) have detailed requirements on donor evaluation to ensure the safety of the product for the recipient but do not address donor safety issues. For HSC URDs, the World Marrow Donor Association (WMDA) has published detailed recommendations for donor assessment [6] and a donor suitability tool [7] open access file reflecting WMDA recommendations to ensure donor and recipient safety as well as the quality of the cellular product. In addition, the Worldwide Network for Blood and Marrow Transplantation (WBMT) has established a consensus statement for a standardized assessment of donor outcome data [8]. Donor eligibility criteria for related donors [9], who still comprise almost half of all donors, are less strict than for URDs [6], with few definite criteria and significant variation between HSCT centers. URDs are only eligible if they are unrestrictedly healthy, most often very similar to eligibility criteria for blood donation. Further differences between related donors and URDs may exist in mobilization and collection practices [8,10-12]. Published data suggest that the risks for serious adverse events and reactions might be higher for related donors than for URDs, but the amount of adequate prospective data in the related setting is still limited [13,14].

Involved physicians often struggle with the decision about whether a related donor not meeting suitability criteria for an URD can be regarded suitable for donation in the related HSCT setting. This article intends to give recommendations to support decision-making, with the goal of minimizing medical risk to the donor and protection of the recipient from transmissible diseases.

METHODS

On behalf of the WBMT Standing Committee on Donor Issues, a workshop with international representatives (Supplementary Table 1) involved in related and/or unrelated HSC donation from various member societies of WBMT took place in Vienna in September 2013. The purpose of this workshop was to develop a consensus document with recommendations for donor workup and final clearance of family donors who would not be able to serve as an URD because of their age (<18 or >60 years) or pre-existing diseases. In preparation for this workshop, different sections regarding organ system assessment, medical conditions, and pediatric donation were defined and assigned to experts in the field who served as group leaders for the particular sections (Supplementary Table 1). Group members performed a thorough review of the literature presented at the workshop and came to a consensus on recommendations for standardized related donor screening.

Sources of information included English-language articles extracted from PubMed (www.ncbi.nlm.nih.gov/pubmed) published until May 31, 2013, focusing on clinical studies of HSC mobilization and donation, guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery [15], and G-CSF application for other conditions than HSC mobilization [16], and the UK, Canadian, Italian, National Marrow Donor Program [17] and WMDA [18] recommendations for evaluation of URD were provided. In addition, group leaders received the S(P)EAR (Serious (Product) Events and Adverse Reactions) Committee Annual Report from 2011 provided by the WMDA (http://www.worldmarrow.org/fileadmin/Committees/SEAR/PRES/20110707-CLWG-SEAR_Summary_2003-2010.pdf) and the report of NOTIFY, a global consultation organized by the Italian National Transplant Centre and the European Union–funded Project "Vigilance and Surveillance of Substances of Human Origin" exploring vigilance notification for organs, tissues, and cells (published in February 2011; http://www.notifylibrary.org/sites/default/files/BOOK%20NOTIFY.pdf).

A consensus was achieved that a classification system for evaluating the physical status of a donor would be very useful to enable assessment by independent physicians or respective specialists for donors with disorders (eg, cardiologists, dermatologists, rheumatologists) who should preferably have knowledge of PBSC mobilization and/or PBSC and bone marrow (BM) donation modalities. Especially for related donor evaluation assigned to BM donation, the implementation of the American Society of Anesthesiologists Physical Status (ASA-PS) classification system [19] was discussed as a possibly useful tool because it records only the individual's preoperative physical status rather than the surgical risk. The ASA system consists of 5 categories that classify individuals according to the severity of their systemic disease and is used worldwide by anesthesia providers [20] (Supplementary Table 2).

The term "disorders" expresses all medical conditions that may affect the safety and efficacy of donation. The participants agreed that the term "generally not recommended" instead of "deferral" should be used to categorize certain medical conditions in the related donor setting.

RESULTS

General Considerations

During the process of donor selection and evaluation, the following general considerations need to be taken into account.

