Int J Hematol (2008) 87:289–297
DOI 10.1007/s12185-008-0055-x

CASE REPORT

Successful autologous peripheral blood stem cell transplantation in a Jehovah's Witness with multiple myeloma: review of literature and recommendations for high-dose chemotherapy without support of allogeneic blood products

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Received: 3 September 2007 / Revised: 30 November 2007 / Accepted: 19 December 2007 / Published online: 4 March 2008

Abstract We present a case report of a successful high-dose melphalan therapy and autologous stem cell transplantation without the use of allogeneic blood product support in a 70-year-old patient suffering from multiple myeloma. Based on the experience in this case and thorough evaluation of the literature, we consider pre-transplant Hb level of 11–12 g/dl, platelet count higher than 70/nl, good WHO performance status of two and lower and informed consent as important eligibility criteria. During cytopenia recommended supportive measures include growth factor support with erythropoietin and G-CSF, p.o. iron treatment as well as prophylactic use of anti-fibrinloytic agents. Furthermore we discuss additional options that might be considered depending on the individual factors as e.g. pre-transplant collection and cryoconservation of autologous platelet concentrates. Moreover, an analysis of socio-economic issues regarding this procedure is presented. We conclude that allogeneic blood product free transplantation is a feasible procedure that can be offered to the patients belonging to distinct religious groups refusing allogeneic blood products as Jehovás Witnesses and patients presenting other contraindications for transfusions.

Keywords Jehova's Witnesses · Multiple myeloma · ABSCT (autologous peripheral blood stem cell transplantation) · Blood product support

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1 Introduction

High-dose chemotherapy followed by autologous transplantation of peripheral blood stem cells is a well-established therapy for patients with newly diagnosed, symptomatic multiple myeloma improving event-free and overall survival [1]. In addition, high-dose chemotherapy and autologous blood stem cell transplantation (ABSCT) are indicated for the patients with relapse of high-grade or indolent lymphoma and Hodgkin's disease. The risk of life-threatening complications or death by this therapeutic strategy in experienced centres ranges between 1 and 3% [2]. Infections during aplasia are the most common serious adverse event during the post-transplantation period [3]. A mean of 3.3 red blood cell units are used after high-dose chemotherapy with consecutive ABSCT for haematological malignancies (Hunault-Berger et al. 2005). In the patients with complications, the requirement for red blood cell transfusions increases up to 20 units [4]. Thrombocytopenia is treated by most transplantation centres with a prophylactic platelet transfusion strategy. One platelet unit per autologous transplant of peripheral blood stem cells as mean and median is used with a range from 0 to 18.

Besides socio-economic aspects associated with support of allogeneic blood products, there are specific adverse

events associated including transmission of infectious diseases, overload of iron, incompatible blood transfusion reactions, hypersensitivity reactions or an antibody response to HLA antigens on human platelets that render further allogeneic platelet transfusions complicated and costly.

A specific situation is encountered in members of the Jehova's Witnesses who form a religious group of about six million members worldwide that were founded in the 1870s in Pennsylvania by Charles Taze Russell. Most members of Jehova's Witnesses refuse the transfusion of allogeneic blood products because of the strict interpretation of certain bible passages in Leviticus. In addition there are patient groups that cannot receive blood products for medical reasons, e.g. patients with antibodies against a broad spectrum of HLA antigens or other reasons for contraindications for platelet transfusions.

In recent years more than 100 multidisciplinary, surgical or medical programs concerning the so-called bloodless treatments were designed for the patients that refused or had medical reasons prohibiting blood transfusions [5, 6]. So far there is one previous publication on the experience with high-dose chemotherapy followed by stem cell support in patients belonging to Jehova's Witnesses. In this publication Ballen et al. [7] describe distinct recommendation for the pre-transplant as well as transplant phase for this group of patients. Until now there are only a limited number of centres world-wide that offer hematopoietic stem cell transplantation without allogeneic blood cell support.

In this case report we describe the induction therapy and subsequent high-dose melphalan with consecutive stem cell support in a Jehova's Witness with symptomatic multiple myeloma without the use of allogeneic blood product support. We summarize and discuss the current treatment strategy and recommendations for patient selection for allogeneic blood product-free, high-dose chemotherapy and stem cell support.

2 Case report

In April 2006 a 70-year-old male patient confessing Jehova's Witnesses presented in our outpatient department for treatment recommendations regarding a IgG-lambda multiple myeloma with Bence-Jones-Lambda proteinuria stage IIIA according to the classification of Durie and Salmon that was diagnosed 2 months before. The patient gave his written informed consent for the publication of anonymized data.

