Cryostorage to What End? – Autologous Stem Cell Products in Burkitt Lymphoma, Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, and Myeloproliferative Neoplasm Patients

Katharina Kriegsmann^a Petra Pavel^b Tilmann Bochtler^{a, c} Anita Schmitt^a
Sandra Sauer^a Mark Kriegsmann^d Thomas Bruckner^e Stefan Klein^f
Harald Klüter^g Carsten Müller-Tidow^a Patrick Wuchter^g

^aDepartment of Hematology, Oncology, and Rheumatology, Heidelberg University, Heidelberg, Germany; ^bStem Cell Laboratory, IKTZ Heidelberg GmbH, Heidelberg, Germany; ^cClinical Cooperation Unit Molecular Hematology/Oncology, Department of Hematology, Oncology, and Rheumatology, German Cancer Research Center (DKFZ), Heidelberg University, Heidelberg, Germany; ^dInstitute of Pathology, Heidelberg University, Heidelberg, Germany; ^eInstitute of Medical Biometry und Informatics, Heidelberg University, Heidelberg, Germany; ^fDepartment of Medicine III, University Medical Center Mannheim (UMM), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; ^gInstitute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, German Red Cross Blood Service Baden-Württemberg-Hessen, Mannheim, Germany

Keywords

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Abstract

Introduction: Recently, we identified a huge discrepancy between the collection practice and the actual utilization of cryopreserved peripheral blood stem cells (PBSCs) for high-dose chemotherapy (HDCT) and autologous blood stem cell transplantation (ABSCT). Specifically, patients with Burkitt lymphoma, acute leukemia, and myeloproliferative neoplasms (MPN) were frequently not referred for ABSCT after successful PBSC collection. **Objective:** The aim of this study was to identify variables that are associated with the non-utilization of PBSC grafts. **Methods:** We retrospectively analyzed the collection, storage, and disposal of PBSC grafts in Burkitt lymphoma ($n = 18$), acute lymphoblastic leukemia (ALL, $n = 22$), MPN ($n = 18$), and acute myeloid leukemia

(AML, $n = 71$) patients. Patients who underwent autologous PBSC collection at 2 collection and transplantation centers between 2001 and 2012 were included and followed up until 2016. **Results:** None of the Burkitt lymphoma patients were referred for ABSCT. Only in 1 (6%) patient, the graft was discarded after the patient's death. In all other patients ($n = 17$, 94%), the grafts were stored independently of the patient's status (death, $n = 4$, 22%; no follow-up, $n = 6$, 33%; no indication for ABSCT given, $n = 7$, 39%). In ALL patients, 4 (18%) patients underwent ABSCT after a median follow-up of 74 (1–182) months. In the remaining patients, PBSC grafts were either discarded (8 patients, 36%) or stored until the reference date (10 patients, 45%). Seven of 18 MPN patients (39%) underwent ABSCT. ABSCT was performed in 24 (34%) AML patients. In 20 (28%) patients who were not referred to ABSCT, an allogeneic transplantation (TPL) was performed. Fifteen (21%) patients received palliative care or deceased, and their grafts were discarded in all but 1 patient. Additional grafts were discarded in 21 (31%) patients and stored in 9 (13%) patients who underwent ABSCT or allogeneic TPL ($n =$

44). **Conclusions:** As the role and efficacy of autologous HDCT/ABSCT are not established in the analyzed entities, the indication for PBSC collection should be reanalyzed in regular intervals. Moreover, PBSC grafts from patients who have deceased, have insufficient grafts, or have already undergone an allogeneic TPL should be considered for disposal or (if applicable) for research use, to economize storage costs on a rational basis.

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Introduction

High-dose (HD) chemotherapy (HDCT) followed by autologous blood stem cell transplantation (ABSCT) represents a standard therapy for a variety of malignant and nonmalignant diseases, and mobilized peripheral blood stem cells (PBSCs) have become the most widely used source for hematopoietic stem cells in this setting [1–7]. Considering the difficulties in collecting an additional PBSC graft during the late course of disease [8], many centers routinely collect and store >1 PBSC graft during the induction treatment to ensure the availability of a stem cell source for tandem transplant or salvage ABSCT in case of relapse [9–12]. However, for a variety of reasons, ABSCT is often not performed in clinical practice despite the availability of ≥ 1 cryopreserved PBSC grafts. Depending on the diagnosis, the reasons might be the primary intention to use PBSC grafts for a stem cell boost only when required during intensive chemotherapy, the availability of novel treatment options, the decision to proceed to allogeneic transplantation (TPL), the relapse or progression of the disease, the deterioration of the general condition, or the existence of severe comorbidities.