1. *A 10/10 HLA-identical URD should be preferred to a related donor with health disorders exposing himself or herself or the recipient to a higher risk for adverse events as described in the entire article.* For many diseases outcome after URD transplantation is comparable with HSCT with related donors [21]. For these situations an URD if available should be preferred to a related donor with health disorders.
2. *Suitability might be assessed also in donors below and above the age limits for URD.* No strict chronological age limit can be recommended for related donors, but experience is available up to a donor age of 75 years. However, physicians assessing the donor's suitability

should be aware that the prevalence of many health disorders increases with age. Transplant physicians should pay attention to the fact that collection yield as well as graft composition in older donors might be different from young donors [22,23]. In addition, number of $CD34^+$ cells in peripheral blood and $CD34^+$ yield in apheresis products reportedly are lower in older donors [24], and apheresis complications have been more frequently observed [25].

3. *A related donor not meeting donor eligibility criteria for URD might be considered suitable for HSC donation after careful assessment of both the donor's and recipient's risk, including consideration of alternative therapies for the recipient.* Although maximum donor safety is a mainstay in URD HSC collection, related donors are often willing to accept higher risks associated with the donation procedure to help their family members. Indeed, personal experience of the workshop participants as well as a recent publication [26] suggest that beyond the strict suitability and eligibility criteria for URDs, there is a gray area where related donors might donate safely. Furthermore, some disorders lead to donor deferral because of a risk for transmission of a (most often infectious) disease to the recipient. However, transplant physicians and recipients might be willing to accept a certain risk for disease transmission to treat another, more serious, life-threatening malignant disease in a given patient.
4. *Providers responsible for donor care should not be involved in recipient's care.* Standards of the National Marrow Donor Program [17] and the WMDA [18] state that the medical evaluation of an URD must be performed by a physician who is not a member of the HSCT team caring for the patient, and participants of the workshop believed this should be mandatory also for related donors. This is even more important in situations that leave room to physician's discretion to decide on donor suitability. However, this issue is not yet mandatory according to standards of the Foundation for the Accreditation of Cellular Therapy—Joint Accreditation Committee of the International Society for Cellular Therapy and European Group for Blood and Marrow Transplantation [27].
5. *Donor selection and health assessment should be started early and be efficient to provide a sound basis for decision on donor suitability considering risks for donors and recipients. Efforts should be undertaken to prevent any delay of HSCT (eg, due to delayed start of an URD search).* Early in the related donor evaluation process, donor medical assessment may be performed before HLA tissue typing by a limited questionnaire to assess donor fitness and willingness to donate. For investigation of health disorders, disease specialists should be consulted at an early stage of donor workup if appropriate. Based on these results, risk assessment should be made considering all factors that increase risk for donor health and increase risk for recipient health compared with the risk associated with an HSCT from an URD.

   In case of an increased risk for the donor, this individual should be informed thoroughly by a separate evaluator who serves only the donor's interests (*cf.* consideration 3). The donor must be able to decide for or against donation without coercion. In case of increased risk for the recipient, the HSCT center and recipient shall be informed and must decide whether to accept or decline the donor. This raises issues about informing the recipient of donor medical conditions the donor may not wish to share. Detailed information-sharing about medical conditions from the donor to family members must be at the discretion of the potential donor. If a donor is ineligible for medical reasons, the only information that should be shared with the transplant physician (or the recipient and the family) is the statement that the donor is ineligible for donation without communicating further details (eg, HIV). If a donor is not willing to donate, the information given should be the same. In case of a medical condition that may allow an HSCT but is associated with an increased risk for the recipient (eg, hepatitis B virus infection), the donor has to give informed consent for transmission of the information; otherwise, the donor would be ineligible.
6. *The informed consent process plays a central role in donor assessment. The fact that donor and recipient know each other and are in an emotional relationship needs to be considered carefully.* All individuals should fully understand the donation process and give their informed consent to the process and to the testing of their blood and other medical exams for diseases that may affect the suitability of their HSCs. Furthermore, donors have to give separate informed consent for transmission of information about health issues that may affect the recipient's health. Third-party interpreters must understand the requirements of the national and local regulations relevant to the donation process and not be personally known to the potential donor or recipient.
7. *Registration in a donor outcome database is needed to improve our knowledge on risk assessment for HSC donation.* The intent of this article's recommendations is to support decision-making, acknowledging that these are mainly expert opinions that need to be validated in the future. For this reason, as well as to meet the World Health Organization guiding principles on human cell tissue and organ transplantation [28], donor outcome data need to be prospectively collected and analyzed in registries.