Diagnosis of multiple myeloma stage III was based on positive immunofixation in serum for IgG-lambda with a total IgG level of 35 g/l, a positive urine immunofixation for Bence-Jones-lambda protein with a total lambda-light chain excretion in urine of 531 mg over 24 h, multiple osteolytic lesions and vertebral fractures, detected by X-ray skeletal survey and 56% bone marrow infiltration with monoclonal malignant plasma cells determined by histological assessment of a bone marrow biopsy specimen obtained from the iliac crest. Magnetic resonance imaging of the spine confirmed multiple myeloma lesions in the spine. Upon presentation the patient was anaemic with an Hb of 11.1 g/dl. Other routine laboratory values were in the normal range (data not shown). The patient suffered from myeloma-related bone disease with severe pain at the thoracic and lumbar spine because of impression fractures of thoracic vertebral bodies 8, 10 and 11 as well as lumbar vertebral body 1 to 3.

Before first admission to our centre the patient had been treated with one cycle of an oral chemotherapeutic regimen using cyclophosphamide and dexamethasone (Fig. 1, cyclophosphamide 200 mg p.o. d1-4 and dexamethasone 40 mg d1-4). Analysis of disease activity parameters after the first cycle (1 month) revealed no response with unchanged paraprotein levels in serum and urine. The patient still suffered from pain in the vertebral region of lumbar and thoracic spine and the haemoglobin level further decreased to 10.0 g/dl. Therefore, we switched to a thalidomide/dexamethasone regimen (Fig. 1, thalidomide 200 mg p.o. every day continuously and dexamethasone 40 mg d1-4, 9–12, 17–20, repeated after 28 days) for two cycles (2 months). After two cycles of thalidomide/dexamethasone a partial remission was achieved with reduction of paraprotein to 14 g/l. In addition a significant improvement of bone and vertrebral pain (course of paraprotein is demonstrated in Fig. 1) was achieved.

The Thal/Dex therapy was combined with the following supportive therapy: ibandronate 6 mg every 4 weeks i.v., darbepoetin alfa (Aranesp®), 500 µg once every week s.c., 200 mg of oral divalent iron (ferro sanol duodenal®, 100 mg, daily twice application). In 2 months the haemoglobin level increased from 10.0 to 11.4 g/dl.

Eight weeks after initiation of thalidomide/dexamethasone the patients's peripheral blood stem cells were mobilized with G-CSF in a concentration of 10 µg/kg/day subcutaneously for 4 days without application of a mobilizing chemotherapy. 2.3×10^6 $CD34^+$-cells/kg could be harvested and were frozen according to standard protocols.

A decision was made to attempt the collection of 1–3 autologous platelet concentrates and accompanying plasma for cryopreservation as backup for a potential thrombocytopenic bleeding episode after high-dose therapy.

The first collection of a platelet concentrate was performed 10 days after the collection of stem cells, with 181/nl platelets before the collection and 102/nl platelets after collection (total amount of 3.68×10^{11} platelets).

