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Analysis

Collection, Cryostorage, Transplantation, and Disposal of Hematopoietic Stem Cell Products

Katharina Kriegsmann[1], Maurizio Wack[1], Petra Pavel[2], Anita Schmitt[1], Mark Kriegsmann[3], Thomas Bruckner[4], Carsten Müller-Tidow[1], Patrick Wuchter[5,*]

[1] *Department of Medicine V, Heidelberg University, Heidelberg, Germany*
[2] *Stem Cell Laboratory, IKTZ Heidelberg, Heidelberg, Germany*
[3] *Institute of Pathology, Heidelberg University, Heidelberg, Germany*
[4] *Institute of Medical Biometry und Informatics, Heidelberg University, Heidelberg, Germany*
[5] *Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, German Red Cross Blood Service Baden-Württemberg–Hessen, Mannheim, Germany*

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Many transplantation centers routinely collect 1 or more autologous peripheral blood stem cell (PBSC) grafts in patients with hemato-oncologic and autoimmune disorders. However, subsequent high-dose chemotherapy and autologous blood stem cell transplantation (ABSCT) are often not performed, for various reasons. Currently, little is known about the actual utilization rate of stored PBSCs. We retrospectively analyzed the collection, storage, and disposal practices of PBSC products from a large cohort of patients (n = 1020) with hematologic, oncologic, and autoimmune disorders at our institution over a 12-year period. Patients with multiple myeloma were excluded. Based on our institution-specific charges, we estimated the costs for PBSC collection/processing and storage. The median number of sufficient PBSC collections per patient in the whole cohort was 2 (range, 1 to 6). We could demonstrate that only 67% of all patients who had collected sufficient PBSCs for transplantation actually underwent ABSCT, and only a small minority of all patients (4%) underwent multiple ABSCTs. The actual use of the stored PBSC grafts varied among disease entities from >80% to 0%. From a retrospective standpoint, the collected and discarded (definitively not used) or stored (potentially not used) cryostored PBSCs were associated with considerable costs of collection, cryopreservation, and long-term cryostorage. Although keeping open the therapeutic option for future transplantations may be important, there is currently a huge discrepancy between collection/storage practices and actual utilization of the cryopreserved PBSCs, at a considerable cost and strain on patients. Our study provides a rationale for reevaluating the present standards.

INTRODUCTION

High-dose chemotherapy (HD-CHT) followed by autologous blood stem cell transplantation (ABSCT) is a standard therapy for various malignant and nonmalignant diseases, including leukemia, lymphoid malignancies, multiple myeloma (MM), solid tumors (eg, germ cell tumors, sarcoma), amyloid light chain (AL) amyloidosis, and autoimmune disorders [1-5]. Peripheral blood stem cells (PBSCs) have become the most widely used hematopoietic stem cell source in this setting [6,7]. Considering the difficulty of collecting an additional PBSC graft after an initial myeloablative HD-CHT and ABSCT, many centers routinely collect and store 2 or even more PBSC harvests to ensure the ability to perform tandem and/or salvage ABSCT [8].

In patients with MM, clinical trials have showed improved overall survival from tandem ABSCT compared with single ABSCT [9,10] and have revealed that salvage ABSCT after a prolonged remission can be an effective treatment option at the time of relapse [11-13]. Many centers collect up to 3 adequate PBSC grafts for transplantation-eligible patients with MM in first-line therapy. This stem cell graft may be valuable even after many years, given that a mobilization approach in case of relapse can be cumbersome [14]. As a matter of fact, the use of HD-CHT and ABSCT in cases of relapse may decline in the coming years with the advent of novel therapies for MM, including CAR-T cells and daratumumab. However, up to now the potential benefit of these grafts has not been broadly under debate, and thus no data from patients with MM were analyzed in the present study.

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* Correspondence and reprint requests: Patrick Wuchter, MD, Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, German Red Cross Blood Service Baden-Württemberg–Hessen, Friedrich-Ebert-Straße 107, 68167 Mannheim, Germany.
E-mail address: patrick.wuchter@medma.uni-heidelberg.de (P. Wuchter).

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As a matter of fact, in many other diseases, despite the availability of 1 or several PBSC harvests for transplantation, HD-CHT and ABSCT are often not performed for various reasons, such as disease relapse or progression, deterioration of general condition, severe comorbidities, or the availability of novel treatment options. Currently little is known about the ratio of stored and "unused" autologous PBSCs in patients other than those with MM. In the present study, we evaluated the PBSC collection, storage, and disposal practices and associated costs in a large cohort of patients with hematologic, oncologic, and autoimmune disease entities who underwent PBSC collection at our institution over a 12-year period.

PATIENTS AND METHODS

Patient Selection, Data Collection, and Matching

All non-MM patients who underwent autologous PBSC collection at the Department of Medicine V (Hematology, Oncology, and Rheumatology) at the University Hospital Heidelberg between January 2001 and December 2012 were included (n = 1020). Clinical characteristics and disease-related parameters (diagnosis, sex, age at diagnosis) and the dates of PBSC collection, ABSCT, and, if applicable, PBSC disposal were collected retrospectively from the medical records. Data were evaluated separately for each patient. The final dataset analysis was performed in June 2016, which was set as the reference date. Therefore, the minimum follow-up time of PBSC harvest was 4.5 years. Written informed consent for data evaluation was obtained from each enrolled patient. This retrospective data analysis was approved by the Ethics Committee of the Medical Faculty of Heidelberg University.

