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Autologous Stem Cell Transplantation in the Treatment of Amyloidosis – Can Manipulation of the Autograft Reduce Treatment-Related Toxicity?

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1. Introduction

Autologous stem cell transplantation (ASCT) is used for disease stabilization and improvement of performance status in patients with immunoglobulin light chain amyloidosis. This therapeutic strategy has a relatively high treatment-related mortality. Therefore the limited treatment efficiency (cure is not possible) versus the risk of severe toxicity must be considered in each individual patient. The treatment-related mortality (TRM) has been up to 24% (Jaccard et al., 2007) and even 70% in certain studies (Moreau et al., 1998), but mostly lower mortality is reported (Vesole et al., 2006). These differences are probably due to patient selection criteria because TRM seems, among the other factors, to be associated mainly with cardiac amyloidosis. However, two main questions need to be answered with regard to efficiency versus toxicity of ASCT in amyloidosis. Firstly, one would appraise ASCT to be an effective treatment also in patients with cardiac amyloidosis, and ASCT could be considered also for these patients if the risk of severe toxicity could be reduced. Secondly, it can be difficult to select patients without cardiac amyloidosis for ASCT due to some uncertainty in assessment of cardiac involvement.

Determination of cardiac involvement is routinely performed by echocardiography despite the fact that the sensitivity of echocardiography is limited. Endomyocardial biopsy provides more reliable diagnosis but is associated with 1-2% complications (Cooper et al., 2007; Yilmaz et al., 2010). Thus, increased safety for patients with cardiac involvement may also reduce the risk of severe toxicity for patients without detectable cardiac involvement.

Dimethyl sulfoxide (DMSO) is used for cryopreservation of the stem cell autografts and the amount of DMSO infused together with the transplant may probably contribute to the early TRM in patients with amyloidosis. Several reports have described fatal outcome of autograft infusion, especially in patients with cardiac amyloidosis (Saba et al., 1999; Zenhäusern et al., 2000). By reducing the amount of infused DMSO, it may be possible to reduce the risk of ASCT-associated mortality and thereby make this treatment available for additional patients. In this chapter we will review various strategies that can be used to reduce the amount of DMSO infused together with autologous stem cell grafts.

2. Autologous stem cell transplantation in primary systemic amyloidosis

Primary systemic amyloidosis (AL) is a serious disease with a short survival (12-18 months) when conventional treatment with melphalan and prednisone is given (Dispenzeri et al., 2001). Patients with manifest cardiac involvement, being the worst prognostic indicator (Dubrey et al., 1998), have even poorer prognosis and a shorter survival; 4-6 months. Cardiac involvement is seen approximately in 50% of patients and half of them have congestive heart failure (Eshaghian et al., 2007). Arrhythmias and/or heart failure are the most frequent reasons of death in these patients.

Autologous stem cell transplantation is performed for disease stabilization and improvement of performance status in eligible AL patients. However, this therapeutic strategy has a high TRM; 15% to 70%, depending mostly on the patient selection criteria; meaning multiorgan involvement and especially advanced cardiac amyloidosis (Skinner et al., 2004; Moreau et al., 1998). Considering that TRM is less than 4% for patients with multiple myeloma (Segeren et al., 2003), even the lowest reported 15% TRM is unacceptably high for AL patients. Therefore, patient selection for transplantation is a key issue (Tichelli et al., 2008). Underdiagnosed cardiac involvement may also be assumed to be an underlying factor in the high early TRM. DMSO used for cryopreservation of the stem cell autografts, is a cardiotoxic agent, and when infused together with the transplant DMSO may contribute to the treatment-related toxicity in AL patients. Several case reports have described fatal outcome of autograft infusion, especially in patients with cardiac amyloidosis (Saba et al., 1999; Zenhäusern et al., 2000). Severe arrhythmias including atrial fibrillation are reported in the early stage of transplantation. Reduction of complications related to stem cell infusion may be achieved by different strategies for decreasing the amount of DMSO in the infused autologous stem cell grafts, since DMSO reduction may in turn promote/endorse improvement of early phase survival in AL patients.