Recently, we analyzed the collection, storage, and disposal practices of PBSC products from a large cohort of patients with hematological, oncological, and autoimmune disorders over a 10-year period [13]. We identified a huge discrepancy between the collection and storage practices on the one hand and the actual utilization of the cryopreserved PBSCs on the other hand, causing considerable PBSC collection and storage costs. In some entities, the probability of ABSCT was particularly low, and the majority of PBSC grafts were cryostored for a long-time period and/or discarded. Therefore, we evaluated specifically the utilization of PBSC grafts in Burkitt lymphoma, acute lymphoblastic leukemia (ALL), myeloproliferative neoplasm (MPN), and acute myeloid leukemia (AML) patients by time and with regard to the clinical status of the patients. The aim of this study was to identify parameters that indicate unnecessary collection and storage of PBSC grafts in these entities.

Patients and Methods

Patient Selection and Data Collection

Burkitt lymphoma ($n = 18$), ALL ($n = 22$), MPN ($n = 18$), and AML ($n = 71$) patients who underwent autologous PBSC collection at the Department of Hematology, Oncology, and Rheumatology at the University Hospital Heidelberg and Mannheim between January 2001 and December 2012 were included. Some of these patients were previously analyzed as a part of a larger cohort with regard to PBSC collection and storage costs [13]. However, the current study focuses on the treatment strategy and clinical course that led to an ABSCT and the storage or disposal of PBSC grafts. Clinical characteristics, disease-related parameters, treatment, and follow-up data were collected retrospectively. Moreover, dates of PBSC collection, ABSCT, and, if applicable, PBSC disposal were collected retrospectively from medical records to calculate the time until ABSCT (time period from PBSC collection to ABSCT), disposal (time period from PBSC collection to disposal), and storage (time period from PBSC collection to reference date). The final data set analysis was performed in June 2016, which was set as the reference date. Therefore, the minimum follow-up time of PBSC harvests was 4.5 years. If reported, the median follow-up time (min-max) also includes the duration until ABSCT. As the vast majority of patients underwent ABSCT timely after PBSC collection, the minimum and median of the follow-up might be short. However, stored transplants were followed for at least 4.5 years to ensure that no late ABSCTs were missed. This is reflected by the maximum follow-up time. Written informed consent for data evaluation was obtained from all patients. Retrospective data analysis was approved by the Ethics Committee of the Medical Faculty, Heidelberg University.

PBSC Cryopreservation, Storage, and Disposal

The minimum number of CD34+ cells for 1 transplant was defined as $\geq 2.0 \times 10^6/\text{kg}$ body weight (BW), with the goal of collecting enough CD34+ cells for 1–3 transplants depending on the diagnosis. Prior to cryopreservation, the PBSC products were centrifuged and diluted with autologous plasma or medium and CryoSure dimethyl sulfoxide (DMSO, WAK-Chemie Medical, Steinbach, Germany) to obtain a target nucleated cell concentration of $\leq 5 \times 10^8/\text{mL}$ 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 $\leq -140^\circ\text{C}$ after controlled-rate freezing. PBSCs were processed and stored in accordance with the German Medical Council and responsible scientific society guidelines [14–16]. PBSC products were usually stored for ≥ 5 years (60 months), as this is the timespan for which adequate quality of the cells could be guaranteed by the stem cell laboratory (IKTZ Heidelberg GmbH). The disposal of PBSC products was usually performed during a review of PBSC product stocks initiated by the stem cell laboratory every 2–3 years. At this occasion or upon specific request of the Department of Medicine (in which the patients were treated), PBSC products were disposed when the IKTZ received a confirmed notice that a patient was deceased.

Statistical Analysis

Statistics were performed in R Studio (version 0.99.451, 2009–2015, R Studio Inc.). Data are presented as absolute numbers/percentages and as medians (min-max). ABSCT over time was calculated and plotted using a Kaplan-Meier survival analysis.