PBSC Cryopreservation, Storage, and Disposal

The minimum number of $CD34^+$ cells for 1 transplantation was defined as $\geq 2.0 \times 10^6$/kg of body weight (bw), with the goal of collecting enough $CD34^+$ cells for 1 to 3 transplants, depending on the diagnosis. Before cryopreservation, the PBSC products were centrifuged and diluted with autologous plasma or resuspension medium (Plasmalyte A; Baxter, Unterschleissheim, Germany or Composol PS; Fresenius Kabi, Bad Homburg, Germany) and CryoSure-dimethyl sulfoxide (DMSO; WAK-Chemie Medical, Steinbach, Germany) to obtain a target nucleated cell concentration of $\leq 5 \times 10^8$/mL and a total volume of 100 mL per bag. By increasing the cell concentration, the number of cryostored bags could be reduced to a minimum; however, in some cases, 1 PBSC harvest ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg bw) still had to be stored in several bags. The final product included 10% DMSO and was stored in vapor-phase nitrogen at a temperature of ≤ -140°C after controlled-rate freezing. PBSCs were processed and stored in accordance with the German Medical Council and responsible scientific society guidelines [15-17]. PBSC products were stored until ABSCT or disposed after of a minimum of 5 years of storage at the stem cell laboratory (IKTZ Heidelberg). The disposal of PBSC products was usually performed during a review of PBSC product stocks initiated by the stem cell laboratory every 2 to 3 years. At this occasion or on specific request of the Department of Medicine (in which the patients were treated), PBSC products were disposed when the IKTZ received confirmed notice that a patient was deceased.

PBSC Storage Period and Cost Estimation

Two types of costs were calculated and are discussed: the costs for the leukapheresis (LP) sessions required to collect/process the PBSCs and the costs to store the unused transplants. It should be noted that costs and charges may be different. Because stem cell collection and cryostorage were performed by the stem cell laboratory of IKTZ Heidelberg, which is a nonprofit institution, the charges came very close to the costs.

To calculate the costs to collect/process the unused transplants, all patients who did not undergo ABSCT was not performed after PBSC collection were identified. Subsequently, the number of LP sessions that was required to collect these PBSC harvests was determined in this (not transplanted) patient cohort. Thereby, a distinction was made between the definitively not used transplants (1.A: ABSCT not performed and transplants discarded) and the thus far not used transplants, which theoretically still could be used in the future (1.B: ABSCT not performed and transplants stored until reference date). The institution-specific charges were defined as €3000 for an LP session plus processing of the collected PBSCs (including patient workup, CD34 measurement, cryopreparation, quality control, and cryostorage for 12 months). Patients who failed to collect a quantitatively sufficient harvest of PBSCs for transplantation were excluded from the additional LP cost assessment, because ABSCT a priori was infeasible.

The duration of storage (in months) was determined separately for (2) transplanted bags (time from PBSC collection to ABSCT), (3) discarded bags (time from PBSC collection to disposal) and (4) bags stored until the reference date (time from PBSC collection to June 2016).

The PBSC products were usually stored for a minimum of 5 years (60 months), because this is the timespan for which an adequate quality of cells could be guaranteed by the stem cell laboratory (IKTZ Heidelberg). Therefore, an additional differentiation regarding the storage period was made: (A) the sum of cost-relevant storage months if the bag was stored for >12 months or (B) the sum of cost-relevant storage months if the bag was stored for >60 months. The costs for the storage of PBSC harvests were estimated based on our institution-specific charges: €13 per cryopreserved bag per month starting at 13 months of storage.

Statistical Analysis

Descriptive statistics were determined in RStudio version 0.99.451, 2009-2015 (RStudio, Boston, MA). Data are presented as absolute numbers and percentages, as median (range), and, in the case of additional storage periods, as mean (SD). The time points of PBSC use (ie, time of ABSCT) were calculated and plotted using Kaplan-Meier survival analysis.

RESULTS

Patient Characteristics and PBSC Collection Results

Our study cohort comprised 1020 patients with various hemato-oncologic and nonhematologic diseases (excluding MM) who underwent autologous PBSC collection at our institution between January 2001 and December 2012. Among these patients were 74 with acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS), 18 with myeloproliferative neoplasm (MPN), 20 with acute lymphatic leukemia (ALL), 17 with Burkitt lymphoma, 13 with chronic lymphocytic leukemia/prolymphocytic leukemia (CLL/PLL), 9 with marginal zone lymphoma (MZL), 4 with lymphoplasmacytic lymphoma (LPL), 104 with follicular lymphoma (FL), 91 with mantle cell lymphoma (MCL), 227 with diffuse large B cell lymphoma/gray zone lymphoma (DLBCL/GZL), 61 with T cell non-Hodgkin lymphoma (T-NHL), 57 with Hodgkin lymphoma (HL), 163 with amyloidosis (AL), 3 with light chain deposition disease (LCDD), 96 with sarcoma, and 29 with germinal cell tumor, 9 with rare entities (ie, primary central nervous system [CNS] tumor, ovarian cancer, metaplastic breast cancer, esthesioneuroblastoma, and thymoma), and 25 with autoimmune disorders (AIDs). Almost all patients were able to reach the collection goal (ie, $\geq 2 \times 10^6$ $CD34^+$ cells/kg bw), and <5% experienced collection failure. Median numbers of collected transplants were 1 in patients with AML/MDS, ALL, MZL, LPL, FL, MCL, and T-NHL; 2 in patients with MPN, Burkitt lymphoma, CLL/PLL, DLBCL/GZL, HL, AL amyloidosis/LCDD, sarcoma, rare entity and an AID; and 3 in patients with germ cell tumors. The median number of cryopreserved bags per patient in the whole cohort was 2 (range, 1 to 8). A detailed summary of patient characteristics and PBSC collection parameters is provided in Table 1.

Proportions of Performed and Not Performed ABSCTs

First, the data were evaluated for the patients who underwent PBSC collection (Figure 1, **Supplementary Table 1**). We found that not nearly all patients who underwent 1 or more PBSC collections were actually referred to an ABSCT. Considerable differences in the proportion of patients who underwent ABSCT were observed based on disease entity. Specifically, patients with CLL/PLL (77%), MCL (85%), DLBCL/GZL (70%), HL (72%), AL amyloidosis/LCDD (91%), germ cell tumor (83%), rare entity (78%), and an AID (88%) were frequently (≥70%) referred to ABSCT on sufficient PBSC collection. ABSCT was performed less frequently (50% to <70%) in patients with MPN (56%), MZL (67%), LPL (50%), FL (61%), T-NHL (59%), and sarcoma (51%). Less than 50% of patients with AML/MDS (35%) and ALL (20%) who underwent previous PBSC collection received an autologous transplant in the course of disease, and none (0%) of the patients with Burkitt lymphoma was referred to ABSCT.