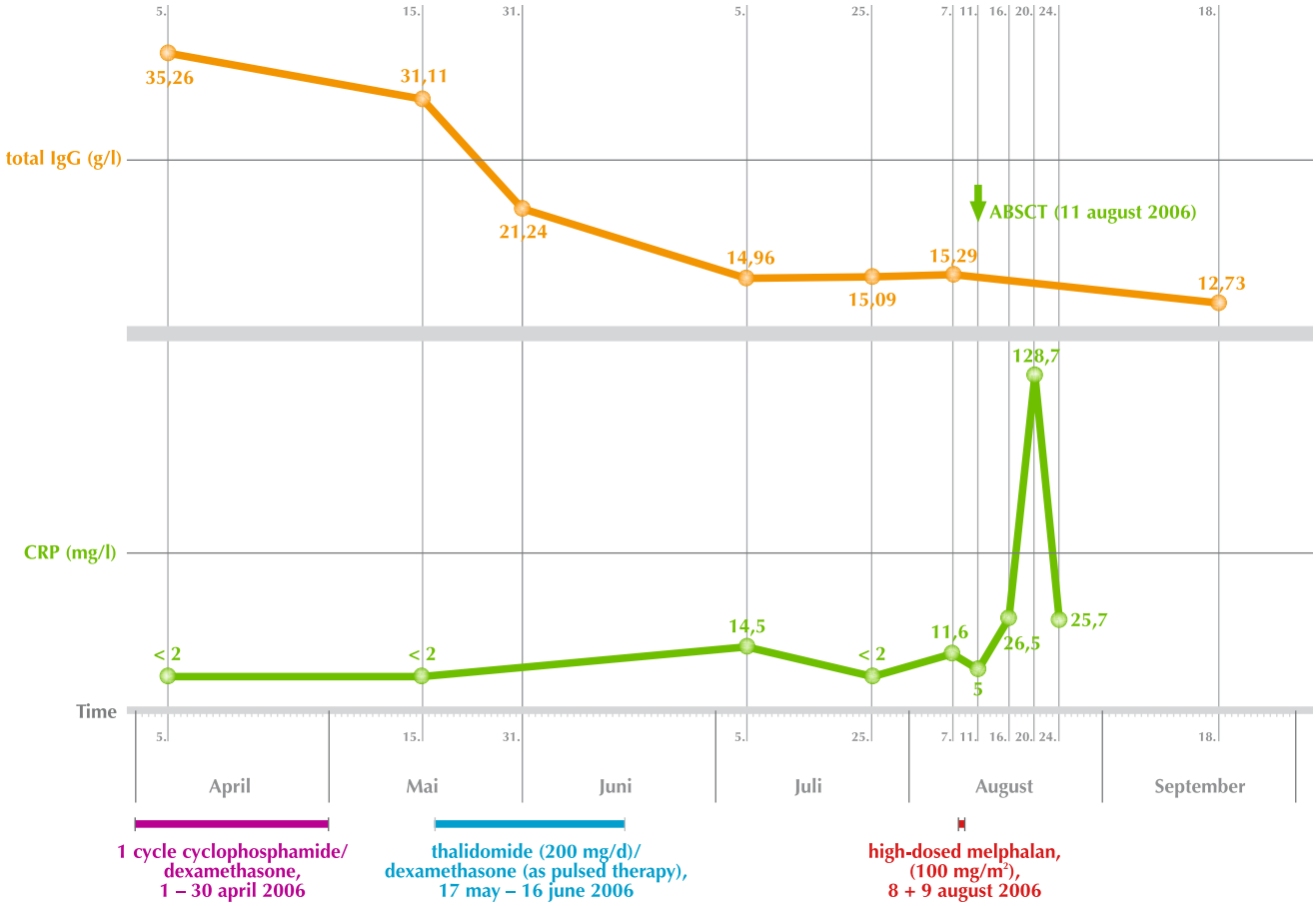

Fig. 1 Course of serum IgG- and CRP-concentration and corresponding myeloma therapy

Two days and eight days after the first collection further platelets were collected and cryopreserved reaching a total amount of 0.18×10^{11} (124/nl platelets before and 121/nl platelets after collection) and 0.63×10^{11} (157/nl platelets before and 76/nl platelets after collection), respectively. Hence, overall 4.5×10^{11} platelets were collected within 10 days following the mobilization of stem cells. After platelet collection the products were irradiated with 30 Gy to prevent tumour cell survival. Cryopreservation was done with 5% DMSO in autologous plasma in a controlled deep-freezer at a cooling rate of 1°C/min on the day of apheresis. The products were stored below −130°C in the gas phase of liquid nitrogen. The devices for cell collection were TRIMA Accel and a Cobe Spectra (Gambro BCT). The platelet count dropped from 221/nl before to 172/nl after the mentioned procedures. On a separate day, one unit of autologous whole blood was collected, processed to a unit of packed red cells and a unit of fresh frozen plasma and stored at 4 and −30°C, respectively.

Approximately 1 week after the collection of the third platelet concentrate high-dose melphalan (200 mg/m^2 body surface split on two consecutive days, each with 100 mg/m^2) was administered (day −3 and −2). Autologous peripheral blood stem cell transplantation was performed after 1 day of rest (day 0) (Fig. 2). Until reconstitution, the patient was treated with recombinant human erythropoietin in a dose of 4,000 IU/day i.e. 52 IU/kg/day, beginning on day 4 after the start of the melphalan therapy. During transplantation and recovery the patient was treated with 200 mg iron p.o. per day in the form of iron-II-ions (ferro sanol duodenal®, 100 mg/m^2 body surface) starting on the first day of high-dose melphalan. Furthermore, G-CSF, 480 µg once daily, was injected s.c. starting on day 4 of transplantation until hematopoietic recovery (day 14).