A summary of conditions, suitability, and individuals at risk is given in Supplementary Table 3.

Suitability Criteria in Pulmonary Diseases

Asthma

Donor suitability is dependent on disease severity and its control. Individuals are suitable if symptoms are controlled with topical treatment, whereas HSC donation is generally not recommended in subjects dependent on oral corticosteroids because of disease exacerbation. In the case of an acute exacerbation requiring i.v. or oral corticosteroids and/or emergency care/hospitalization, individuals are temporally unsuitable. If possible, corticosteroid administration should be completed within 7 days before HSC donation because corticosteroid therapy can mask signs of infection. In donors classified as >ASA P2, PBSC donation might be considered to avoid intubation during general anesthesia for BM harvest. Individuals with exercise-induced asthma are suitable.

Other pulmonary diseases

HSC donation is generally not recommended for individuals with a history of repeated attacks of coughing or dyspnea at rest to avoid further deterioration of pulmonary function, because there is evidence that administration of G-CSF is associated with significant gas exchange disturbance resolving on discontinuation of the drug [29]. Individuals with cystic fibrosis can be suitable depending on their pulmonary function tests. BM donation requiring intubation is generally not recommended in donors classified as >ASA P2.

Suitability Criteria in Gastrointestinal Disorders

For gastroesophageal reflux, peptic ulcer disease, celiac disease, and irritable bowel syndrome, individuals are suitable if no active bleeding is detected and they are stable under treatment with only mild impact on daily living. After an episode of diverticulitis/diverticulosis, individuals are suitable if they have completely recovered. In ongoing or poorly controlled situations, HSC donation is generally not recommended.

Suitability Criteria for Noninfectious Liver, Biliary Tract, Spleen and Pancreatic Disorders

For hereditary hemochromatosis, donors are suitable if they are fit for blood donation and no organ dysfunction is present (eg, cirrhosis, heart failure). In case of elevated liver enzymes (not associated with infectious disease), the cause should be assessed, and HSC donation is temporally not recommended until a diagnosis has been clarified. Individuals with proven nonalcoholic fatty liver disease are suitable. In Wilson's disease, suitability depends on the disease stage. In subjects with symptomatic disease and organ impairment (eg, Child-Pugh Score B and C), HSC donation is generally not recommended. The latter is also the case for individuals with liver cirrhosis or sclerosing cholangitis [30].

Individuals after splenectomy or with splenomegaly are suitable depending on its cause. There is evidence that spleen size increases during G-CSF administration by 11% to 13%, with splenic rupture as a known, but rare, complication. Donors should be advised to avoid contact sports during G-CSF application, HSC donation, and early thereafter. In chronic pancreatitis the cause should be assessed, and in severe organ impairment HSC donation is generally not recommended.

Suitability Criteria for Kidney and Genitourinary Tract Diseases

In cases of acute renal failure, HSC donation is generally not recommended until recovery and after evaluation of cause. In individuals with chronic renal failure, the cause should be investigated, and donors might be suitable if there are no other contraindications (eg, cardiovascular disease) found. Individuals with a history of glomerulonephritis are suitable if they have fully recovered (including normal urine tests) from an acute infection and no residual kidney impairment has been observed. In cases of chronic infection or an association with systemic disease (eg, systemic lupus erythematosus, diabetes mellitus [DM]) and/or recovery with decreased kidney function (<30 mL/min), HSC donation is generally not recommended. There is evidence that G-CSF may induce transient urinary protein excretion and macroscopic hematuria in HSC donors with IgA nephropathy (Annelies Billen, personal communication, April 2014) or pre-existing microscopic hematuria [31,32]. Based on this, it would be reasonable that donors with a history of immune-mediated glomerulonephritis and abnormal urine tests should preferably donate BM. Individuals with polycystic kidney disease are suitable when they have normal kidney function and normal blood pressure. The major extrarenal complications of autosomal dominant polycystic kidney disease include cerebral aneurysms, presence of cysts in other organs, cardiac valve disease, colonic diverticula, and aortic root dilatation. Therefore, cerebral aneurysms should be excluded during medical workup.