3. Cardiac involvement in primary amyloidosis

Cardiac involvement is quite often in AL amyloidosis, occurring in up to 63 percent of the patients (Merlini et al., 2008). Symptoms are related to the localization and the degree of the amyloid accumulation in the heart. Since cardiac involvement that may result in congestive heart failure is rapidly fatal, it is important to realize the condition and choose the right treatment option as soon as possible.

Assessment of heart involvement is mostly made by evaluation of the clinical symptoms, electrocardiography (ECG), detection of biomarkers N terminal Pro brain natriuretic peptide (NT-proBNP) and troponins, scintigraphy, echocardiography, magnetic resonance imaging (MRI) and/or endomyocardial biopsy. Except for the latter method all the assessments are non-invasive. Low voltage, arrhythmias and conduction abnormalities may be found in ECG (Eshaghian et al., 2007). The biomarkers are sensitive markers of heart damage, but they are not specific for damage caused by amyloid light chains. NT-proBNP was reported to be very valuable in diagnosis of ventricular dysfunction (Krishnaswamy et al., 2001), in assessing prognosis of heart failure and after myocardial infarction (Palladini et al., 2003). In one study, NT-proBNP appeared to be more sensitive than conventional echocardiographic parameters in detecting clinical improvement or worsening of amyloid cardiomyopathy during follow-up, meaning that NT-proBNP is a powerful prognostic determinant in AL amyloidosis (Palladini et al., 2003) and not necessarily diagnostic. However, as mentioned above high values of NT-ProBNP and cardiac troponins are seen also in other cardiac diseases like coronary artery disease and atrial fibrillation. NT-ProBNP is elevated as a

result of left ventricular dysfunction in congestive heart failure. On the other hand, a normal NT-ProBNP can be used to eliminate myocardial amyloidosis.

Scintigraphy with various tracers has some value in diagnosis; either with technetium 99 m-pyrophosphate to differentiate AL amyloidosis from other transthyretin-associated amyloidosis or with I¹²³-labeled serum amyloid P (Hazenberg et al., 2006). Increased interventricular septum thickness and “granular sparkling” of the myocardium at echocardiography is helpful but not specific and sensitive enough. Increased myocardial echogenicity and valve-thickening are also frequent findings by echocardiography (Dubrey et al., 1998). Late gadolinium enhancement-cardiac MRI may detect early cardiac abnormalities in patients with amyloidosis with normal left ventricular thickness (Syed et al., 2010).

Finally, demonstration of amyloidosis by endomyocardial biopsy confirms the diagnosis in a patient whose echocardiography shows a mean left ventricular wall thickness more than 12 mm, when no other cardiac cause can be identified (Gertz et al., 2004). Tissue biopsies from other organs than the heart, showing amyloid deposits are not diagnostic for cardiac amyloidosis (Eshaghian et al., 2007). On the other hand, the endomyocardial biopsy being a diagnostic, yet invasive method may be associated with complications like bleeding, arrhythmias, thrombosis, infection, injury to the recurrent laryngeal nerve, heart block, injury to the vein/artery of the catheterization, pneumothorax and tricuspid regurgitation due to damage to the valve. Another seldom complication can be the rupture of the heart with pericardial tamponade (Cooper et al., 2007; Yilmaz et al., 2010). Complication rates vary between 0.6 and 6 percent (Cooper et al., 2007; Yilmaz et al., 2010), and the frequency of the complications depends on various factors including the experience of the operator, clinical status of the patient, and presence or absence of left bundle-branch block (Cooper et al., 2007).