High-dose melphalan was well tolerated by the patient. Routine laboratory tests were performed every other day [including coagulation parameters such as prothrombin time (PT) and partial thromboplastin time (PTT)] in order to reduce blood loss by blood sampling. Antibiotic and antiviral prophylaxis was administered according to standard care in our centre. Course of peripheral platelet counts as well as haemoglobin and leukocyte values during post-transplant period are presented in Fig. 2. The patient developed lower right lobe pneumonia on day 7 after transplantation (that led to a sharp increase of CRP on day 9 post-transplant, see Fig. 1). Pneumonia was treated

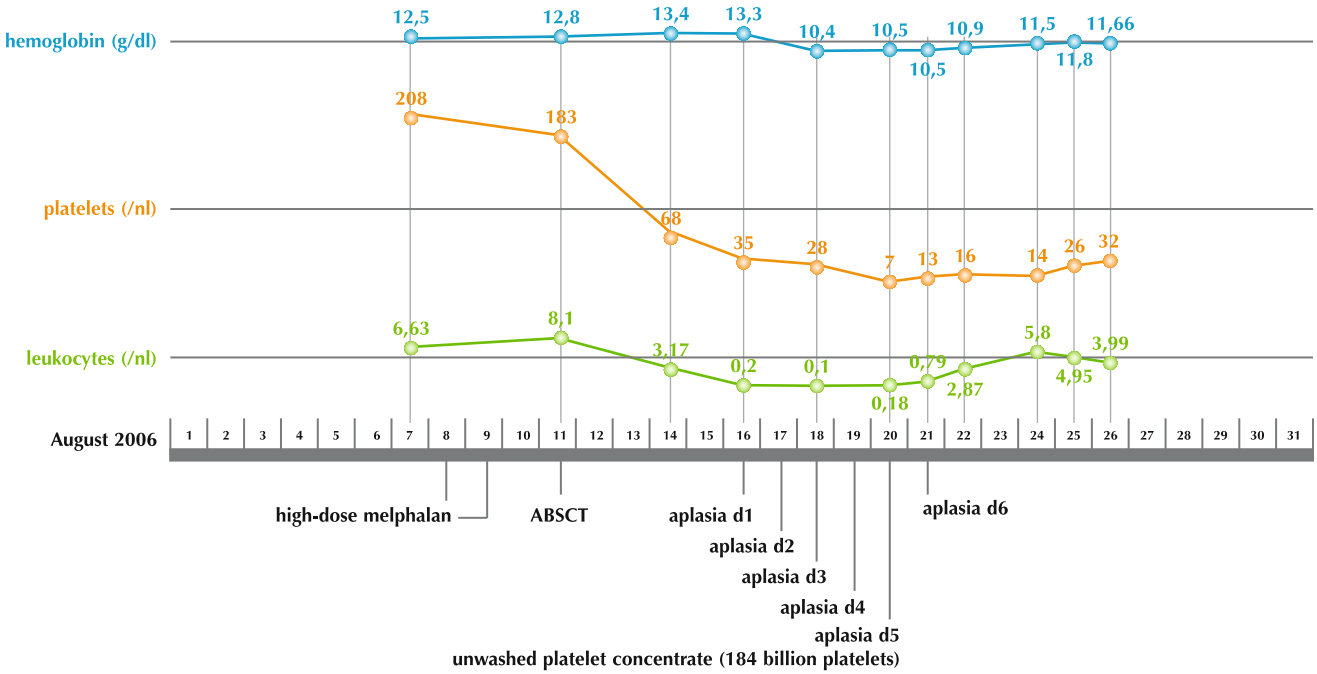

Fig. 2 Course of haemoglobin concentration, platelet and leukocyte counts during high-dose chemotherapy and consecutive ABSCT

empirically with ceftazidime 3 × 2 g/day i.v. and was changed to imipenem/cilastatin with the addition of clarithromycin because of persisting fever. Subsequently, the patient developed a clostridium difficile colitis with diarrhoea that was treated with metronidazole p.o. according to the international guidelines.

