VIA MEDICA

Short review

NOWOTWORY Journal of Oncology
2018, volume 68, number 4, 205–211
DOI: 10.5603/NJO.2018.0033

ISSN 0029–540X
www.nowotwory.edu.pl

"No" for the allogeneic stem cell transplantation in young patients diagnosed with multiple myeloma

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Autologous stem cell transplantation (ASCT) is considered the standard of care in younger patients diagnosed with multiple myeloma (MM). However, despite an increase in the number of sustained responses, MM remains an incurable disease. Allogeneic stem cell transplantation (alloSCT) may have a curative potential resulting from induction of graft-versus-myeloma effect, but several factors limit its implementation in routine clinical practice. Myeloablative conditioning is associated with high (> 30%) treatment-related mortality (TRM), primarily due to graft-versus-host disease and infections, while the use of reduced-intensity conditioning increases the risk of relapse and disease progression, and also results in an unacceptably high TRM (21–23%). Auto/allotransplantation is not superior to tandem ASCT in terms of progression-free survival and overall survival, even in high-risk MM patients. The majority of younger patients may achieve sustained remissions after novel agents and ASCT, and nowadays alloSCT should be considered mainly in the context of clinical trials.

NOWOTWORY J Oncol 2018; 68, 4: 205–211

Key words: multiple myeloma, allotransplantation, allogeneic transplantation, treatment-related mortality, graft-versus-host disease

Introduction

Autologous stem cell transplantation (ASCT) is considered the standard of care in younger patients diagnosed with multiple myeloma (MM) [1, 2]. Despite a significant improvement in treatment outcomes, resulting primarily from the use of novel agents in induction, consolidation and maintenance therapy, MM still remains an incurable disease [3]. Although the term "operational cure", referring to progression-free survival (PFS) longer than 10 years, was established [4–6], still there is no medication potent enough to kill all neoplastic cells. Theoretically, allogeneic stem cell transplantation (alloSCT) could be a curative option, due to immunologic effect of the graft, the so-called graft-versus-myeloma (GVM) effect, exerted by immunocompetent donor lymphocytes [7, 8]. Unfortunately, it is theoretical only. The role of alloSCT in MM treatment has been widely discussed in the recent decades. Early studies, conducted in Europe in 1990s, revealed that full myeloablative allogeneic transplantation (the so-called "full allo") is associated with high, approximately 45%, risk of treatment-related mortality (TRM) [9]. Consequently, a concept of reduced-intensity conditioning (RIC) was developed, in order to decrease the treatment toxicity and TRM without compromising the GVM effect. Then, the idea of RIC allogeneic transplantation (also referred to as "mini allo") following the autologous transplant was introduced by the Seattle group. However, despite a plethora of comparative studies of tandem auto and autologous/RIC allogeneic transplantations that have been conducted since then, there are still more questions than answers. Who? When? According to which protocol? The role of alloSCT in MM is still a matter of debate due to high treatment-related mortality and morbidity and the lack of convincing evidence for a survival benefit. No treatment strategy should be implemented to routine clinical practice if there are still too many questions that have not been adequately addressed by researchers. Consequently,

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in this paper we try to answer the question "Why not to use alloSCT in MM patients?".

High risk plus high risk make ultra-high risk

According to the data from the Institute of Hematology and Transfusion Medicine in Warsaw, a total of 60 allogeneic stem cell transplantations were performed in Polish MM patients in 1993–2016. This included 26% of patients who underwent myeloablative conditioning and 74% subjected to reduced intensity conditioning. The median age of the patients was 46 years. Overall survival (OS) and PFS amounted to 26 and 23 months respectively. Thirty-seven patients (62%) died. The primary causes of TRM were disease progression, infections and graft-versus-host disease (GVHD) (Fig. 1).

According to the European Bone Marrow Transplantation (EBMT) report, TRM associated with myeloablative conditioning may reach up to 45%, with infections, GVHD and regimen-related toxicities as primary mortality causes [10, 11]. When the outcomes of 334 patients who received myeloablative alloSCT in 1983–1993 were compared with the results of 356 patients treated with the same methods in 1994–1998, a decrease in 2-year TRM rate was documented, from 46% to 30% [12]. Nevertheless, the TRM rate was still unacceptably high. As a result, at the end of the 20th century, myeloablative alloSCT was no longer performed in most countries [13]. Some authors compared the outcomes of ASCT and myeloablative alloSCT [14, 15]. Although myeloablative alloSCT resulted in sustained responses in some patient subpopulations and, therefore, seemed to have a curative potential in MM [16], the treatment was associated with high TRM (> 30%), even when applied as a component of the first-line therapy [15]. Based on those findings, myeloablative alloSCT definitely should not be considered a treatment of choice, especially when taking into account that long OS can also be achieved through effective induction therapy and ASCT.