In the vast majority of patients, ABSCT was performed only once during the course of the disease. A second ABSCT was performed only in 1 patient each with AML (within 28 months of the first ABSCT), MPN (PMF; 3 months), PLL (5 months), MZL (2 months), FL (4 months), and pinealoblastoma (4 months). Moreover, ABSCT was performed twice in 3 patients with AL amyloidosis (within 2, 74, and 14 months) and in 4 patients with CLL (within 1, 1, 1, and 5 months). Four patients with DLBCL underwent 2 PBSC collections and 1 or 2 transplantations on each PBSC collection, and in 2 patients, ABSCT was performed twice within an interval of 75 months in 1 patient and 5 months in the other. Autologous stem cell support was performed twice in 6 patients with sarcoma at 1, 7, 8, 1, 5, and 6 months after PBSC collection. A sequential repetition of ABSCT at monthly intervals was frequently found in patients with germ cell tumors. In this group, 6 of 24 patients were referred to ABSCT twice and 10 were referred 3 times.

Fate of Collected PBSC Bags and Probability of ABSCT Over Time

A data analysis of cryopreserved PBSC bags (n = 2063) was performed (Figures 2 and 3, Table 2, **Supplementary Table 2**). Similar to the proportion of ABSCTs performed, only a subset of the initially collected PBSC bags were used in transplantations, ranging from 0% in patients with Burkitt lymphoma to 74% in those with rare entities. Regarding the time to ABSCT, except for the patients with FL (median, 2 months; mean, 10 months), the median and mean duration of storage of PBSC bags before ABSCT was ≤6 months. Only 5 patients (7%) with AML, 1 (8%) with CLL/PLL, 11 (11%) with FL, 3 (3%) with MCL, 3 (1%) with DLBCL, 1 (1%) with AL amyloidosis, and 4 (4%) with sarcoma underwent ABSCT beyond 12 months after PBSC collection and storage. In addition, the number of patients in whom harvested PBSCs were used after a storage period of 60 months was very low: 1 patient each with AML (1%), FL (1%), DLBCL (.4%), AL amyloidosis (.6%), and sarcoma (1%). Figure 3 summarizes and illustrates 2 aspects of the use of stored PBSC bags over the time: (1) a large proportion of collected PBSC bags were not used over the course of the disease in several diseases, such as those collected from patients with AML/MDS, ALL, LPL, FL, T-HNL, HL, sarcoma, and AIDs, and (2) the probability of PBSC graft use was <50%. The collected PBSCs were not used in any of the analyzed patients with Burkitt lymphoma. Moreover, ABSCT was performed early after PBSC collection in patients within all disease entities. Only in very rare cases were PBSCs transplanted after 12 or 60 months from PBSC collection.

The percentage of discarded PBSC bags among those that were not used for ABSCT ranged between 0% and 76% depending on the disease entity. In the patients with MPN, Burkitt lymphoma, CLL/PLL, and MZL, no PBSC bags (0%) have been discarded so far, and all were still in storage on the reference date. In the patients with ALL, LPL, FL, MCL, DLBCL/GZL and T-NHL, the percentage of discarded PBSC bags among those unused was <50%. In the patients with AML/MDS, HL, AL amyloidosis, sarcoma, germ cell tumor, a rare entity, and an AID, >50% of the not transplanted PBSCs were discarded. However, the median storage period for the unused PBSC harvests before disposal was relatively long, ranging from 32 to 150 months, depending on the disease entity.

A large proportion of the unused PBSC harvests was not discarded and was stored until the reference date. Specifically, in the patients with MPN, Burkitt lymphoma, CLL/PLL, MZL, LPL, FL, MCL, DLBCL, T-NHL, and germ cell tumors, ≥80% of the unused PBSC grafts were stored until the reference date. In the patients with ALL, HL, AL amyloidosis/LCDD, sarcoma, rare entities, and AIDs, the proportion of not discarded unused PBSC grafts ranged between 41% and 54%. In patients with AML, 24% of the unused PBSCs were stored until the reference date. The median duration of storage of the not transplanted and not discarded PBSC bags varied between 50 and 177 months, depending on the disease entity.

Estimation of Additional Costs for Unused PBSC Harvests

The costs for LP sessions that were necessary to collect/process PBSCs and the costs to store the unused transplants were calculated separately. **Supplementary Table 3** provides a detailed calculation and an overall summary of the additional estimated costs by disease entity.

Patients in whom an ABSCT was not performed (designated as 1) were differentiated from those in whom the PBSCs were definitively not used (1.A: ABSCT not performed and transplants discarded) and from those in whom ABSCTs will most likely never be performed after prolonged storage (1.B: ABSCT not performed and transplants stored until reference date). The number of LP days necessary to collect the PBSCs was known for every patient, so we were able to calculate the overall number of LP sessions required to collect the discarded bags and the PBSCs stored until the reference date (**Supplementary Table 1**). This calculation served as a basis for estimating additional collection/processing costs for the patients who did not undergo transplantation. Specifically, transplantation was not performed in 47 of the 74 patients with AML/MDS (64%), although sufficient PBSCs were available for autologous transplantation. In 33 of these patients who did not undergo transplantation, the PBSCs were discarded, and for 14 patients with AML/MDS, the PBSCs were still being stored at the reference date. In this cohort, 82 and 28 LP sessions were required to collect the discarded PBSCs and the PBSCs stored until the reference date, respectively. Therefore, the additional LP costs were €246,000 (82 LP sessions × institution-specific charges of €3000) for the discarded bags and €84,000 (28 LP sessions × institution-specific charges of €3000) for the stored PBSCs. The sum of the additional LP/processing costs in the overall cohort for the discarded/definitively unused PBSCs (€627,000) and for PBSCs stored until the reference date and potentially not used (€897,000) was €1,524,000.