In total, antibiotics were given on 16 consecutive days (day 3 to day 12 with ABSCT on day 0). Fever resolved on day 12. Course of CRP as a marker of infection is shown in Fig. 2. Hematologic reconstitution (leukocytes >1/nl on day 14, platelets >20/nl) occured on day 15. During the infectious episode we observed a rapid decline of platelets (Fig. 2) which reached a nadir of 7/nl on day 9. Obviously no preemptive substitution of platelets was performed. But, when the patient developed lower gastrointestinal bleeding (hematochezia) one cryopreserved autologous platelet concentrate (the first collected with 3.68×10^{11} platelets) was transfused. Thereby, bleeding could be stopped immediately. Because of the urgent clinical need for these transfusions and to omit loss of platelets during the washing procedure, platelets were applicated without removing the DMSO by washing. This was considered safe and acceptable, especially as the patient had received DMSO during re-infusion of autologous stem cells before without any significant side effect. Platelet count on the day following the platelet transfusions was increased in comparison to the pre-transfusion values demonstrating the effectiveness of the cryopreserved platelets (Fig. 2). As additional supportive measure the patient received parenteral nutrition for 1 week because of a mucositis CTCAE-grade III after ABSCT.

On day 16 the patient could be discharged from the hospital in very good general condition (ECOG 0).

About 1 month after ABSCT a complete restaging was performed demonstrating a further improvement in reduction of paraprotein level to 8.1 g/l. According to ECOG criteria the patient had still a partial response and the immunofixation was positive for IgG-kappa in serum.

Thalidomide maintenance therapy was initiated at a dose of 100 mg/day. Eight months after stem cell transplantation the patient suffered from a relapse during thalidomide maintenance.

3 Discussion

In our report we describe a successful autologous peripheral blood stem cell transplantation (ABSCT) in a Jehovás Witness being the second publication on this issue after a collection of case reports published by Ballen et al. [7].

Performing high-dose chemotherapy and consecutive ABSCT as well as other treatment strategies with or without restrictive use of allogeneic blood transfusion is a procedure with importance for the patients belonging to religious minorities such as Jehovás Witnesses, but can also be helpful for patients with distinct contraindications for erythrocyte or thrombocyte transfusions as an effect of

alloimmunization with development of antibodies against HLA or human platelet antigens (HPA).

Based on our experience and taking into account previously published reports on this issue we propose a checklist of criteria that should be fulfilled and other criteria that should be excluded for these patients in order to perform a safe and feasible myeloablative chemotherapy with consecutive ABSCT. In this context we also want to refer to the article of Tenenbaum et al. [8] where different strategies (application of EPO, G-CSF and iron besides the administration of interleukin 11 for reconstitution of thrombopoesis amongst others) were described being appropriate to reduce the amount of blood loss and the degree of anemia as well as thrombo- and leukopenia in paediatric cancer patients who belong to the religious group of the Jehova's Witnesses.

In Table 1 we list the criteria indicative of eligibility for transfusion-free transplantation. This list is based on the criteria introduced by Ballen et al. [7], our own experience and the current status of literature in the field. In Tables 2 and 3 we summarize our recommendations for supportive treatment and specific diagnostic procedures for the post-transplant period aiming at reducing blood loss and other complications.

Finally, in Table 4, we provide a brief analysis of economic aspects and costs of this procedure by comparing savings by avoiding allogeneic blood transfusion and additional costs caused by cryoconservation of autologous thrombocytes and increased use of cytokines.

The criteria for eligibility and exclusion of patients undergoing allogeneic transfusion-free autologous peripheral blood stem cell transplantation have to be subjected to a detailed evaluation. We will structure the discussion into three sections with focus on recommendation based on the support of haemoglobin level, prevention and treatment of bleeding complications and issues regarding neutropenic fever.

A prerequisite for transfusion-free transplantation is a pre-transplant Hb level of (11–) 12 g/dl. If the conditioning therapy is started with an Hb level lower than 11 g/dl a considerable risk for potential life-threatening complications has to be taken into account. In the report by Ballen et al. [7] one patient was described that developed gastrointestinal bleeding (hematemesis, epistaxis as well as hematochezia) after high-dose chemotherapy with a decline in Hb level to 2.5 g/dl on day +9 after ABSCT when cryoprecipitates were applicated empirically with immediate bleeding cessation. As a consequence, the platelets recovered to 20×10^9/l on day +11. And the haemoglobin level increased up to 9.1 g/dl 19 days later. Even with the use of EPO and iron treatment before and after high-dose chemotherapy a median decrease of the Hb level of 4.7 g/dl is expected ranging from 2.0 to 9.2 g/dl [7]. Compared to the experiences reported by Ballen we observed only a moderate decrease of Hb in our patient from 12.5 g/dl (pre-transplant) to 10.4 g/dl (nadir on day 7) corresponding to a decline of 2.1 g/dl (Fig. 2). Although EPO is generally not required for the post-transplant phase of regular transplantations, patients in an allogeneic transfusion-free transplant program should be treated with EPO to exploit all options for supporting Hb level. Indeed, several publications have indicated an advantage in favour of the usage of EPO after transplantation. Pirelli et al. [9] found evidence in a phase I/II study, compared to historical controls, that the combination of G-CSF (5 μg/kg s.c.) and EPO (150 I.U./kg s.c., every 48 days) after transplantation of peripheral blood stem cells might be superior to the single therapy with respect to recovery of white blood cells