The promising outcomes of RIC alloSCT in patients with low-grade lymphoproliferative disorders again stimulated a discussion about the role of allotransplantation as a treatment option in MM. The researchers from the Seattle group conducted a pioneering study of autologous transplantation followed by RIC allografting. The treatment consisted of high-dose melphalan and autograft, followed by 2 Gy total body irradiation (TBI), with fludarabine or without it, and alloSCT from HLA-identical siblings. The five-year non-relapse mortality rate after the allografting was 18%; up to 95% of the fatal outcomes resulted from GVHD or infection [17]. A number of conditioning regiments (including various doses of melphalan, fludarabine, cyclophosphamide and busulfan, with TBI or without it) and various anti-GVHD preventive measures, among them anti-thymocyte globulin (ATG) and alemtuzumab, were tested in further studies [18–26]. TRM rates varied between 11% and 38%. However, those

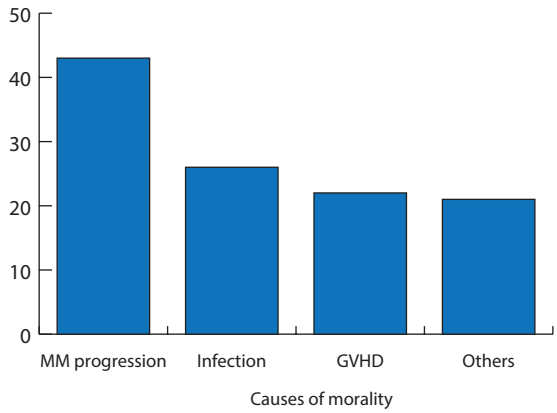

Figure 1. Causes of treatment-related mortality in 37 Polish patients with multiple myeloma subjected to allogeneic stem cell transplantation in 1993–2016. Data courtesy of the Institute of Hematology and Transfusion Medicine in Warsaw. MM — multiple myeloma, GVHD — graft-versus-host disease

results should be interpreted with caution, considering heterogeneity of patient populations and study protocols, and no definite conclusions should be drawn with regards to the superiority of any treatment regimen in terms of its efficacy and safety. In recent large studies [27–29], TRM rates at one year after alloSCT were 21–23% and then increased to 38% at two years from the transplantation (Table I). The only significant determinant of greater TRM was the age above 50 years [27]. This is quite an important finding, considering that MM is a disease of the elderly, with a median age at the diagnosis amounting to 70 years [2].

The authors of the EBMT report compared the outcomes of RIC alloSCT (in 320 patients) and myeloablative alloSCT (in 196 patients) [30]. While TRM at two years was significantly lower after RIC alloSCT (24% vs 37%, $p = 0.002$), the two groups did not differ in terms of OS, and higher PFS rate was documented in the myeloablative alloSCT group (34.5% vs 18.9%, $p = 0.001$). Multivariate analysis demonstrated that RIC alloSCT was associated with lower likelihood of TRM (HR = 0.5), but higher relapse risk (HR = 2.0). Based on those findings, it cannot be concluded what the optimal type and intensity of the induction are; while deep, sustained treatment response is with no doubt a priority, it must not be achieved at the expense of the compromised safety of the patient and greater toxicity of the therapy.

GVHD is one of the most significant contributors to TRM. Classic acute GVHD (aGVHD) is diagnosed whenever the disease manifestations (erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic liver disease) occur within the first 100 days after the transplantation, and classic chronic GVHD (cGVHD) is defined as the disease without any characteristic features of aGVHD [31]. In the previously mentioned pioneering study of autologous transplantation followed by RIC allografting, conducted by the researchers from Seattle, grade

Table I. Treatment-related mortality in multiple myeloma patients subjected to allogeneic stem cell transplantation

Study	N	Median age	Stage	Cytogenetics	RIC	Follow-up	TRM
Schilling et al. [27]	101	52 years	ISS III (74%)	FISH(+): 71%	yes	1 year	21%
Kröger et al. [28]	73	49 years	ISS II/III	del(13q): 59% t(4;14): 11% del(17p): 11%	yes	1 year	23%
Roos-Weil et al. [29]	143	51 years	D&S III (81%)	del(13q): 59% t(4;14): 25% del(17p): 25% t(14;16): 4%	yes (77%)	2 years	20% 29% 38% 23%