Table 1. Patients with Burkitt lymphoma, acute lymphoblastic leukemia (ALL), myeloproliferative neoplasm (MPN), and acute myeloid leukemia (AML): characteristics, treatment, and PBSC collection and usage

Parameter/diagnosis	Burkitt lymphoma	ALL	MPN	AML
Patients, <i>n</i>	18	22	18	71
Diagnosis specification, <i>n</i> (%)	–			
	–	B cell ALL 16 (72%)	PMF 9 (50%)	Primary 63 (89%)
	–	T cell ALL 6 (28%)	CML 7 (39%)	Therapy related 4 (6%)
	–	–	ET 1 (6%)	MDS derived 1 (1%)
	–	–	Not specified 1 (6%)	Myeloid sarcoma 1 (1%)
	–	–	–	BPDCN 2 (3%)
<i>Clinical parameters and treatment</i>				
Gender, <i>n</i> (%)				
Male	14 (78%)	14 (64%)	8 (44%)	38 (54%)
Female	4 (22%)	8 (36%)	10 (56%)	33 (46%)
Age at diagnosis, years	42 (15–70)	42 (17–60)	55 (37–68)	55 (18–72)
First-line treatment, <i>n</i> (%)				
GMALL ALL NHL 2002 protocol	18 (100%)	20 (91%)	–	–
Not known	0 (0%)	2 (19%)	–	–
<i>PBSC collection</i>				
Indication				
Per treatment protocol	18 (100%)	20 (91%)	–	–
Not known	0 (0%)	2 (19%)	–	–
Age at PBSC collection, years	43 (16–71)	43 (17–61)	60 (39–70)	56 (18–72)
Transplants/patient, <i>n</i>	2 (1–4)	1 (0–2)	2 (1–3)	1 (0–3)
Collection failures (<2×10 ⁶ CD34 ⁺ /kg BW), <i>n</i> (%)	0 (0%)	3 (14%)	0 (0%)	1 (1%)
Overall collection result/patient, ×10 ⁶ CD34 ⁺ /kg BW	7.9 (2.6–32.0)	2.9 (0.1–80.0)	6.9 (2.9–99.7)	4.7 (0.1–419.0)
Collection days, <i>n</i>	1 (1–3)	1 (1–3)	1 (1–6)	2 (1–7)
Cryopreserved bags, <i>n</i>				
Overall, <i>n</i>	35	42	41	170
Per patient, <i>n</i>	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–7)
Usage of PBSC grafts, <i>n</i> (%)				
Transplanted	0 (0%)	4 (18%)	10 (56%)	24 (34%)
Discarded	1 (6%)	8 (36%)	0 (0%)	33 (46%)
Stored	17 (94%)	10 (45%)	8 (44%)	14 (20%)

Data are given as medians and ranges or *n* (%). BPDCN, blastic plasmacytoid dendritic cell neoplasm; CML, chronic myeloid leukemia; ET, essential thrombocythemia; PBSC, peripheral blood stem cells, PMF, primary myelofibrosis.

Results

PBSC Usage in Burkitt Lymphoma Patients

Among the Burkitt lymphoma patients analyzed, 14 (78%) were male, and 4 (22%) were female. Their median age at first diagnosis was 42 years. All patients were treated in accordance with the German Multicenter Study Group for Adult ALL (GMALL) B-ALL NHL 2002 protocol, and PBSC collection was performed as indicated per treatment protocol [17]. Their median age at PBSC collection was 43 years. None of the patients failed to reach the collection goal. The median number of PBSC transplants ($\geq 2.0 \times 10^6$ CD34⁺ cells/kg BW) per patient was 2. The median collection result per patient was 7.9×10^6 CD34⁺ cells/kg BW and was reached after a median of 2 leukapheresis (LP) procedures. A summary of the clinical and PBSC collection data is given in Table 1.