Table 1 Eligibility criteria and contraindications for allogeneic transfusion-free autologous peripheral blood stem cell transplantation

Criteria indicating qualification for transfusion-free transplantation
Pretransplant hemoglobin level ≥12 (11, in selected cases) g/dl
Thrombocytes ≥100/nl
CD34-positive stem cells $\geq 2.5 \times 10^6$/kg body weight
WHO-performance status 0–2
No elevation of transaminases and of total bilirubin over the 2,5-fold of normal upper limit (except when due to the treated disease)
Informed consent signed by patient
Contraindications for transfusion-free transplantation
Clinically evident heart failure (NYHA II or higher) with an injection fraction <40% in the echocardiography
Serious pulmonary, neurological or psychiatric disorders
Disorders of coagulation
Elevation of transaminases or total bilirubin over 2.5-fold the upper limit of normal control
Systemic amyloidosis with organ manifestations (except amyloidosis of the skin and/or the bone marrow)
Known HIV-positivity
Any condition that leads to increased likelihood for bleeding or infection during the transplant phase
Active and uncontrolled infections

Table 2 Recommendations for post-transplant period after autologous peripheral blood stem cell transplantation

Use of EPO in a concentration of 4,000 I.U. each day, beginning on day 1 after ABSCT
G-CSF in a concentration of 5 μg/kg s.c. 1-0-0 each day, beginning on day 1 after ABSCT
Application of oral iron-II-ions, 200 mg/day, starting on day 3
Routine blood sampling every other day in paediatric tubes

Table 3 Additional diagnostic or therapeutic options with potential to reduce complications during transplantation and aplasia

Treatment with ε-aminocaproic acid or tranexamic acid as prophylaxis for bleeding
Collection and cryoconservation of autologous platelet concentrates
Cerebral magnetic resonance imaging for identification of potential bleeding sites in central nervous system

Table 4 Cost comparison between allogeneic transfusion-supported ABSCT (regular transplantation) and allogeneic transfusion-free ABSCT in our case report

Measure/medication	Costs (Euro) in our case report	Cost per regular transplantation (Euro)
EPO 4,000 IU/day on day 1–14 after ABSCT	728	None
G-CSF 5 μg/kg/day on day 4–14 of ABSCT	1217.59	(1217.59)
Collection + cryopreservation of autologous thrombocytes (at least 4.0×10^{11} cryopreserved autologous thrombocytes), also including transport costs	3435	None
Collection + processing of one unit whole blood to a unit of packed red cells and a unit of fresh frozen plasma (including storing at 4°C, respectively, −30°C)	131	None
Mean expenses for allogeneic blood product support (erythrocytes and platelets)	None	704
Additional expenses for blood withdrawals after high-dose melphalan[a]		21.33
Summary costs	5511.51	725.33
Cost differences between standard and allogeneic TFT	4786.18	
Cost differences between standard and allogeneic TFT for centres that routinely use G-CSF	3568, 59	

[a] Number of routine blood tests reduced by 50% in transfusion-free transplantation

and platelets. Therefore, we decided to use a combination of the mentioned regimen with a fixed [10] dose of 4,000 I.U. EPO each day as equivalent of the above-indicated dose.

The activity of EPO in reducing transfusion requirements, prevention of cancer and chemotherapy related anaemia and improving quality of life (QoL) has recently been reviewed by Bokemeyer et al. [10]. Therefore we consider EPO also as an important supportive measure for pts. during the induction therapy. In our patient the improvement of Hb from 10.4 g/dl to 12.5 g/dl during the induction was possible by successful treatment of myeloma disease and by the use of EPO. Besides, thalidomide could have also contributed to the increase in Hb [11–13].

In summary, EPO can be considered as a safe and well-tolerable agent that is recommended for induction therapy and high-dose therapy for the patients eligible for transfusion-free transplantation.