RIC — reduced intensity conditioning, TRM — treatment-related mortality, ISS — International Staging System, D&S —Durie and Salmon stage, FISH — fluorescence in situ hybridization

II–IV aGVHD was documented in 42% of the recipients at a median of 42 days post-transplantation (range 8–107), and cGVHD was diagnosed in 74% of the patients at a median of 167 days after the allografting (range 90–830) [17]. As shown in Table II, the risk of GVHD after alloSCT is unacceptably high. Even if only high-risk allograft recipients are considered, the likelihood of aGVHD exceeds 50% [27–29]. In one study, the incidence of grade II–IV aGVHD was shown to be significantly lower in patients subjected to RIC alloSCT than in those after myeloablative alloSCT (35.5% vs 45.9%, $p = 0.02$); the risk of aGVHD and its severity were not associated with the implementation of GVHD prophylaxis, use of a T-cell depletion, source of stem cells, and any specific donor-recipient sex combinations [30]. Moreover, no link was found between the type of conditioning regimen and the development of cGVHD or the severity thereof. The use of a T-cell depletion was associated with a lesser incidence of cGVHD (53.7% vs 77%, $p < 0.001$), but higher risk of disease relapse or progression (HR = 2.0, 95% CI 1.4–2.9, $p < 0.001$), plausibly due to an attenuation of the GVM effect. Higher incidence of cGVHD was also observed in male recipient--female donor combinations (60% vs 46%, $p < 0.001$) and in patients who received peripheral blood stem cells (51.5% vs 44.7%, $p = 0.03$) [30]. GVHD is a key determinant of survival and a principal factor limiting the use of alloSCT in MM. aGVHD was shown to be associated with higher TRM rates (32.5% in patients with grade II–IV aGVHD vs 14.8% in recipients with grade 0–I aGVHD, $p < 0.001$) and lower OS rates at three years (43% vs 56%, $p < 0.001$) [30].

To summarize, available evidence shows that alloSCT results in profound GVM effect, which may contribute to long-term remission. However, owing to high TRM rates after alloSCT, even used as a frontline therapy, this treatment should always be considered inferior to ASCT. The principal limitations for routine use of alloSCT in MM patients seem to be high mortality and high risk of potential complications. Moreover, allotransplantation is known to additionally increase the already high cytogenetic risk to an ultra-high, unacceptable level. Considering all the above, the Latin sentence *Primum non nocere* becomes particularly meaningful.

Is it worth it?

A final therapeutic decision should be based on a careful analysis of the risk-to-benefit ratio. The efficacy of alloSCT can be verified by prospective comparison of auto/allotransplantation with a gold standard, tandem autotransplantation. However, biologic randomization for alloSCT based on the availability of an HLA-identical sibling donor is a widely accepted and reliable surrogate criterion. Unfortunately, the studies using this protocol showed unequivocally that alloSCT is no more effective than ASCT.

The most definite conclusions about the role of alloSCT in standard-risk MM originate from a very large (710 patients from 37 transplant centers) Blood and Marrow Transplant Clinical Trials Network (BMT CTN) phase III tandem auto vs auto/mini allo trial. The study did not demonstrate statistically significant differences between both regimens in terms of PFS and OS rates at three years [32]. Noticeably, patients

Table II. The incidence of acute and chronic graft-versus-host disease in multiple myeloma patients subjected to allogeneic stem cell transplantation

GVHD	Schilling et al. [27] (n = 101)	Kröger et al. [28] (n = 73)	Roos-Weil et al. [29] (n = 143)
Acute	overall: 39% grade I: 13% grade II: 21% grade III: 1% grade IV: 4%	overall: 57% grade I: 17% grade II: 27% grade III: 12% grade IV: 1%	overall: 47% grade II–IV: 32%
Chronic	24%	26% (in patients who achieved CR)	43% (100 days post-transplantation)

GVHD — graft-versus-host disease, CR — complete response

from the auto/mini allo arm more often suffered from complications related to organ dysfunction and immune system deregulation resulting from chronic immunosuppression and the development of GVHD or the treatment thereof. Also, TRM rate in the auto/mini allo arm turned out to be significantly higher than in the tandem auto group (11% vs 4%, $p < 0.001$), even despite the use of a non-myeloablative regimen; the primary causes of mortality were GVHD and infections. Thus, a potential beneficial effect of GVM was outweighed by the increase in TRM.