After a median follow-up of 92 (4–140) months, none of the patients were referred to ABSCT, and the PBSC grafts were either stored (*n* = 17, 94%) or discarded (*n* = 1, 6%), as shown in Figure 1a. Four (22%) patients reached sustained complete remission (CR) upon first-line treatment. Eight (44%) patients had CR but were no longer followed up. Five (28%) patients died due to progressive disease (PD), and 1 (6%) patient was not available for follow-up. Regarding the storage and disposal of PBSC grafts, only in 1 (6%) patient was the graft discarded after the patient's death. In all other patients, PBSC grafts were stored independently of the patient's status. Therefore, in 4 (22%) patients who deceased after PBSC collection, grafts were stored until the reference date for 51, 83, 96, and 117 months. In addition, in patients who were not available for follow-up (*n* = 6, 33%) and patients with recent follow-up but no indication for an ABSCT thus far (*n* = 7, 39%), grafts were stored until the reference date.

Fig. 1. The probability of an ABSCT (defined as an event) by time is shown. Censored data represent either the end of storage follow-up or the time when the PBSC graft was discarded. **A** In the Burkitt lymphoma cohort, none of the patients who collected an PBSC graft was referred to ABSCT, and the grafts were either stored for a long time period and/or discarded. **B** Only a few ALL patients

were referred to ABSCT after PBSC collection, and if applicable, ABSCT was performed in close timely relation to PBSC harvest. **C** More than 50% of MPN patients were referred to ABSCT after PBSC collection. **D** If referred to an ABSCT upon PBSC collection, ABSCT was performed in AML patients timely to PBSC harvest. However, some AML patients underwent ABSCT after >2 years.

PBSC Usage in ALL Patients

Sixteen (72%) B-cell ALL and 6 (28%) T-cell ALL patients were identified for the current analysis. Among these patients, 14 (64%) were male, and 8 (36%) were female. The median age at diagnosis was 42 years. Except for 2 patients in whom no data on first-line treatment was available, all were treated in accordance with the GMALL protocol, and the indication for PBSC collection was based on the treatment protocol. Their median age at PBSC collection was 43 years. Three (14%) patients failed to collect at least 2.0×10^6 CD34+ cells/kg BW for 1 transplant. A total of 19 (86%) patients reached the collection goal upon a median of 1 LP session. The median overall collection result per patient was 2.9×10^6 CD34+ cells/kg BW (Table 1).

After a median follow-up of 74 (1–182) months, 4 (18%) patients underwent an ABSCT, which was performed in a timely manner close to PBSC collection and within a period of 1–5 months (Fig. 1b). In the remaining patients, PBSC grafts were either discarded ($n = 8$, 36%) or stored until the reference date ($n = 10$, 45%). Of the 4 patients who underwent ABSCT, 1 patient died. Nine (41%) patients reached CR upon first-line treatment, and allogeneic TPL was performed in 5 (23%) patients. With respect to the PBSC grafts and patient status, we found that additional grafts of patients who underwent ABSCT or allogeneic TPL ($n = 7$, 32%) were discarded. However, before discarded grafts were stored for a long period, the median delay before discarding was 19 (5–152) months. Surprisingly, insufficient grafts ($<2.0 \times 10^6$ CD34+ cells/

kg BW) were stored until the reference date in 2 (9%) of 3 patients who failed to reach the collection goal. Moreover, only in 2 (9%) patients who reached CR upon first-line treatment, unused PBSC grafts were discarded after a storage duration of 83 and 127 months. In the other 7 (32%) patients who reached CR, PBSC grafts were stored until the reference date.

PBSC Usage in MPN Patients

Of the 18 analyzed MPN patients, 9 (50%) were diagnosed with primary myelofibrosis (PMF), 7 (39%) with chronic myeloid leukemia (CML), and 1 (6%) with essential thrombocythemia (ET). In 1 (6%) patient, the MPN diagnosis was not further specified. Eight (44%) patients were female, and 10 (56%) were male. Their median age at first diagnosis was 55 years, and 60 years at PBSC collection. All patients reached the collection goal of at least 1 sufficient PBSC graft ($\geq 2.0 \times 10^6$ CD34+ cells/kg BW), and the median overall collection result per patient was 6.9×10^6 CD34+ cells/kg BW. Two sufficient transplants were collected per patient after 1 LP session (Table 1).