4. Adverse effects related to stem cell infusion

In allogeneic stem cell transplantation setting, allografts harvested from healthy donors are usually infused to patients freshly. Autologous stem cell grafts, however, must be cryopreserved because of the time needed for in vitro quality controls (e.g. aerobic and anaerobic bacterial cultures, CD34+ cell enumeration and/or colony-forming unit assays) of the grafts and administration of high-dose chemotherapy before stem cell infusion. Autografts are commonly stored in nitrogen tanks at minus 160-180°C after controlled-rate freezing either on the harvesting day or the day after. Various controlled-rate freezers provide gentle cooling by -1 to -2°C/min to about -40 to -50°C, thereafter -5 to -10°C/min to about -80 to -90°C/min. At this point some centres transfer the bags to nitrogen tanks for storage, others continue the controlled-rate freezing until the temperature is equivalent to the nitrogen containers'. Despite the fact that liquid phase of nitrogen provides more stable temperature for storage, higher risk of contamination from other bags is documented and vapor phase appears consequently to be safer (Fountain et al.; Tedder et al., 1995). Cryoprotectants prevent intracellular formation of ice crystals that can damage cellular structures, and are therefore added to autografts before freezing (Szmant, 1975). The most commonly used cryoprotectant is DMSO, which is associated with well-known adverse effects during and shortly after autograft infusion, corresponding to the early transplantation stage. Besides DMSO itself, the adverse effects can also be due to DMSO-induced histamine release, and cell debris/lysis products released by graft white blood cells (WBCs) (Calmels et al., 2007; Milone et al., 2007; Saur-Heilborn et al., 2004). The frequency and severity of the adverse effects seems to increase with the amount of infused DMSO (Halle et al. 2001; Stroncek et al., 1991; Zambelli et al. 1998), a high number of granulocytes

in the autograft (Cordoba et al., 2007), and a high patient age (Milone et al., 2007). Mild adverse reactions like transient nausea, vomiting, headache, flushing, chest tightness, hypotension, bradycardia, and abdominal cramps are common (Alessandrino et al., 1999; Donmez et al., 2007; Zambelli et al. 1998), whereas serious reactions like hypertension, arrhythmias, cardiac arrest, anaphylaxis, respiratory arrest, multiorgan failure, and neurologic complications are rare (Bauwens et al., 2005; Chen-Plotkin et al., 2007; Nishihara et al., 1996; Hentschke et al., 2006). The risk of DMSO-associated fatal complications, however, is increased for certain diseases, for example, primary amyloidosis (Benekli et al., 2000; Saba et al., 1999; Zenhäusern et al., 2000).

5. Reduction of infused DMSO

Infusion of lesser DMSO may improve the treatment-related mortality in primary amyloidosis patients, especially in the early transplantation period. There are several methods of reducing the amount of infused DMSO and consequently decreasing the risk of adverse effects in association with stem cell infusion:

5.1 Reduction of the autograft volume and increasing the cell concentration

Increasing the cell concentration in the autograft and thereby reducing both the autograft volume and the amount of DMSO needed for cryopreservation is a simple strategy (Cabezudo et al., 2000; Martin-Henao et al., 2005; Rowley et al., 1994). The final mononuclear cell concentration in the autografts varies between transplantation centers; the most common concentration being $2 \times 10^8/\text{mL}$ (Windrum et al., 2005). Some centres use higher and some use lower concentrations (for example $1 \times 10^8/\text{mL}$), whilst others do not have any limits (Windrum et al., 2005). Several reports describe cryopreservation with high cell concentrations not resulting in additional loss of hematopoietic progenitor cell function, and not impairing the hematopoietic reconstitution (Cabezudo et al., 2000; Rowley et al., 1994), despite lower viability in samples with high concentration; 0.9 (range: 0.6-1) versus 2.9 (range: 2.2-4.7) $\times 10^8/\text{mL}$ (Cabezudo et al., 2000).