The storage costs were determined separately for the (**2**) transplanted, (**3**) discarded, and (**4**) stored until reference date PBSC bags. The institution-specific charges of €13 per cryopreserved bag/month starting at 13 months of storage were included in the calculation.

In the entire cohort, 51 of all transplanted PBSC bags were stored longer than 12 months and 8 bags were stored longer than 60 months. This resulted in a total of 1167 cost-relevant storage months that cost €15,171 (2.A) for transplants stored for >12 months before ABSCT and 193 cost-relevant storage months that cost €2509 (2.B) for transplants stored for >60 months before usage.

Overall, 342 and 279 bags were stored for >12 and >60 months, respectively, before disposal. This translated into 29,243 cost-relevant storage months (ie, €380,159) for transplants stored for >12 months before being discarded (3.A) and 14,681 cost-relevant storage months (ie, €190,853) for transplants stored for >60 months before disposal (3.B) in the whole cohort.

For the overall cohort, 660 and 559 bags were stored until the reference date for >12 months. Eighty-five percent of these PBSC bags were also stored for >60 months (n = 559) at the end of data analysis. This resulted in 66,230 cost-relevant

Table 1
Patient Characteristics and PBSC Collection Result by Disease Entity

Diagnosis	AML/ MDS	MPN (PMF/CML/ ET/Other)	ALL	Burkitt Lymphoma	CLL/ PLL	MZL	LPL	FL	MCL	DLBCL/ GZL	T-NHL	HL	AL Amyloidosis/ LCDD	Sarcoma*	Germ Cell Tumors	Rare Entities†	AID (Ssc/MS/SLE/ PM/Other)
Number of patients	74 (73/1)	18 (9/7/1/1)	20	17	13 (10/3)	9	4	104	91	227 (224/3)	61	57	166 (163/3)	96 (55/8/7/ 7/19)	29	9 (5/1/1 / 1/1)	25 (11/6/2/2/4)
Sex, n (%)																	
Male	39 (53)	8 (44)	14 (70)	13 (76)	12 (92)	7 (78)	2 (50)	57 (55)	71 (78)	128 (56)	44 (72)	31 (54)	99 (60)	55 (57)	26 (90)	4 (44)	11 (44)
Female	35 (47)	10 (56)	6 (30)	4 (23)	1 (8)	2 (22)	2 (50)	47 (45)	20 (22)	99 (44)	17 (28)	26 (46)	67 (40)	41 (43)	3 (10)	5 (56)	14 (56)
Age at diagnosis, yr, median (range)	55 (18-72)	55 (37-68)	42 (17-60)	42 (15-70)	47 (27-58)	58 (34-61)	57 (29-65)	50 (26-69)	60 (29-73)	54 (13-69)	51 (18-72)	37 (12-71)	54 (31-69)	26 (6-65)	36 (15-62)	13 (4-52)	38 (15-66)
Age at PBSC collection, yr, median (range)	56 (18-72)	60 (39-70)	47 (17-61)	42 (16-71)	48 (31-61)	60 (36-67)	58 (29-67)	54 (30-69)	61 (29-71)	56 (14-73)	51 (18-72)	41 (14-72)	55 (34-69)	27 (10-66)	39 (15-62)	13 (7-52)	45 (17-67)
Number of collection days, median (range)	2 (1-7)	1 (1-6)	1 (1-3)	1 (1-3)	1 (1-5)	1 (1-3)	5 (1-6)	1 (1-7)	1 (1-5)	1 (1-7)	1 (1-4)	1 (1-4)	1 (1-5)	1 (1-6)	1 (1-5)	1 (1-6)	1 (1-4)
Overall collection result per patient, x 10^6 $CD34^+$/kg, median (range)	4.9 (.1-419)	6.9 (2.9-99.7)	4.1 (.1-80.0)	7.7 (2.6-32.0)	8.7 (2.6-52.7)	6.4 (.8-17.3)	2.6 (2.4-5.6)	6.2 (.1-111.5)	6.4 (.8-40.1)	7.3 (0-58.9)	6.2 (.6-74.0)	9.3 (1.1-54.8)	7.8 (.7-45.5)	5.6 (2.0-39.9)	9.1 (2.3-72.9)	5.7 (.8-41.0)	8.2 (2.4-33.0)
Number of transplants (ie $\geq 2 \times 10^6$ $CD34^+$/kg) per patient, median (range)	1 (0-3)	2 (1-3)	1 (0-2)	2 (1-3)	2 (1-4)	1 (0-2)	1 (1-2)	1 (0-4)	1 (0-3)	2 (0-4)	1 (0-3)	2 (0-3)	2 (0-3)	2 (1-4)	3 (1-4)	2 (0-3)	2 (1-6)
Collection failures (ie $< 2 \times 10^6$ $CD34^+$/kg), n (%)	1 (1)	0 (0)	2 (10)	0 (0)	0 (0)	1 (11)	0 (0)	4 (4)	1 (1)	3 (1)	1 (2)	1 (2)	2 (1)	0 (0)	0 (0)	1 (11)	0 (0)
Number of cryopreserved bags																	
Overall, n	174	41	33	29	31	16	18	214	167	406	103	109	330	208	95	23	66
Per patient, median (range)	2 (1-7)	2 (1-6)	2 (1-3)	2 (1-3)	2 (1-5)	2 (1-3)	5 (2-6)	2 (1-8)	2 (1-8)	2 (1-7)	2 (1-4)	2 (1-5)	2 (1-5)	2 (1-6)	3 (1-7)	2 (1-6)	2 (1-6)

* Sarcoma entities include PNET, synovial sarcoma, osteosarcoma, leiomyosarcoma, and other.
† Rare entities include primary CNS tumor, ovarian cancer, metaplastic breast cancer, esthesioneuroblastoma, and thymoma.