Before the era of novel agents, prognosis in patients with unfavorable cytogenetics, i.e. with t(4,14), t(14,16) and/or del(17p) was generally poor [33, 34]. Thus, the discovery of donor-mediated GVM raised many hopes as a potentially effective treatment in high-risk MM. The French Intergroupe Francophone du Myelome (IFM) conducted two parallel phase II trials in patients with high-risk MM (beta-2-microglobulin > 3 mg/l and the presence of 13q deletion confirmed by fluorescent in situ hybridization). The IFM99-03 study included 65 patients with available HLA-matched sibling donors, who received RIC alloSCT after ASCT with busulfan, fludarabine and ATG conditioning. The outcomes of this group were compared with the results of 219 participants of IFM99-04, the auto-auto dose-intensified (220 mg/m^2), melphalan-based trial. No significant between-group differences in event-free survival (EFS) and OS rates were found in the intent-to-treat analysis [35]. While the two arms did not differ significantly in terms of their TRM rates, the incidence of relapse/progression was markedly higher in the RIC alloSCT group (56.5%); this might be associated with the fact that the outcomes were analyzed solely in high-risk patients and the GVM effect might have been partially attenuated due to the use of conditioning regimen prior to the allotransplantation [30, 36]. In updated IFM study [37], patients subjected to tandem ASCT and individuals who received ASCT/RIC alloSCT were followed-up for a median of 56 months. While the study groups did not differ significantly in terms of median EFS (22 vs 19 months, $p = 0.58$), median OS tended to be better in patients from the tandem ASCT arm (48 vs 34 months, $p = 0.07$). However, it must be stressed that the study was criticized for the use of high-dose ATG conditioning (12.5 mg/kg), as it might have a negative impact on GVM and contribute to a relatively low proportion of complete responses (CR, 23%) [36].

Schilling et al. [27] conducted a retrospective analysis of 101 patients subjected to RIC alloSCT. While participants of this study presented with an array of various cytogenetic abnormalities, including del(13q14) (61%), t(4;14)(p16.3;q32) (19%), del(17p13) (16%) and t(14;16)(q32;q23) (5%), cytogenetic profile exerted no effect on treatment responses and TRM rates. In a prospective study of 100 patients with newly diagnosed MM, all younger than 65 years, Bruno et al. [18] found no significant differences in median OS of individuals with del(13)q and without (4.3 years vs not reached, $p = 0.18$); nevertheless, patients without del(13) had better median EFS than those presenting with this cytogenetic defect (4.3 vs 2.2 years, $p = 0.01$). Unfortunately, due to a small number of patients included in the studies mentioned above, we still cannot conclude whether RIC alloSCT may provide an additional benefit in patients with unfavorable cytogenetics.

Whether the patient was subjected to tandem ASCT or auto/allotransplantation, relapse of MM seems to be a major problem. This puts particular emphasis on long-term control of the disease and identification of patients in whom MM is more likely to relapse. A multivariate analysis conducted within the framework of a large retrospective study [29] demonstrated that better PFS at three years was associated with younger age at the transplantation and at least very good partial response (VGPR) to alloSCT, whereas larger number of prior therapies and presence of cGVHD were identified as independent predictors of worse survival (Table III). These findings point to effective frontline therapy with ASCT as a key determinant of sustained response to the first-line treatment.

According to Keith Stewart from the Mayo Clinic: "The continued pursuit of safe and effective allogeneic stem cell transplantation for myeloma appears to be a triumph of hope over experience" [38]. However, the results of three randomized trials [17, 18, 39] suggest that the long-term outcomes of RIC alloSCT in MM are not encouraging; 11–18% of patients died within five years of the allotransplantation (most of them within the first two years), 50–74% developed a severe cGVHD, and one-third still required immunosuppressive therapy at five years post-alloSCT. Furthermore, no statistically significant differences were found in PFS and OS of patients subjected to alloSCT and tandem ASCT. Finally, little is known about a survival plateau after the allotransplantation. AlloSCT was shown to be inferior to tandem ASCT even in patients at very high risk of early progression and death from the disease. Paradoxically, the only group that may benefit from RIC alloSCT, are not the high-risk patients, but individuals with a favorable prognosis and expected survival of up to 10 years [38]. This seems

Table III. Independent predictors of better progression-free survival in multiple myeloma patients with high cytogenetic risk subjected to allogeneic stem cell transplantation

Predictor	HR (95% CI)	p-value
Number of treatment lines	0.29 (0.15–0.56)	0.0002
Age at the transplantation	1.1 (1.01–1.18)	0.01
At least VGPR after alloSCT	2.0 (1.11–3.62)	0.02
Chronic GVHD	0.3 (0.16–0.52)	0.001

Based on Roos-Weil et al. [29]. PFS — progression-free survival, VGPR — very good partial response, alloSCT — allogeneic stem cell transplantation, GVHD — graft-versus-host disease, HR — hazard ratio, CI — confidence interval

to be the additional argument against the routine use of allotransplantation in MM patients.