In case of nephrectomy due to disease included in the list of contraindications, HSC donation is generally not recommended. If an individual has only one kidney because of traumatic injury, kidney donation, or birth with a single kidney, donation is suitable if fully recovered with normal kidney function.

Suitability Criteria for Cardiovascular, Cerebrovascular, and Peripheral Vascular Diseases

Because these disorders are more common in elderly individuals or ones afflicted by comorbidities, a thorough evaluation of clinical risk factors has to be performed during the medical workup to identify subjects at risk for developing peridonation cardiac problems and to allow medical optimization of the condition to potentially improve donor's outcome. In addition to the ASA-PS classification system, clinical risk factors should be considered according to the European Society of Anaesthesiology (ESA) [19,33] and American College of Cardiology/American Heart Association guidelines [34]. Clinical risk factors include a history of ischemic myocardial disease, current stable, or a history of heart failure and a history of cerebrovascular disease, insulin-dependent DM, and renal failure. Cardiac conditions that necessitate further evaluation and treatment include unstable coronary syndromes, recent myocardial infarction within 30 days, decompensated heart failure, significant arrhythmias, and severe valvular disease [33,35]. The ESA guidelines state that cardiac risk but not age should be used to trigger increased medical assessment and that the likelihood of postoperative mortality and morbidity depends on an individual's background risk interacting with the grade of intervention (level of evidence B) [33,35]. In the ESA and European Society of Cardiology guidelines for preoperative cardiac risk assessment in noncardiac surgery, a preoperative cardiac risk stratification according to the Lee index including a history of ischemic heart and/or cerebrovascular disease, heart failure, insulin-dependent DM, impaired renal function, and high-risk type of surgery is recommended (level of evidence A) [36]. Furthermore, measurements of brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) could serve as biomarkers for cardiac impairment (level of evidence B). Participants at the workshop agreed that noncardiac surgery is comparable with BM and PBSC donation and recommend the use of ASA-PS classification and European Society of Cardiology/ESA and American College of Cardiology/American Heart Association guidelines for predonation assessment by general medicine physicians and specialists.

G-CSF has been used in a substantial number of patients with acute myocardial infarction to improve regeneration [16,37,38]. In a meta-analysis studying the efficacy and safety of G-CSF of 6 randomized trials with 320 patients, including 160 given G-CSF, 16% and 19% of cardiac events were reported in the G-CSF and the control group, respectively, including 2 deaths in each cohort. Of note, no increase in target-vessel stenosis was observed in the G-CSF group [16]. The

literature on autologous PBSC harvests in patients with severe chronic ischemic heart disease suggests that fewer $CD34^+$ cells are mobilized by G-CSF compared with age-matched control subjects; however, no increase in cardiac site effects was observed [37,39-41].

Participants of the workshop recommend that a thorough evaluation of clinical risk factors preferably by an independent physician should be performed during the medical check-up. In case of an active cardiac disease, thorough evaluation by a cardiologist is required and cardiac risk stratification should be performed by a cardiologist or anesthesiologist. Furthermore, existing comorbidities should be evaluated during the medical check-up, including heart failure, ischemic heart disease, transient ischemic attack or stroke, renal failure, brain failure (dementia and delirium), and peripheral arterial disease. A potential donor's physical fitness and predonation risk score for BM or PBSC donation should be assessed using criteria for noncardiac surgery. If a donor is found to be suitable, a plan for peridonation treatment and supportive care should be established before start of the donation procedure.

Eligibility Criteria in Noninfectious Eye Diseases

Noninfectious inflammatory eye diseases (uveitis, iritis, iridocyclitis, chorioretinitis, scleritis, conjunctivitis) can occur as an isolated manifestation of an autoimmune disease in association with systemic diseases (eg, arthritis, connective tissue diseases, Behçet disease), as a result of a trauma, or as a side effect of medications. HSC donation is generally not recommended during an acute inflammatory process because uveitis has been reported as an adverse event after G-CSF administration [42,43]. In the presence of systemic disease suitability has to be assessed accordingly. A potential transmission of autoimmune disease has to be considered with the recipient before donation [44].