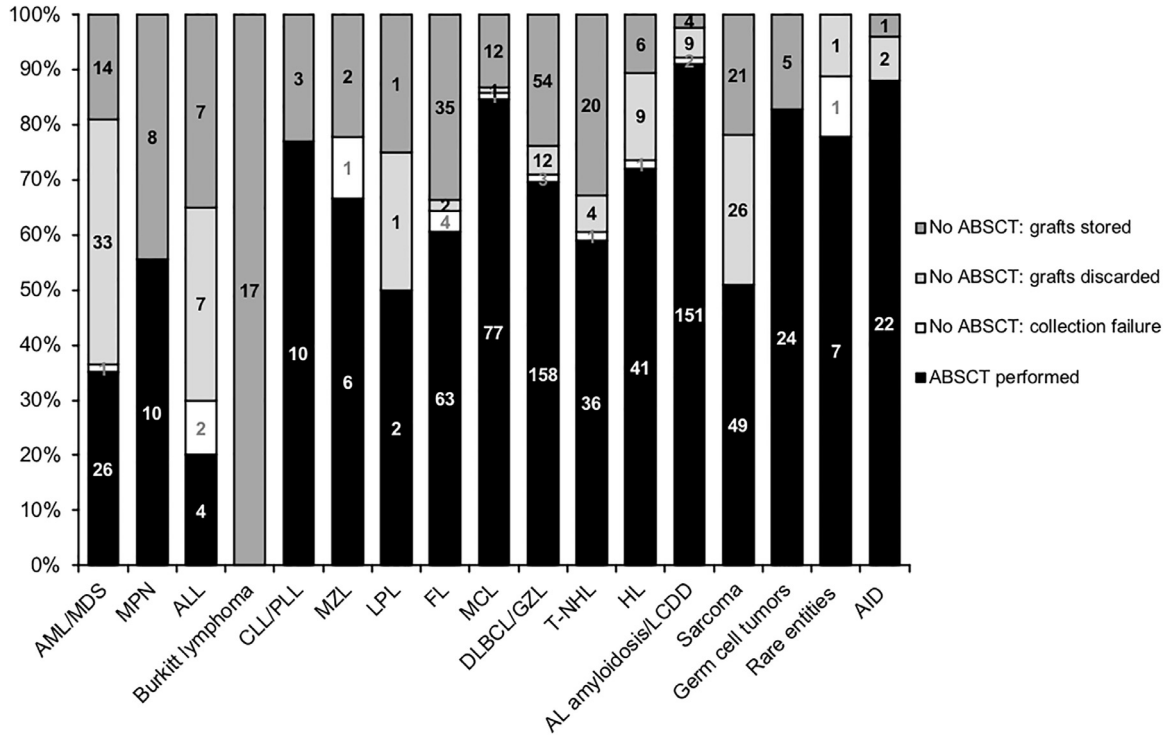

Figure 1. Absolute numbers and relative distribution of performed and not performed ABSCT after PBSC collection by disease entity. In a few cases, ABSCT could not be performed a priori owing to collection failure. In the case of a not performed ABSCT, the transplants were discarded or stored at least until the reference date (June 2016). The data are presented by diagnosis. The numbers inside the bars represent the absolute number of patients. MPN entities include PMF, CML, ET, other. Sarcoma entities include PNET, synovial sarcoma, osteosarcoma, leiomyosarcoma, other. Rare entities include primary CNS tumor, ovarian cancer, metaplastic breast cancer, esthesioneuroblastoma, and thymoma. AID entities include Ssc, MS, SLE, PM, other. ET indicates essential thrombocythemia; MS, multiple sclerosis; PM, polymyositis; PNET, primitive neuroectodermal tumor; SLE, systemic lupus erythematosus; Ssc, systemic sclerosis.