Ten (56%) ET/PMF patients were referred for ABSCT after treosulfan conditioning 1 month (median) after PBSC collection. In 8 (44%) patients, ABSCT was not performed, and PBSC grafts were stored until the reference date. Two (11%) patients in whom ABSCT was not performed deceased, 1 (6%) patient was not available for follow-up, and 5 (28%) CML patients received treatment other than ABSCT (Fig. 1c). In 7 (39%) of 10 patients who underwent ABSCT, no further grafts were available, and in 3 (17%) patients, additional grafts were stored after ABSCT until the reference date. In 2 (11%) patients who died, PBSC grafts were stored for at least 154 and 163 months after death until the reference date. Moreover, in 6 (33%) patients who were not referred for ABSCT, PBSC grafts were also stored until the reference date.

PBSC Usage in AML Patients

The majority ($n = 63$, 89%) of the 71 AML patients analyzed had primary AML, i.e., no therapy-associated AML or AML derived from the myelodysplastic syndrome. Thirty-eight (54%) patients were male, and 33 (46%) were female. Their median age at first diagnosis was 55 years, and at PBSC collection it was 56 years. The median cell number collected per patient was 4.7×10^6 CD34+ cells/kg BW. Collection failed in 1 patient. A median of 1 PBSC transplants was collected per patient after a median of 2 LP sessions (Table 1).

Overall, in 24 (34%) patients, ABSCT was performed 1 month (median) after PBSC collection. Busulfan or total body irradiation/cyclophosphamide were used as the conditioning regimen. In 33 (46%) and 14 (20%) patients, PBSC grafts were discarded or stored, respectively. In 20 (28%) patients who were not referred to ABSCT, an allo-

geneic TPL was performed. Six (8%) patients reached a remission of AML upon initial treatment, and no indication for ABSCT or allogeneic TPL was given. Fifteen (21%) patients relapsed, received palliative treatment, or died. Six (8%) patients were not available for follow-up (Fig. 1d). Of the 44 patients who underwent ABSCT or allogeneic TPL, additional grafts were discarded in 9 (13%) and 13 (18%) patients, and stored in 2 (3%) and 7 (10%) patients. In all but 1 of the 15 patients who suffered from AML relapse, received palliative treatment, or succumbed, PBSC grafts were discarded.

Discussion

In most stem cell collection facilities worldwide, huge numbers of autologous stem cell products are kept stored for many years and often decades. The resulting costs may rise up to millions of Euros over the years, depending on the size of the collection center [13]. However, it is challenging to define a comprehensive strategy for handling these grafts due to various legal, ethical, and medical issues that have to be taken into account. At present, there are only very few papers published addressing this topic, and no guidelines have been established by any respective scientific society. Furthermore, if stem cell grafts which are no longer needed for the original purpose are identified, the question arises if this material might be cleared for research use. Depending on the respective laws and regulations, this should be legally clarified, permitted by the donor, and approved by a local ethics committee beforehand.

To identify parameters for redundant PBSC collection and cryostorage, we performed a retrospective analysis of PBSC graft usage for ABSCT in Burkitt lymphoma, ALL, MPN, and AML patients. All Burkitt lymphoma patients were treated in accordance with the GMALL B-ALL NHL 2002 protocol, which consists of 6 chemotherapy cycles of triple intrathecal therapy, HD methotrexate, HD cytarabine, cyclophosphamide, etoposide, ifosfamide, corticosteroids, and rituximab. This protocol suggests PBSC collection to perform HDCT and ABSCT in cases of treatment failure and PD [17]. However, in the current study, none of the Burkitt lymphoma patients were referred to HDCT and ABSCT despite collecting PBSC grafts during the first-line treatment. In particular, patients with PD had a significant deterioration in their general condition and deceased shortly after PD was diagnosed.

Indeed, the role of HDCT/ABSCT in Burkitt lymphoma patients has still to be defined, and there are no prospective randomized clinical trials providing evidence. Conceivable in the first remission and at relapse/advanced stage, several retrospective analyses focus on the role of HDCT/ABSCT in Burkitt lymphoma patients.