Glaucoma describes a group of ocular disorders leading to intraocular pressure-associated optic neuropathy. Individuals are suitable if glaucoma is well controlled and stable and if an underlying disease does not exclude suitability. Temporary deferral should be considered in newly diagnosed or unstable situations until treatment is established to avoid donor risk. Subjects with age-related macular degeneration or retinitis pigmentosa, an inherited or spontaneously occurring degenerative eye disease, are considered suitable. Eligibility of individuals with corneal grafts has been addressed by many national and international regulations and guidelines. Transmission of variant Creutzfeldt-Jakob disease (vCJD) by infected cornea grafts has been reported [45,46], and in theory transmission to the HSC recipient might be possible if the donor has been exposed to CJD by a corneal transplant before donation, although this has not been reported to date. In view of the long latency until manifestation of clinical disease [47], individual cases should be decided by the HSCT center and the respective recipient.

Suitability Criteria for Hematological Diseases and Coagulation Disorders

In case of anemia the underlying cause should be evaluated. Subjects are eligible if anemia is mild (<2 g/dL below lower limit of normal) or corrected unless the underlying condition is a contraindication for HSC donation. PBSC rather than BM collection might be considered to avoid further RBC loss. Individuals with hemolytic anemia are suitable if the disease has been infectious- or drug-induced and they have fully recovered. HSC collections from individuals with RBC abnormalities such as spherocytosis and elliptocytosis are generally not recommended, whereas subjects with G6PD deficiency are eligible [48]. Individuals with thalassemia trait, mild α-thalassemia, or β-thalassemia minor are suitable, whereas donations in case of intermediate/major forms are generally not recommended. The same holds true for sickle cell anemia. Subjects with sickle cell β-thalassemia minor may be suitable for BM donation. However, it is strongly recommended to avoid G-CSF in donors with sickle cell β-thalassemia, sickle cell disease, or other complex sickle hemoglobinopathies because this may provoke severe sickle cell crisis [49,50].

Individuals with neutropenia or lymphocytopenia without an underlying condition despite thorough medical evaluation are suitable if cytopenia does not exceed less than 1.0×10^9 neutrophils/L or less than 0.5×10^9 lymphocytes/L (expert opinion). It is not clear if an adequate mobilization can be achieved in these conditions.

Individuals with leukocytosis and lymphocytosis are suitable if no underlying condition known to be a contraindication to donation is present. In individuals with monoclonal B cell lymphocytosis with confirmed clonality, HSC donation is generally not recommended. In individuals with a persistent (>3 months) monoclonal paraproteinemia detectable by protein electrophoresis, HSC donation is generally not recommended.

HSC collections from individuals with platelet disorders are generally not recommended if excessive bleeding or bruising is to be expected or from individuals with excessive thrombocytosis due to the potentially increased risk for venous thromboembolism (VTE). Individuals with mild thrombocytopenia (100 to 130 $\times 10^9$/L) are suitable unless the underlying condition is a contraindication for HSC donation. Individuals with thrombocytopenia of unknown origin or secondary immune thrombocytopenia (due to an underlying disease or drug exposure) are suitable if the disease has completely resolved. HSC donation is generally not recommended if subjects are symptomatic or are less than 6 months from recovery.

Individuals with a history of VTE are suitable if a specific cause other than cancer has been identified and anticoagulant therapy has already ceased. VTE prophylaxis needs to be considered during the collection process. HSC donation is generally not recommended in recurrent VTE (≥2 episodes in 12 months). Individuals with hereditary thrombophilia without VTE, such as subjects with factor V Leiden, may be suitable, but prophylaxis for VTE should be considered. Subjects with bleeding diathesis (eg, von Willebrand disease) are suitable if the disease is mild and asymptomatic or well controlled by replacement therapy. Donors with acquired hemophilia and/or bleeding diathesis are considered ineligible. Subjects with hemophilia are suitable if they are only carriers or in case of factor XII deficiency. In all other cases of hemophilia, donors may become suitable for donation after adequate factor replacement.

Suitability Criteria for Malignancies

Several studies describe the risk of donor-derived malignancy transmission in solid organ transplantation, whereas no data exist for HSCT [9,51,52]. The main reason for this is that almost all donors with a history for malignancy are excluded from stem cell donation. This is also defined in several national and international legislations stating that all

individuals with a history or presence of invasive cancer should not be considered for HSC.