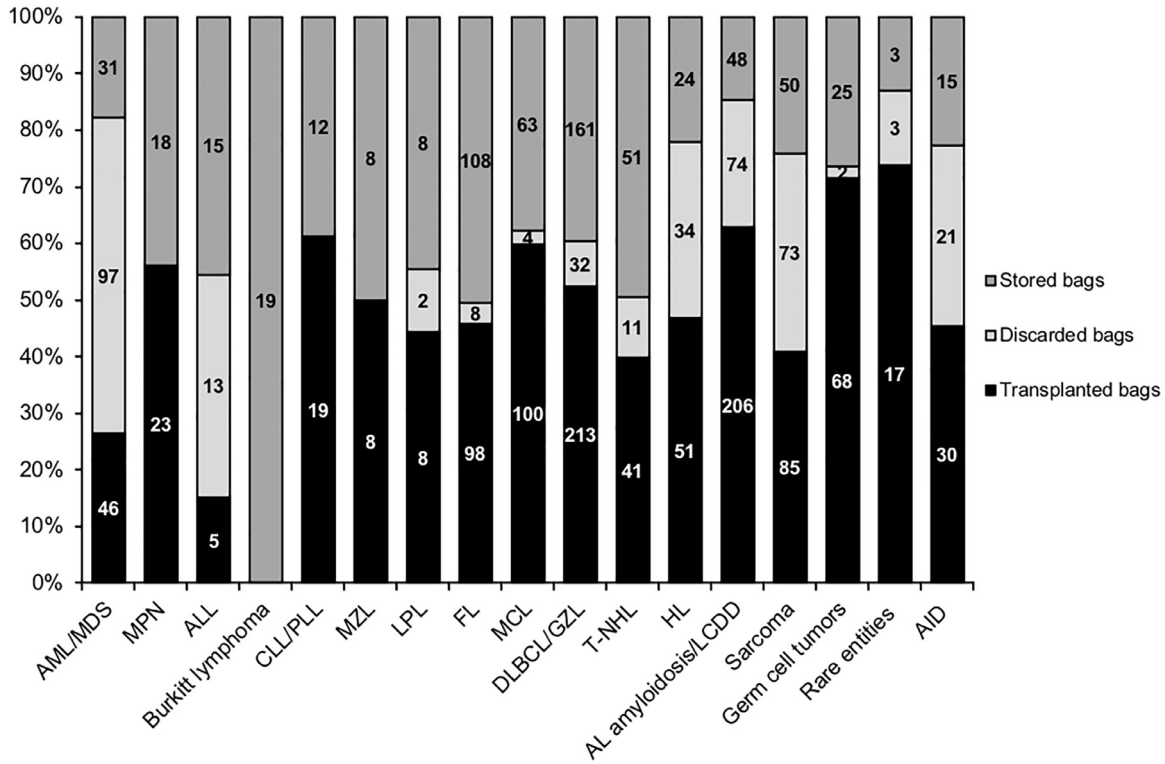

Figure 2. Absolute numbers and relative distribution of cryopreserved PBSC bags that were transplanted, discarded, or stored until the reference date (June 2016). The data are presented by diagnosis. The numbers inside the bars represent the absolute number of cryopreserved bags. MPN entities include PMF, CML, ET, other. Sarcoma entities include PNET, synovial sarcoma, osteosarcoma, leiomyosarcoma, other. Rare entities include primary CNS tumor, ovarian cancer, metaplastic breast cancer, esthesioneuroblastoma, and thymoma. AID entities include: Ssc, MS, SLE, PM, other.

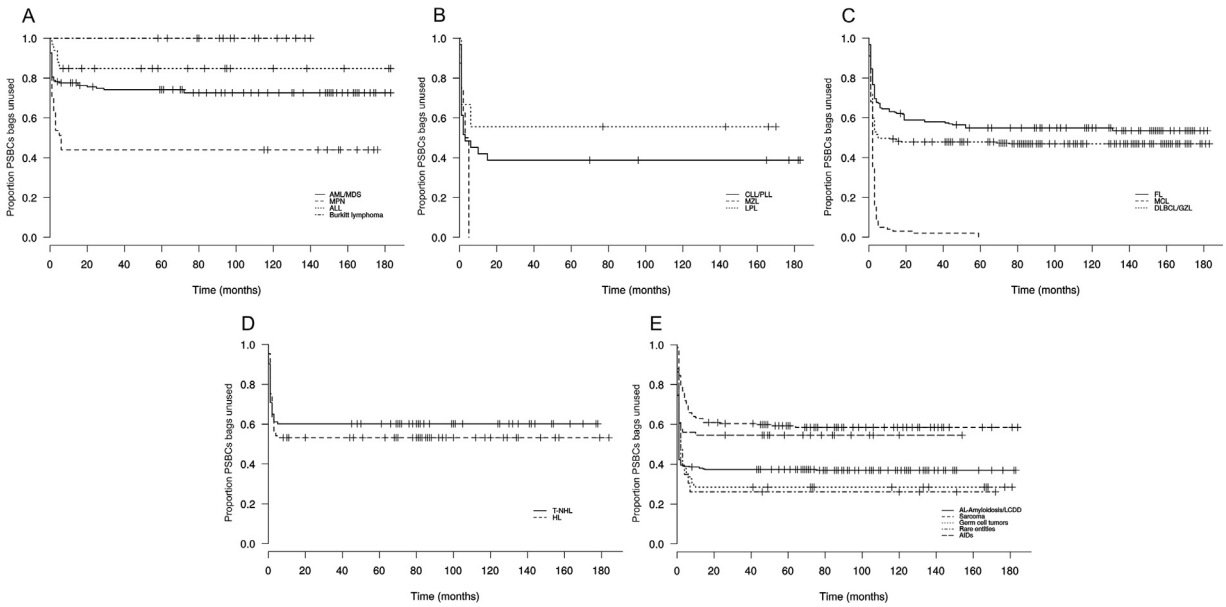

Figure 3. Kaplan-Meier plots showing the probability of ABSCT using cryopreserved PBSC bags by time and disease entity. The fate of each PBSC bag was transplantation, discard, or storage until the reference date (June 2016). The use of a cryopreserved PBSC bag for an ABSCT was defined as an event; therefore, censored data represent either the end of the follow-up or the time of discard for individual PBSC bags. The grouping of entities in Kaplan-Meier plots is more or less arbitrary and serves the purpose of simplicity. MPN entities include PMF, CML, ET, other. Sarcoma entities include PNET, synovial sarcoma, osteosarcoma, leiomyosarcoma, other. Rare entities include primary CNS tumor, ovarian cancer, metaplastic breast cancer, esthesioneuroblastoma, and thymoma. AID entities include: Ssc, MS, SLE, PM, other.

storage months (ie, €860,990) for transplants stored for >12 months until the reference date (4.A) and 35,285 cost-relevant storage months (ie, €458,705) for transplants stored for >60 months until the reference date (4.B).

In summary, the storage of transplanted PBSCs, discarded PBSCs, and PBSCs stored until the reference date resulted in storage costs of €1,256,320 (€15,171 [2.A] + €380,159 [3.A] + €860,990 [4.A]) in PBSC bags stored for >12 months and €652,067 (€2,509 [2.B] + €190,853 [3.B] + €458,705 [4.B]) in PBSC bags stored for >60 months.

DISCUSSION

In this study, an analysis of the collection, autologous transplantation, storage, and disposal practices of PBSCs from patients with hematologic, oncologic and autoimmune disorders was performed. In addition, an estimation of PBSC collection/processing and storage costs was included. To the best of our knowledge, this is the largest investigation in this field, comprising a total of 1020 patients and 2063 cryopreserved PBSC storage bags.

Our analysis revealed that by far, not all patients who had 1 or more PBSC harvests collected were actually referred to an ABSCT. Particularly, in patients with Burkitt lymphoma, none of the collected PBSCs was ever transplanted, and likewise, the probability of PBSC graft use in patients with AML/MDS, ALL, LPL, FL, T-HNL, HL, sarcoma, and AIDs was <50%. From a retrospective standpoint, the collected and definitely not used and potentially not used PBSC harvests were associated with considerable LP/PBSC processing costs (€1,524,000 [1.A + 1.B]) and >12-month storage costs (€1,241,149 [3.A + 4.A]). Moreover, it should be taken into consideration that every PBSC mobilization by chemotherapy and/or granulocyte colony-stimulating factor and LP represents a burden for the patient and is accompanied by considerable side effects and medical risks [18-22]. To avoid medically unnecessary procedures and to minimize costs, the indication for ABSCT should be critically reevaluated in all patients before PBSC collection. Reevaluation is of special relevance in patients with disease entities with ABSCT rate <50%, which were AML/MDS, ALL and Burkitt lymphoma in the present study.