Reduction of the autograft volume by centrifugation prior to cryopreservation of the stem cells, as we performed, results in lower autograft volumes that will consequently require reduced amounts of DMSO for cryopreservation (Akkok et al., 2009). Cell concentration before freezing was kept at minimum $2 \times 10^8/\text{mL}$ in our study. We could therefore report low frequencies of side effects in our patients who also received DMSO-depleted autografts, since we followed a combination strategy with both volume reduction and DMSO-depletion procedure (the latter method will be explained detailed in 5.4) (Akkok et al., 2009).

5.2 Infusion of autografts over longer time

Infusion of autografts over longer time, if necessary several days (Martino et al., 1996), will reduce the daily DMSO exposure and limit the toxicity. The necessity is due to large volumes of the autografts to be returned to the patients. Patients in whom stem cell harvesting has to be performed in several subsequent days or patients who have to be re-mobilized usually have larger autograft volumes. Approximately 60% (57 out of 97 centres) of the European Group for Blood and Marrow Transplantation (EBMT) transplantation centres that replied a questionnaire, which was performed to assess current practice in the use of DMSO, had an upper limit in the amount of DMSO given per day varying between 20 to 80g (Windrum et al., 2005). Among the other centres the most frequently used limit was 1g/kg/day (33 out of 97 centres) or the centres did not have an upper limit of DMSO given per day.

Approximately one third of the centres preferred to return cells in split doses (Windrum et al., 2005). This study reveals the fact that there are no guidelines or agreement on the daily maximum dose of DMSO expected to be tolerated rather safely of the patients. In our study, when the total autograft volume exceeded 500 mL (i.e., total DMSO amount >50 mL for unmanipulated grafts), the stem cell infusion was divided into two separate sessions with at least a 2-hour interval or two subsequent days (Akkok et al., 2009).

5.3 Using DMSO concentrations lower than 10 percent

Using DMSO concentrations lower than 10 percent reduces complication rate (Akkok et al., 2009; Curcoy et al., 2002; Galmes et al., 2007; Windrum et al., 2005). There are only a few clinical studies where DMSO is used as the sole cryoprotectant at a 5 percent or lesser concentration (Akkok et al., 2009; Curcoy et al., 2002; Galmes et al. 1996, 2007). One other group used 3.5% DMSO, which is the lowest reported DMSO concentration in a clinical study but it was used in combination with 2.5% hydroxyethyl starch and followed by storage at -80°C (Halle et al., 2001). Galmés and colleagues, on the other hand, reported cryopreservation using only 5% DMSO and promptly hematopoietic engraftment as expected after short-time storage but slower hematopoietic recovery following long-time storage at -80°C (Galmes et al., 1996, 1999, 2007). Nevertheless, hematopoietic reconstitution was similar in both groups, when the patients were transplanted with more than $1.5 \times 10^6/\text{kg}$ CD34+ cells (Galmes et al., 2007). In addition, they showed reduced infusion-related toxicity (19% versus 6.8%) compared to 10 % DMSO. However, the authors do not recommend storage of grafts at -80°C for longer than 6 months due to progressively diminishing viability of mononuclear cells (MNC) and recovery rates of colony-forming units; granulocyte-macrophage (CFU-GM) and burst-forming unit erythroid (BFU-E) reaching zero after 24 months, when grafts are cryopreserved with 5% DMSO (Galmes et al., 2007).

In a pediatric setting, Curcoy and colleagues reported successful engraftment after short time storage at -80°C by using only 5% DMSO (Curcoy et al., 2002). It was also illustrated by in vitro studies that the numbers of both total and viable CD34+ cells were higher, CD34+ cells were less apoptotic and necrotic plus early hematopoietic progenitor cells were better preserved with 5 compared to 10% DMSO (Abrahamsen et al., 2002, 2004). As we reported from our clinical study, autografts stored in nitrogen gave similar hematopoietic recovery with hematopoietic stem cells cryopreserved either using 5 or 10% DMSO (Akkok et al., 2008). These findings strongly suggest that cryopreservation of autologous stem cell grafts with 5 instead of 10% DMSO reduces the complication rate during stem cell infusion, without any adverse effect on time until hematopoietic reconstitution (Akkok et al., 2008; Games et al., 2007).