In cases of a history of basal cell carcinoma or a carcinoma in situ of the uterine cervix, responsible physicians need to have written histological confirmation to exclude invasive disease and to avoid malignant disease transmission. However, if a donor is in remission from an invasive cancer for more than 5 to 10 years, that donor could at least be considered if no other donor is available. As guidance, risk categories for donor tumor transmission in solid organ transplantation could be used [51]. In case of intermediate risk of tumor transmission, the use of this donor is generally not recommended. On occasion, a lifesaving transplant may be acceptable in circumstances where recipient expected survival without transplantation is short. Informed consent of the recipient should be required. Women without a history of cancer but with *BRCA1/2* positivity and on antihormonal medication for breast cancer prevention (tamoxifen/aromatase inhibitors) are considered suitable if more than 4 weeks have passed after the last dosage of medication.

Suitability Criteria for Immunodeficiencies and Autoimmune Disorders

Currently, over 120 conditions associated with primary immunodeficiencies are known [53]. Nearly all individuals diagnosed with primary or acquired noninfectious immunodeficiencies are permanently ineligible for HSC donation. Subjects with recovered immunodeficiency proven by laboratory test results may be eligible on an individual basis. Individuals with selective IgA deficiency may be suitable to donate if they are otherwise doing well.

For many autoimmune disorders adoptive transfer of diseases from the donor to the recipient during allogeneic HSCT has been documented [44,54,55], although it is currently unclear whether these were transferred by donor HSC, T cells, other cells, and/or antibodies [44,56]. Thus, in all cases a careful risk-to-benefit analysis has to be performed for both the donor and the recipient. However, HSC donation is generally not recommended in individuals with systemic multiorgan involvement, including ankylosing spondylitis, antiphospholipid, antibody syndrome, arteritis cranialis (temporal arteritis), thromboangiitis obliterans (Buerger's disease), dermatomyositis, polymyositis, polymyalgia rheumatic, multiple sclerosis/optic neuritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis syndromes, Cogan's syndrome, and Behçet's disease, because these diseases can be transmitted and have a severe impact on a recipient's quality of life, need for additional therapy, and survival beyond the risks for the donor. Based on expert opinion, participants of the workshop stated that in the presence of any immunosuppressive medication other than low-dose steroids (ie, $\leq$5 mg prednisolone/day), HSC donation is generally not recommended because these medications may increase a donor's susceptibility for opportunistic infections.

Of note, their impact on the recipient's immune reconstitution and on risk for graft-versus-host disease is not known yet. Therefore, the transplant physician and the recipient should weigh the risk and benefits on an individual basis. Furthermore, the potential risk of disease flare-up in the donor mainly through administration of G-CSF [29,57,58] but in rare cases also in BM donation should be taken into consideration [59].

Single-organ autoimmune disease, including thyroid disease (eg, Hashimoto thyroiditis, Graves' disease), pernicious anemia, psoriasis, alopecia areata, and vitiligo usually are not life-threatening, and individuals are often otherwise medically fit for HSCT donation. Subjects with mild or moderate psoriasis requiring only topical treatments are suitable when collection sites are unaffected. In thyroid disease, thyroid dysfunction should be controlled and a state of euthyroid function should be achieved before donation. No data on donor suitability are available for HSC donation, but in analogy to recommendations for pregnancy, donors might be suitable at the earliest 6 months after radioiodine therapy in relation to the complete clearance of radioiodine from the body after therapy or 1 month after administration of thyrostatic drugs, respectively [60]. PBSC donation is feasible, because G-CSF treatment in patients with Graves' disease and agranulocytosis after administration of thyrostatic drugs reportedly did not cause an exacerbation of the underlying disease [61,62].

Individuals with DM type 1 are suitable if DM is controlled and no evidence of late effects (eg, vasculopathy) are present, leading to an increased risk for donation. In case of active autoimmune hepatitis, HSC donation is generally not recommended. Subjects are suitable if they are asymptomatic and have not been under immunosuppressive medication for at least 3 months. BM is the preferred source of HSC [29,57,58].

Only in asymptomatic subjects with inflammatory bowel disease (ulcerative colitis, Crohn's disease) without signs of inflammation and no immunosuppressive medication for at least 3 months is HSC donation suitable. Because there is no evidence that G-CSF worsens the symptoms of inflammatory bowel disease [63,64], no preference for donation can be stated.