In terms of time, our findings demonstrate that when the PBSCs were used, ABSCT was performed early after LP in all disease entities except FL, and the median and mean duration of storage of PBSC bags before ABSCT was ≤6 months. Only very few patients underwent ABSCT after a storage period of >12 months (n = 28; 3%) or >60 months (n = 5; .5%) months. As at our institution, some internal or external guidelines might prescribe a minimum PBSC storage period to guarantee the availability of autologous stem cells (eg, 60 months). However, numerous PBSC harvests were stored for >60 months before disposal owing to missing follow-up information and a rather conservative storage strategy. This resulted in considerable costs for the storage of definitively unused/discarded and potentially unused transplants or those stored until the reference date in the overall cohort (€649,558 [3.B + 4.B]). To minimize storage efforts and costs, we suggest a periodic reevaluation of the need for PBSC storage for each patient at defined intervals (eg, every 6 months) starting 6 months after PBSC collection.

To address the storage of more than 1 PBSC harvest per patient, we determined the percentage of patients who were referred for ABSCT 2 or 3 times. In the present study, ABSCT was performed only once in the clear majority of patients (96%) during the course of disease, and ABSCT was performed 2 or 3 times in only 41 patients (4%). In contrast, the median number of sufficient PBSC harvests per patient in the whole cohort was 2 (range, 1 to 6). However, this implies that at least 1 sufficient PBSC harvest per patient remained in storage after an ABSCT was performed. Therefore, to minimize the number of potentially unused PBSC harvests, the following strategies should be considered and discussed for each individual patients: initial collection of only 1 PBSC harvest, disposal of additional PBSC harvests after the first ABSCT, and simultaneous reinfusion of any surplus PBSCs at the time of the first

Table 2
Fate of PBSC Bags by Disease Entity

	AML/ MDS	MPN (PMF/ CML/ET/ other)	ALL*	Burkitt Lymphoma	CLL/ PLL	MZL*	LPL	FL*	MCL*	DLBCL/ GZL*	T-NHL*	HL	AL Amyloidosis/ LCDD†	Sarcoma‡	Germ Cell Tumors	Rare Entities§	AIDs (Ssc/ MS/SLE/ PM/Other)
Transplanted bags																	
Total, n (% of overall collected)	46 (26)	23 (56)	5 (15)	0 (0)	19 (61)	8 (50)	8 (44)	98 (46)	100 (60)	213 (52)	41 (40)	51 (47)	206 (62)	85 (41)	68 (72)	17 (74)	30 (45)
Storage time per bag, mo																	
Median (range)	1 (0-72)	1 (0-6)	4 (1-5)	/	1 (0-15)	4 (0-5)	1 (1-6)	2 (0-131)	2 (0-59)	1 (0-76)	1 (0-5)	1 (0-5)	1 (0-75)	2 (0-64)	1 (0-10)	1 (0-7)	1 (0-10)
Mean (SD)	6 (8)	1 (1)	3 (1)	/	3 (3)	3 (2)	2 (2)	10 (15)	4 (7)	3 (6)	1 (1)	2 (1)	1 (6)	6 (7)	2 (2)	2 (2)	1 (1)
Total storage time, mo	283	50	16	0	51	26	18	964	359	642	49	84	267	488	133	32	35
Bags stored for >12 mo, n	7	0	0	0	1	0	0	19	4	8	0	0	3	9	0	0	0
Bags stored for >60 mo, n	2	0	0	0	0	0	0	2	0	2	0	0	1	1	0	0	0
Discarded bags, n (% of total collected/ not transplanted)	97 (56/76)	0 (0/0)	13 (39/46)	0 (0/0)	0 (0/0)	0 (0/)	2 (11/20)	8 (4/7)	4 (2/6)	32 (8/17)	11 (11/18)	34 (31/59)	74 (22/61)	73 (35/59)	2 (2/7)	3 (13/50)	21 (32/58)
Storage time per bag, mo																	
Median (range)	150 (4-175)	/	55 (7-158)	/	/	/	77 (77-77)	41 (17-130)	33 (20-84)	32 (0-112)	84 (50-100)	87 (8-155)	92 (0-163)	90 (2-181)	125 (116-133)	46 (46-120)	84 (26-154)
Mean (SD)	112 (73)	/	56 (41)	/	/	/	77 (25)	67 (15)	43 (8)	47 (16)	83 (26)	90 (48)	94 (33)	94 (52)	125 (18)	71 (28)	82 (41)
Bags stored for >12 mo, n	84	0	10	0	0	0	2	8	4	27	11	30	72	68	2	3	21
Bags stored for >60 mo, n	72	0	4	0	0	0	2	3	1	12	10	29	68	57	2	1	18
Bags stored until reference date, n (% of total collected/ not transplanted)#	31 (18/24)	18 (44/100)	15 (45/54)	19 (100/100)	12 (39/100)	8 (50/100)	8 (44/80)	108 (50/93)	63 (38/94)	161 (40/83)	51 (50/82)	24 (22/41)	48 (15/43)	50 (24/41)	25 (26/93)	3 (13/50)	15 (23/42)
Storage time per bag, mo																	
Median (range)	123 (59-183)	156 (115-176)	120 (58-183)	93 (58-140)	177 (70-183)	129 (73-136)	166 (143-170)	152 (47-182)	84 (43-183)	108 (41-183)	101 (45-178)	84 (44-184)	106 (43-183)	59 (41-184)	104 (41-181)	151 (131-172)	50 (47-106)
Mean (SD)	120 (50)	152 (77)	114 (64)	98 (25)	153 (80)	111 (61)	159 (82)	135 (73)	99 (54)	110 (60)	109 (61)	85 (40)	105 (38)	79 (40)	116 (58)	151 (52)	60 (27)
Total storage time, mo	3972	2577	1704	2856	1832	884	1271	14584	6242	17817	5556	2045	5031	4015	3008	454	902
Bags stored for >12 mo, n	31	18	15	19	12	8	8	108	63	160	51	24	48	51	26	3	15
Bags stored for >60 mo, n	27	18	13	19	12	8	8	98	54	142	47	17	*42*	25	23	3	3

* In patients with collection failure, an insufficient number of transplants were stored until the reference date (June 2016).
† Data not available for 2 bags.
‡ Sarcoma entities include PNET, synovial sarcoma, osteosarcoma, leiomyosarcoma, and other.
§ Rare entities include primary CNS tumor, ovarian cancer, metaplastic breast cancer, esthesioneuroblastoma, and thymoma.
# Final dataset analysis was performed in June 2016, which was set as the reference date.