Additionally, as a backup in case of severe bleeding, we had collected and processed (to a unit of packed red cells and a unit of fresh frozen plasma) one unit of whole blood before the beginning of high-dose chemotherapy. This procedure was not recommended by Ballen et al. [7]. We performed this procedure as we felt that this would increase safety. As the patient́s Hb level never dropped below 10.4 g/dl we were not urged to retransfuse the autologous donation. Indeed, if all eligibility criteria are met and EPO is used in the pre- and post-transplant phase the likelihood of benefiting from autologous erythrocytes is very small. There are additional arguments against the collection of autologous erythrocytes. The collection of a larger set of full blood products is not possible for most patients as many of them are anaemic in the pre-transplant phase, and erythrocyte concentrates cannot be collected and cryoconserved effectively in most cases before the conditioning regimen. In this situation collection of an autologous red blood cell (RBC) unit would counteract the aim of achieving a sufficient pre-transplant Hb level. In addition, even if one RBC unit could be collected, this would not compensate the blood loss during a severe bleeding

episode. For the majority of patients undergoing chemotherapy, it is not possible to collect a sufficient number of blood products being required in case of severe bleeding. Patients suffering from upper gastrointestinal bleeding need erythrocyte support with a median requirement of 4 to 6 units of packed red blood cells [14, 15]. For the majority of patients planned for transfusion-free transplantation it is not possible to collect such a number of RBC units.

In summary, given the reduced collection efficacy in this situation and the fact that in case of severe bleeding several blood units would be needed, we consider this measurement as not required for patients preparing for transfusion-free high-dose chemotherapy. In addition, collection of autologous blood products can by itself be associated with considerable morbidity and is a relevant cost factor [16].

As a contribution to the reduction of potential blood loss during the post-transplant phase frequency and amount of routine blood sampling should be reduced (e.g. use of paediatric tubes, routine blood sampling every other day).

Recommendations for prevention and treatment of bleeding are of pivotal importance for allogeneic transfusion-free transplantation and are therefore discussed in the following section. A further eligibility criterion for allogeneic transfusion-free transplantation is a thrombocyte count of at least 100/nl before high-dose chemotherapy. Regular decay of platelets with a median half-life of 7 days should protect the patients from the development of severe (<10/nl) thrombocytopenia, but in the transplantation setting, due to mucositis and infections, decline of platelets is usually significantly faster. Previously it has been shown that the transfusion of platelets in the posttransplant period is not necessary if there are no significant bleeding signs [17–19]. In the study by Ballen et al. [7] five patients developed bleeding during the thrombocytopenic period with two fatal outcomes (an intracranial lethal haemorrhage in a patient with a brain tumour and a gastrointestinal bleeding event).

Our patient was treated with a previously collected autologous platelet concentrate during an episode of thrombocytopenic gastrointestinal bleeding. Application of the platelet concentrate led to an immediate arrest of gastrointestinal bleeding and to a measurable increase of peripheral platelet count from 7/nl to 14/nl on the same day and to 13/nl on the following day with a CCI value of 3.228 (24 h after transfusion).

The fact that the second and third apheresis of autologous platelets in our case report led to insufficient results for the collected cells (numbers shown above) should be seen in the context of a potential negative effect on platelet recovery and collection efficiency by preceeding stem cell mobilisation with G-CSF. So the low platelet yield in a second and third apheresis should not be unexpected if the corresponding time delay between the three procedures is too small.

Whereas autologous red blood cells can be transfused safely and without a significant haemolysis after several weeks, platelets can only be stored under constant agitation at +22 (± 2°C for less than a week without the loss of a significant amount of activity. Therefore, cryopreservation of platelet products is needed and has to be performed [20] with dimethylsulfoxide (DMSO) at a concentration of 5% and dextrose. Clinical applications of cryopreserved platelets in first studies were done without employing a post-thaw washing step as platelets can be activated by this procedure. In order to avoid the adverse effects of the cryoprotectant DMSO Raymond et al. [21] used a post-thaw washing step and introduced the use of autologous plasma to resuspend the platelets after the washing step [21, 22]. Another method described includes freeze-drying with trehalose [23].

Cryopreservation of platelets is mainly hampered by the loss of platelet viability during this procedure [24]. While there are no standardized in vitro assays to determine in vivo recovery of transfused platelets without extravagant expenses, the corrected count increment (CCI) 1 h after the transfusion is a reliable parameter [25]. By these studies a CCI of roughly 60% in comparison with fresh platelet transfusions in other patients was found.