Individuals with arthritis (rheumatoid, psoriatic, other cause) are suitable if disease is mild and only requires nonsteroidal anti-inflammatory drugs. To avoid G-CSF as a trigger of joint inflammation, PBSC collection is not recommended [65]. In addition, it has been shown that individuals with severe rheumatoid arthritis mobilize significantly less $CD34^+$ cells than healthy individuals [66].

Other Musculoskeletal Diseases

Subjects with asymptomatic osteoporosis are suitable for PBSC or BM donation. In symptomatic individuals BM donation is generally not recommended because of the higher incidence of procedure-related side effects. Individuals with a history of osteomyelitis are suitable if they are cured and clearance of osteomyelitis is documented. Subjects with mild/occasional back or spine pain are suitable for PBSC donation if there is no underlying condition leading to deferral. A history of current herniated or slipped disc, severe/chronic pain, and of back surgery mandates PBSC donation only. Individuals with scoliosis are suitable if no functional impairment is detected. Subjects with muscular dystrophy are suitable for PBSC donation if they are able to tolerate the length of the procedure. Individuals with a history of malignant hyperthermia are suitable for PBSC donation only.

Suitability Criteria for Allergies and Allergic Reactions

Donors with allergies or anaphylactic reactions might be suitable if the precipitating agent is known and preventive actions ensure that donors will not be exposed to these agents (eg, iodine, latex, lidocaine, acid-citrate-dextrose) during PBSC or BM collection. The same is true for IgE-mediated allergies, but because these can also be

transferred to the recipient the potential impact might be severe. If a previous allergic reaction to G-CSF has been documented but the individual is otherwise healthy, he or she is suitable for BM donation only. To avoid sequelae due to allergic reaction in association with G-CSF, standards shall be followed to ensure at least the first G-CSF dose is administered under medical supervision [18,27]. If an allergic reaction occurs during the currently ongoing mobilization process, the donor shall not receive further doses of G-CSF but may be considered for BM collection if possible [67,68].

Suitability Criteria for Endocrine and Metabolic Diseases

Individuals with well-controlled DM type 2 are suitable if they do not have any late effects leading to an increased risk for donation. In case of a history of gestational DM, individuals are suitable after its resolution. DM type 1 is covered above in Suitability Criteria for Immunodeficiencies and Autoimmune Disorders. In individuals with gout, BM should be considered the preferred HSC source to avoid acute gouty arthritis due to G-CSF exposure [69]. Subjects with hyperlipidemia with or without treatment are only suitable if they do not have symptomatic cardiovascular disease.

Obese subjects are generally suitable if body mass index (BMI) in adults is $\leq$40. Centers should consider deferral of individuals with BMI $>$ 40 because these individuals are known to experience higher rates of donation-related adverse events [70]. Getting adequate venous access and/or BM collection can be more challenging and anesthesia-related risk increases (eg, ASA P3 for BMI $>$ 40). Individuals with Addison's disease need to be evaluated for the cause of adrenal insufficiency. If medical workup does not lead to a deferral (eg, infections, amyloidosis, malignancies), asymptomatic individuals on well-controlled replacement therapy are suitable for HSC donation.

In subjects with a history of administration of human pituitary-derived growth or gonadotropin hormones, the HSCT center and the recipient shall be informed on the possible risk for vCJD transmission. Suitability should be assessed accordingly.

Suitability Criteria for Neurological Disorders (Except Cerebrovascular Disease)

Individuals with a history of meningitis/encephalitis are suitable if they have fully recovered. If complement deficiency is the cause of (recurrent) meningitis, HSC donation is generally not recommended. Subjects with epilepsy/seizures are suitable if they are well controlled and are certified to have the fitness to drive (surrogate marker for well-controlled seizures).

In cases of dementia or mentally disabled individuals, careful attention should be paid to the ability of the individual to understand the donation process and to give informed consent to both the medical workup and the collection procedure. Those unable to give appropriate consent should be carefully considered in the light of possible alternative URD. Mentally disabled individuals should be treated similar to children, with an appropriate caregiver and legal advocate helping to decide. During the workshop participants suggested that in donors with mental disorders stem cell harvest and cryopreservation should be considered in advance before the conditioning regimen is started. In cases of disabled subjects or ones with communication difficulties, their ability to consent should be assessed by a special care physician.