ABSCT (up to a maximum of 10×10^6 $CD34^+$ cells/kg bw in total). In earlier days, it was common practice to collect 1 more transplant solely for safety reasons as a "backup" in the case of technical difficulties with the initial transplant. Given the high level of manufacturing quality in today's transplant centers, the routine collection of a surplus technical backup no longer seems justified. At least, such technical backup transplants may be discarded after successful ABSCT and full hematologic reconstitution is achieved. This is in line with Pottinger et al [23], who recommended storage of a secondary source of hematopoietic stem cells only for those transplants associated with an elevated risk of graft failure.

Disease-specific ABSCT strategies that include several ABSCTs should be taken into account when decisions are made about the collection, storage, and/or disposal of additional PBSC harvests. Specifically, the subgroup of patients who underwent 2 or 3 ABSCTs (n = 41) included 16 patients with germ cell tumor and 6 patients with sarcoma. In these disease entities, sequential ABSCTs and repetitive stem cell support are part of established therapy protocols, and quantitatively sufficient PBSC harvests should be considered during PBSC collection [24-26]. However, in the case of a likely second or third ABSCT, the need to store additional PBSC harvests should be reconsidered at defined time intervals after the first ABSCT. This is supported by the fact that sequential ABSCTs in patients with sarcomas and germ cell tumors were performed at intervals of 1 month to a maximum of 8 months, and only 4 patients with another disease underwent a second ABSCT at >12 months after the first ABSCT.

In the present analysis, patients with MM were not evaluated, because currently the rationale for collecting and storing at least 1 transplant for further use in case of relapse is largely unquestioned in this disease entity. In addition, we recently assessed the PBSC collection and ABSCT practices in separate analyses of patients with MM and described standardized procedures regarding the timing and benchmarking of PBSC mobilization and the LP procedure [27-29].

The strengths of this study are the high numbers of analyzed patients and PBSC harvests, the long follow-up period, and the inclusion of disease entities in which an ABSCT is not routinely performed, such as germ cell tumors, sarcomas, and AIDs. Nevertheless, our results should be interpreted carefully due to a limited number of patients in several disease subgroups and its unicentric, retrospective design. Regarding the retrospectivity of the study, for most of the patients at the time of PBSC collection, it cannot be predicted for sure whether an ABSCT will be performed in the future, given that the indication for performing an ABSCT may depend on the course of the disease or may be hampered by unforeseen complications or comorbidities. This is the quandary when the collection goal must be determined. On one hand, all treatment options should be kept open for the individual patient, including HDCHT and ABSCT in the case of relapse. To this end, PBSC collection should occur not too late in the treatment plan [30]. On the other hand, the cost for unused PBSC harvests over the years can easily add up to several million Euros in a large transplant center. These costs include those for PBSC preparations for patients with diseases in which not a single patient ever received a transplant during the entire observation period of 12 years (eg, Burkitt lymphoma). Along with the financial costs, the risks of and patient effort required for unnecessary stem cell mobilization and collection also should be taken into consideration. Therefore, a comprehensive review of the local algorithms for determining the PBSC collection yield is warranted.

Our cost calculation does not include the efforts for mobilization therapy and granulocyte colony-stimulating factor administration, which are commonly part of the therapeutic regimen [20]. The costs for LP/PBSC processing and storage represent a mean value over the observation period, and detailed cost fluctuations over time were not considered in the present analysis. In particular, for centers that do not practice volume reduction of their transplants, the resulting number of cryostored bags is considerably higher. The storage costs for transplanted PBSCs were calculated for information purposes only and should not be considered true additional costs, because these PBSC harvests were transplanted. All costs mentioned are institution-specific and might not be the same at other centers. For example, because our estimated costs per LP (€3000/session) included PBSC collection and cryopreservation, and our institutional costs were lower than those previously reported by Phipps et al [31] in patients with MM (~€7500 [€2500/session + ~€5000 processing charge]), which might be explained by institution- and country-specific differences. Likewise, the costs for PBSC storage were slightly lower at our institution (€13 per cryopreserved bag starting from month 13) compared with institutions in previously published data (~€28/month) [31]. However, because we provide a detailed step-by-step cost analysis that considered the number of PBSC collection days and months for PBSC storage, the numbers can easily be calculated in parallel for other institutions.

Overall, the intent of the present study was not to provide an entity-specific stratification model for collection, storage, and disposal of PBSC harvests, and it does not represent a model that analyzes cost-effectiveness in a strict sense. Rather, our analysis points out discrepancies between the collection yield and storage of PBSC harvests on one hand and their actual use in clinical practice on the other hand, with the goal of deriving cautious suggestions for optimizing clinical practice in the future. The most important issues were the collection of several PBSC harvests per patient even though the vast majority of patients underwent only 1 ABSCT, a missing continuous follow-up and reevaluation protocol of stored PBSC harvests, and an indiscriminately conservative storage strategy. From a retrospective standpoint, this resulted in considerable additional financial costs, clinical effort, and strain on the patient for unnecessary PBSC mobilization, collection, processing, and cryostorage. Therefore, we suggest a reevaluation and adjustment of the current PBSC collection and storage practices in the covered disease entities with the goals of minimizing the patient burden and avoiding unnecessary costs.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.09.013.

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