5.4 Washing autografts to remove DMSO

Washing autografts in order to remove as much DMSO as possible will also expectedly reduce the side effects associated with stem cell autograft infusion. However, there have been some concerns for this procedure based on the risk of CD34+ cell loss. Keeping this risk in mind, DMSO-depletion should be avoided when the CD34+ cell yield is barely $2 \times 10^6/\text{kg}$. Some of the studies where DMSO depletion was utilized, included a large group of patients without bone marrow disease and may not be representative for the present use of autologous peripheral blood stem cell transplantation for hematological malignancies with diffuse infiltration of malignant cells throughout the bone marrow (Calmels et al., 2003; Rodriguez et al., 2005). These preclinical studies investigated grafts of highly selected patients who relapsed or died before autotransplantation could be done (Calmels et al.,

2003; Rodriguez et al., 2005). Furthermore, Foïs et al. cryopreserved autografts with voluven + DMSO 10% and not DMSO alone, and they did not include detailed analyses of engraftment and transfusion. This makes it difficult to evaluate the impact of DMSO-depletion and compare with other studies (Foïs et al., 2007). Lemarie and colleagues used comprehensive automated washing to reach more than 20-fold reduction of DMSO-levels, whereas Syme and coworkers investigated patients with solid tumors and used a relatively extensive manual DMSO depletion (Lemarie et al., 2005; Syme et al., 2004).

In the preclinical studies mentioned above (Calmels et al., 2003; Rodriguez et al., 2005), the researchers used a device; CytoMate™, to perform the washing procedure with phosphate buffered saline (PBS) plus 5% Dextran-40, 5% ACD-A and 1-5% human serum albumin (HSA). While Calmels et al. achieved more than 96% elimination of DMSO and a mean recovery of viable total cells, CD34+ cells and lymphocyte subsets above 60%, Rodriguez et al. reported 98% DMSO elimination and 103% CD34+ cell recovery. Foïs and co-authors used an automatic cell washer (COBE 2991) and diluted thawed autografts with a saline and acid citrate dextrose anticoagulant (ACD) solution. Washing procedure was repeated twice or three times before suspension in a glucose 5% solution (Foïs et al., 2007). Manual washing repeated three times was the method utilized by Syme and colleagues (Syme et al., 2004). They prepared a washing solution also with saline and citrate dextrose solution USP Formula A, and resuspended the final product again in the washing solution before infusion.

Rowley et al. initiated a post-thaw DMSO-reduction study, where autografts cryopreserved with only 10% DMSO were thawed and diluted with 10% dextran-40 and 5% HSA (Rowley et al., 1999). Stem cell components were thereafter centrifuged to remove DMSO and resuspended in dextran and HSA before infusion. However, they had to stop the study for safety reasons due to severe infusion-related toxicity. Even though acute renal failure is a seldom complication associated with dextran use, dextran should probably not be the first choice in AL amyloidosis patients (Boldt, 2010), in whom dextran side effects like anaphylaxis may also bring additional risk. One of our studies described elsewhere, analysed a simple, one-step manual method for DMSO-depletion (Akkok et al., 2009). We diluted thawed autografts with a washing solution prepared by adding acid citrate dextrose (ACD) in saline. Following centrifugation the supernatant was removed and the autograft was resuspended with ACD-saline solution before infusion. By this means we achieved at least 6-fold reduction in the amount of infused DMSO, and the recovery data were comparable to the previous studies with regard to recovery of MNC and CD34+ cells (81.9 and 77 percent, respectively) (Akkok et al., 2009).