Individuals with migraine or Tourette's syndrome are suitable. For the latter, BM donation might be preferred as motoric tics may cause difficulties in PBSC collection.

In cases of CJD, including sporadic, familial, and classic type, donors are permanently deferred. In cases of first-degree relatives with CJD, family risk of CJD ($>$2 relatives with CJD), history of dura mater graft, and use of human-derived growth or human pituitary gonadotropin hormone, HSC donation is generally not recommend. Different national and international legislations need to be considered (*cf.* corneal grafts). If legislations do not preclude donation, individual cases should be decided by the HSCT center and the recipient.

Suitability Criteria for Psychological-Psychiatric Disorders

Subjects with eating disorders (anorexia and/or bulimia) are suitable if their disease is stable under appropriate treatment and their BMI is $>$16.0 in adults. HSC donation in individuals with multiple personality disorders and psychosis is generally not recommended. Subjects with obsessive-compulsive, attention deficit, or attention deficit hyperactivity disorders are suitable if their disease is well controlled. However, the donor's capacity to follow through the donation process may be affected. Individuals with unexplained or chronic fatigue syndrome are only suitable if they are asymptomatic or their symptoms do not affect activities of daily life.

In case of substance abuse such as marijuana, individuals are suitable but may require cessation of use before donation/G-CSF injections. Subjects with a history of cocaine, crack, and methamphetamine (intranasal/oral) abuse might be suitable. Because methamphetamine use is associated with an increased risk of cardiovascular pathologies, a careful assessment is required. Individuals who are on a substitution program but otherwise healthy are suitable. In cases of active i.v. drug abuse, donation is generally not recommended. In all individuals a careful history and medical assessment has to be taken for risk factors for infectious diseases or underlying psychiatric disorders. During the workshop participants suggested that in donors with selected psychiatric disorders (eg, anxiety, depression, and bipolar disorders) HSC harvest and cryopreservation should be considered in advance before the conditioning regimen is started.

Suitability Criteria for Pregnant and Breastfeeding Women

HSC collection during pregnancy is not recommended. Breastfeeding women are suitable for BM and PBSC donation, but breastfeeding has to be temporarily paused from start of the collection procedure (ie, start of anesthesia or first dose of G-CSF) by pumping and discarding breast milk post-anesthesia or after the last dose of G-CSF for 24 hours and then resuming to breastfeeding [71].

CONCLUSIONS

Allogeneic HSC donation is a safe procedure with very low rates of serious adverse events [13]. However, new developments in the treatment of hematological diseases (eg, reduced-intensity conditioning, haploidentical transplantation) confront us with a number of challenges like elderly family donors or donors with comorbidities. Although the WMDA has published detailed recommendations for the assessment of donor health [6], these recommendations focus on URDs only.

It is a reality that, for different reasons, many related donors fall beyond the scope of eligibility and suitability criteria for unrelated donation but still can safely donate cells to save a life. This article of the WBMT Standing Committee on Donor Issues is meant to give physicians some guidance for decision-making. To improve our knowledge in the short and long term, follow-up in all donors with prospective data collection and analysis in large registries is absolutely vital in the future [8,72] in this rapidly evolving field to allow vigilance and surveillance of donations and improve knowledge of the risks of donation.

ACKNOWLEDGMENTS

Financial disclosure: Supported by the Austrian Bone Marrow Donor Registry, especially Gottfried Fischer, and the Swiss Blood Stem Cells, especially Ursula Python, in terms of organizing the workshop in Vienna.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: N.W., A.B., H.T.G., H.H., W.N., M.P., G.N.dF., M.B., A.B., M.F., V.G., K.H., T.N., S.M.vW., V.R., and J.P.H. attended the workshop and wrote the manuscript. G.E., Y.K., H.K., G.L., D.N., C.V., D.W., and H.Y. contributed the comments and wrote the manuscript. N.G., V.H., T.M., H.S., B.S., M.T., and T.T. attended the workshop and contributed the comments. All authors are fully responsible for the content of this manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at 10.1016/j.bbmt.2015.08.009.

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