The overall survival (OS) rates reported in Burkitt lymphoma/Burkitt-like lymphoma patients who underwent HDCT/ABSCT in first CR were 72% for 3 years (Sweetenham et al. [18], $n = 70$) and 81% (van Imhoff et al. [19], $n = 15$), 83% (Maramattom et al. [20], $n = 48$), and 80% (Ahmed et al. [21]) for 5 years. As demonstrated by Ahmed et al. [21], patients in their first very good/partial remission had similar outcomes compared to those with their first CR (71 and 80%, respectively). Therefore, it is questionable whether patients reaching a first remission lower than CR would benefit from HDCT/ABSCT [21]. Overall, these studies differed in conditioning regimens, are impaired by small case numbers, and require a comparison with modern dose-intensive regimens. Therefore, no conclusions can be drawn for/against HDCT/ABSCT in patients with first remission.

In patients with relapsing/advanced disease who are referred to HDCT/ABSCT chemosensitivity, the disease status before the transplant is considered the main determinant of the outcome. Sweetenham et al. [18] demonstrated a 3-year OS rate of 37% for patients with chemosensitive relapse and only 7% for chemoresistant patients. Ahmed et al. [21] reported a 5-year OS of 59% in patients who reached CR upon salvage therapy. In contrast, 5-year OS was significantly lower in patients with advanced disease (25%). Moreover, in a small cohort of 13 Burkitt lymphoma patients who were treated with HDCT/ABSCT at relapse, Kwon et al. [22] reported an encouraging 2-year OS of 75%. Therefore, in the case of chemosensitive relapse, HDCT/ABSCT can be offered as a treatment option, as patients with advanced and chemoresistant disease might benefit from treatment modalities other than HDCT/ABSCT.

Of particular relevance for related costs, PBSC graft storage was not reevaluated in all but 1 patient, who deceased. This resulted in avoidable storage for at least 4 (max 10) years in patients who died after PBSC collection. Prior to this study, neither patients who were alive nor those who did not present at the hospital were followed regularly with specific regard to PBSC storage. This resulted in the storage of a considerable amount of unevaluated PBSC grafts for at least 5 (max 12) years. This underlines the necessity of (re)evaluating the stored PBSCs on a standardized basis.

Almost all ALL patients were treated in accordance with GMALL 06/1999 or GMALL 07/2003 protocols, which are applied in hospitals all over Germany. These protocols refer high-risk ALL patients to allogeneic sibling/matched-unrelated stem cell transplantation (if a donor is available) or ABSCT (if no donor is available) in the first CR. In standard-risk patients, the indication for ABSCT is based on minimal residual disease during treatment. Therefore, autologous PBSC collection per protocol is indicated in high-risk patients without an allogeneic

donor and all standard-risk patients, except for those with already identified allogeneic donors [23, 24].

However, the role of HDCT/ABSCT in ALL patients is controversial. Helbig et al. [25] evaluated the efficacy of ABSCT after prior conditioning with cyclophosphamide, cytarabine, and etoposide in 128 high-risk ALL patients, who had a probability of disease-free survival (DFS) of 27 and 23% for 10 and 20 years, respectively. No difference in DFS between patients in first and second CR prior to HDCT/ABSCT was observed. Due to the low probability of long-term DFS, the efficacy of ABSCT in high-risk ALL was considered unsatisfactory. Moreover, Gupta et al. [26] published a meta-analysis on 5 trials with a randomization between autograft and chemotherapy in Philadelphia chromosome-negative patients ($n = 829$). The authors could not identify any statistical differences in relapse rates or 5-year OS between the chemotherapy (43%) and autograft (38%) arm; therefore, they concluded that there might not be a beneficial effect of ABSCT compared to chemotherapy in adult ALL patients in first remission.

In the current study, of 22 patients analyzed, ABSCT was performed in 4 patients, and 5 patients were referred to allogeneic TPL during the first-line treatment. Nonetheless, in these patients, autologous PBSC grafts were stored for a median of 19 months before being discarded. Additionally, in 2 patients who had collected a stem cell product with insufficient PBSCs, the cells were kept cryostored for over 12 years.

In ALL patients who were not available for follow-up and those in CR, PBSC grafts were stored at least until the reference date without a defined indication to do so.