In the above mentioned study, we demonstrated that time until neutrophil engraftment was not affected by the DMSO-depletion (Akkok et al., 2009). Only three other earlier studies have investigated effects of DMSO-depletion on hematopoietic reconstitution, (Foïs et al., 2007; Lemarie et al., 2005; Syme et al., 2004) and two of them described comparable neutrophil engraftment following DMSO-removal (Lemarie et al., 2005; Syme et al., 2004). Syme and colleagues described 1 day shorter time until neutrophil engraftment for patients receiving DMSO-depleted grafts, but this difference reached only borderline significance (Syme et al., 2004). Thus, DMSO-depletion of stem cell grafts seems to have minimal effects on neutrophil engraftment.

The significantly prolonged time until platelet engraftment for our patients receiving DMSO-depleted grafts was associated with a predictable increase in the number of platelet transfusions (Akkok et al., 2009). Lemarie et al. also described a slightly increased time until platelet engraftment for their patients, but the difference did not reach statistical significance (Lemarie et al. Transfusion 2005). In contrast, Syme et al. could not detect any effect of

DMSO-depletion on platelet engraftment time or platelet transfusion requirements (Syme et al., 2004). Taken together these results suggest that DMSO-depletion has relatively minor effects on platelet reconstitution.

Finally, both our group and others have shown that washing out DMSO, either manually or with an automated device, is associated with fewer adverse effects (Akkok et al., 2009; Foïs et al., 2007; Lemarie et al. Transfusion 2005). However, DMSO is probably not the only reason of adverse effects; factors like patient's age (i.e. the higher the age the higher the frequency of adverse effects) and the content of infused non-mononuclear cells $>0.5 \times 10^8/\text{kg}$ have been reported, yet for non-cardiovascular adverse effects (Milone et al., 2007). Despite a significant reduction, both Lemarie et al. and Foïs et al. reported adverse effects in approximately 20 percent of patients after automated DMSO-depletion, which is very similar to our result (Akkok et al., 2009; Foïs et al., 2007; Lemarie et al. Transfusion 2005). However, since the washing procedure will also reduce the number of neutrophils and the levels of a wide range of platelet- and leukocyte-derived soluble mediators (e.g. cytokines, soluble adhesion molecules, intracellular mediators), this reduction may also influence the frequencies of adverse events. It is important that DMSO-depletion procedures are effective; i.e. a meaningful DMSO-removal can be achieved, the procedure is not very time-consuming and will not result in critical CD34+ cell loss.

6. Conclusion

Autologous stem cell transplantation has an important place in the management of primary amyloidosis patients. However, treatment-related mortality is very high especially in patients with cardiac amyloidosis compared with other hematologic disorders. Therefore, this therapeutic option can only be offered to one fourth of the patients. It may be assumed that underdiagnosed cardiac involvement may bring an additional risk for this patient group. The role of DMSO (used for cryopreservation of the autografts) in early treatment-related mortality is undecided. Nevertheless, it is shown that reduction of DMSO before stem cell infusion reduces adverse effects without essential disturbance of hematopoietic reconstitution, we therefore recommend cryopreservation with 5% DMSO in addition to removal of DMSO before stem cell infusion, whenever patients with primary amyloidosis have adequate yield of CD34+ cells in their autografts.

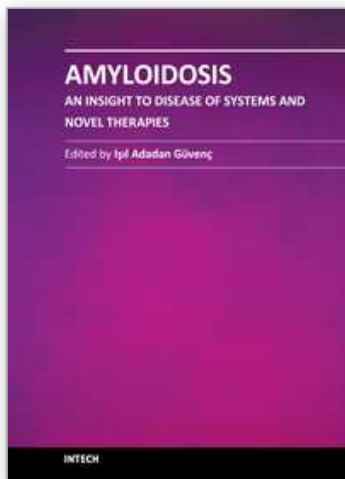
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Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of interest for many researchers and there have been a growing number of case reports in the literature for the last decade. The aim of this book is to help the reader become familiar with the presentation, diagnosis and treatment modalities of systemic and localized amyloidosis of specific organs or systems and also cover the latest advancements in therapy.

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