Low recovery rates may be improved by reagents (e.g. ThromboSol) that modulate second messengers and cellular enzymes and allow the reduction of DMSO concentration down to 2% [26]. Also combinations of epinephrine (EN) and dimethylsulfoxide (DMSO) have been developed in order to reduce loss of viability to a minimum [27]. As a further favourable effect of this technique it was demonstrated that the mechanisms of platelet aggregation are boosted by a combination of DMSO with EN, together reducing the risk of bleeding complications after ABSCT. However, further studies comparing the different techniques to reduce loss of platelet viability during long-term storage will be necessary to define the best method.

Although Ballen et al. [7] did not recommend the collection of a platelet concentrate and Wandt [19] and others have demonstrated the possibility for platelet-free transplantations the collection of at least one cryopreserved platelet concentrate should be considered. Actually, our procedure proposed here is very much in line with the therapeutic transfusion strategy proposed by Wandt [19].

Ballen et al. [7] proposed the use of ε-aminocaproic acid after ABSCT upon decrease of platelets to less than 30/nl, in a dose of 1–6 g per day, given orally every 6 h for the thrombocytopenic period. Ballen et al. [7] recommended to start with 1 g every 6 h and to increase dose in case of clinical evidence for bleeding. Indeed, Kalmadi et al. [28] demonstrated the therapeutic effect of ε-aminocaproic acid in patients with thrombocytopenic haemorrhage where

66% of treated patients achieved a complete response with arrest of bleeding and 17% a partial response [28]. This was associated with a decrease in platelet and red cell transfusions compared to historical controls. Furthermore, adverse effects were well manageable in the individuals suffering from severe disease. Further support of this concept comes from Benoni and Fredin [29] who demonstrated, in 1996, that tranexamic acid can reduce blood loss during surgery to a significant extent.

As ε-aminocaproic acid is not available in the EU we recommend to use tranexamic acid instead, as an agent with minor and well manageable grade 1 adverse effects such as nausea/vomitus, diarrhoea or hypotonia and vertigo. As of now there are no published studies on the use of tranexamic acid in patients undergoing ABSCT after high-dose chemotherapy. We would recommend to use this agent as alternative prophylactic treatment beginning with 1 g every 6 h with increase up to 6 g every 6 h in case of minor bleeding. For major bleeding complications we would consider usage of cryoconserved autologous platelets as detailed above.

In the following section we briefly summarize the rational to use G-CSF to decrease neutropenia and for the prevention of neutropenic fever.

The use of G-CSF shortens the mean time of grade 4 neutropenia after high-dose chemotherapy by about 2 days (6.6 ± 3.9 days versus 8.8 ± 4.9 days, $P < 0.04$) [30]. G-CSF can also decrease the requirement for blood product support due to its positive effects on megakaryopoiesis and erythropoiesis [31]. G-CSF was also shown to reduce infectious complications and febrile neutropenia after ABSCT [32, 33]. Furthermore, we recommend a particularly high clinical awareness of infections requiring antibiotic therapy in order to prevent a delay in antibiotic therapy that could result in an accelerated decrease of platelet counts.

To summarize costs and savings in comparison between allogeneic transfusion-supported ABSCT (regular transplantation) and allogeneic transfusion-free ABSCT (regarding the expenses in this case report) we created a cost comparison table. Additionally, in many protocols for standard ABSCT the application of G-CSF before and after transplantation is a well-established routine also causing costs that are not mentioned in our corresponding table due to the fact that G-CSF would also be used in Jehova's Witnesses in these cases. According to our calculations the allogeneic blood product support-free ABSCT leads to a cost increase between 3568.59 and 4786.18 € (depending whether G-CSF is used for standard procedure or not, see Table 4). To our opinion these additional costs are justified given the fact that a significant improvement for overall survival from the mentioned procedure is expected. If health insurances have to be contacted prior to the treatment procedure for reimbursement of additional costs has to be decided in individual cases.

In summary, we conclude that high-dose chemotherapy and autologous blood stem cell transplantation is possible and feasible without the support of allogeneic blood products for patients with medical or personal reasons prohibiting the usage of allogeneic transfusion. There are strict eligibility criteria and contraindications that apply for this procedure. A dedicated clinical team has to monitor the patient and has to follow specific therapeutic guidelines. Even if all precautions are met our proposed alternative procedure is still associated with an increased risk for life-threatening complications that have to be mentioned in the patient informed consent.

Hereby we guarantee that this case report was developed in accordance with the principles of the Declaration of Helsinki (1964).

Acknowledgment We wish to thank Mrs. Michaela Kriwy, commercial artist and illustrator, Baden-Baden, FRG, for her excellent support in designing the figures of this case report.

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