Among MPN patients, all but 1 PMF patient (8/9) and none of the CML patients (0/7) underwent ABSCT. All patients in the MPN cohort underwent PBSC collection and HDCT/ABSCT before 2007. The high rate of actual ABSCT in PMF is attributable to a clinical trial active at the time. Data on HDCT/ABSCT in MPN patients are limited. Anderson et al. [27] performed a multicenter analysis and reported on 21 myelofibrosis patients who were referred to ABSCT after prior busulfan conditioning. Clinical responses were observed in 7 of 10 patients with splenomegaly, 10 of 17 anemic patients, and 4 of 8 patients with low platelet counts. However, the rate of incomplete hematopoietic reconstitution was high (27% of patients), and graft failure was suspected. In CML, ABSCT was performed earlier with the rationale of a reduction in tumor burden and risk for blastic transformation [28]. Currently, the role of HDCT/ABSCT remains uncertain, and a clear indication is not given for PMF and CML patients [29–32]. Since 2007, no autologous PBSC collections have been performed in MPN patients at our institutions. However, all additional and unused PBSC grafts were not discarded and unnecessarily stored at

least until the reference date for a median of 13 years independently of the patient's entity, treatment status, or death.

Therapy after AML remission is controversially discussed. Though autologous transplantation has been demonstrated to yield clinical benefit in some studies, these studies might be biased by patient selection, with patients with deep remissions and good hematologic reserve overrepresented among transplanted patients in as-treated analyses. HDCT/ABSCT can be performed as an alternative consolidation treatment in individual cases. The therapy-associated mortality of HDCT/ABSCT patients is low, lower than in allogeneic TPL and comparable to high-dose cytarabine arms. Although HDCT/ABSCT has been associated with prolonged DFS, no beneficial effect on OS has been proven thus far. Moreover, the rate of relapse is significantly increased compared to allogeneic TPL [33, 34].

At our institutions, PBSC collections and, if applicable, ABSCTs in AML patients were performed until 2007. Only 1 single patient underwent PBSC harvest after 2007. The last ABSCT was performed in 2012 in a patient with no allogeneic donor available.

Overall, in 16 (23%) patients, PBSC grafts were unnecessarily stored: patients already underwent ABSCT or allogeneic TPL, 1 patient had deceased, patients were not followed up, and patients had AML in remission.

Conclusions

We demonstrated significant discrepancies between the collection yield and storage of PBSC harvests on the one hand and their actual usage in clinical practice on the other hand. However, it must be borne in mind that storage policies may considerably differ in centers worldwide. The standard approach applied currently in most centers results in substantial additional costs and clinical efforts, and strain on the patient for unnecessary PBSC mobilization, collection, processing, and cryostorage [13]. The current analysis specifically focused on PBSC collection, storage, and disposal while referring to patients' treatment status.

In summary, we would like to put the following suggestions forward in order to optimize PBSC storage and disposal practices in Burkitt lymphoma, ALL, MPN, and AML patients:

Timely and repeated consideration of PBSC graft disposal in deceased patients, patients receiving palliative care, patients with insufficient grafts collected, or patients already subjected to allogeneic TPL/ABSCT is recommended.

For PBSC grafts of patients who were not available for follow-up but still stored for years, it is of great impor-

tance to retrieve any information of the patients' current clinical status.

PBSC grafts which are no longer needed for patient treatment should be cleared for research use if the donor agrees and the respective legal and ethical requirements are met. Discarding this valuable material should be the last option.

It is recommended to critically question the indication for PBSC collection in the analyzed entities, as the role and efficacy of HDCT/ABSCT has not been ultimately clarified. Furthermore, in those patients who had already PBSC grafts collected, periodic reevaluation of the necessity of further storage (starting 12 months after collection) is recommended.

Statement of Ethics

The retrospective study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty, Heidelberg University.

Conflict of Interest

The authors confirm that there are no potential conflicts of interest to disclose, except for the following: K.K. received research funding from BMS, Celgene, and Sanofi. A.S. was supported by travel grants (Hexal, Jazz Pharmaceuticals) and a research grant (Therakos/Mallinckrodt); she is co-founder of TolerogenixX GmbH. P.W. served on advisory boards for Sanofi-Aventis.

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Author Contributions

K.K., P.P., Ti.B., and P.W. substantially contributed to the conception of the work, data acquisition, analysis, and interpretation, and drafted the manuscript. A.S., S.S., and Th.B. substantially contributed to the analysis and interpretation of the data and revised the work critically for important intellectual content. M.K., S.K., H.K., and C.M.-T. substantially contributed to the interpretation of the data and revised the work critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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