The potential of youth, the power of medicines

Over the last two decades, the survival of younger MM patients had improved significantly due to the use of novel anti-MM agents. In 1996 Blade et al. evaluated the outcomes of 72 MM patients younger than 40 years [40]. Median overall survival in patients treated with a single alkylating agent or combined chemotherapy was 54 months, while the actuarial survival at 5 and 10 years after initiation of the therapy amounted to 43% and 13% respectively. Implementation of novel therapies resulted in a marked improvement of the treatment outcomes. In our recent study, including 173 patients between 21 and 40 years of age treated with proteasome inhibitors and immunomodulatory agents and undergoing ASCT [41], median overall survival was not reached, and 5- and 10-year OS rates were 83% and 56% respectively. After stratification for the ISS stage, younger MM patients still had a better OS than those aged 41–60 years, but the survival advantage was observed solely for lower ISS stages.

Nowadays, a standard of care in patients who had been diagnosed with MM ≤ 65 years of age is high-dose melphalan followed by ASCT (HDT-ASCT); median OS after the treatment approximates 4 to 6 years [42–44]. In patients who failed to achieve at least near complete response (nCR) [42], or even VGPR [44], after the first transplantation tandem ASCT may produce additional benefits. Hence, the primary objective in treatment-naïve MM patients is to achieve CR or at least VGPR to induction therapy [45]. In the past, vincristine plus doxorubicin plus dexamethasone (VAD) was a standard induction therapy prior to HDT-ASCT [14, 35, 42, 44] with CR rates below 10% [14, 46, 47]. Novel agents, i.e. proteasome inhibitors (such as bortezomib) and immunomodulatory drugs (e.g. thalidomide or lenalidomide) are more effective, both in patients with newly diagnosed MM and in those with the disease relapse [48, 49]. In an open-label phase III study comparing the efficacy and safety of bortezomib plus dexamethasone (Vd) and VAD as induction treatments prior to ASCT in 482 previously untreated MM patients, significantly higher post-induction CR/nCR (14.8% vs 6.4%), at least VGPR (37.7% vs 15.1%) and overall response (ORR) rates (78.5% vs 62.8%) were documented the Vd arm [50]. Vd induction turned out to be superior to VAD even in patients with t(4,14), as shown by statistically significant differences in EFS (28 vs 16 months, $p < 0.001$) and OS rates at four years (63% vs 32%, $p < 0.001$) [51]. All these findings suggest that it is the induction therapy regimen rather than the type of the graft, which has a stronger impact on survival, also in high-risk patients [51].

Until recently, however, the use of the novel agents has been limited to patients with particularly unfavorable prognosis, with high-risk relapsed and refractory MM. Jakubowiak et al. [52] prospectively analyzed the impact of cytogenetic abnormalities, such as del(17p), t(4;14), t(14;16), del(13) and hypodiploidy, on the outcomes of carfilzomib therapy during a phase II trial. Although they found no statistically significant difference in ORR between the high-risk and non-high-risk group (25.8% vs 24.6%, $p = 0.85$), patients from the former group had significantly shorter OS (9.3 vs 19 months, $p = 0.0003$). In the study conducted by Shah et al. [53], patients with relapsed and refractory MM and poor cytogenetics, including del(17p), responded well to combination therapy with carfilzomib, pomalidomide and dexamethasone (CPD), which resulted in sustained control of the disease. The efficacy of novel agents in del(17p) carriers was also confirmed in a multicenter phase II randomized trial using the combination of pomalidomide and dexamethasone in advanced MM [54].

Some yet unpublished evidence suggests that also novel immunotherapies, such as bispecific antibodies and chimeric antigen receptor (CAR) T cells may provide a treatment benefit in ultra-high risk MM patients. However, those treatments are associated with up to 5% TRM, and hence, before their implementation in clinical practice, more data need to be collected about their long-term efficacy, especially PFS.

Due to the lack of treatment algorithms for this group, therapy of high-risk MM patients needs to be personalized, and pharmacotherapy offers much more possibilities in this matter than transplantation. Younger patients are by default more immunocompetent, and further boosting of their immune responses with novel agents seems to be a better option than exposure to toxicity associated with allografting.

Conclusion

A considerable improvement in the outcomes of MM treatment observed in the last decade is primarily related to the implementation of novel agents. Nowadays, the vast majority of younger patients receiving novel therapies may achieve sustained, prolonged remissions, and exposing them to morbidity and mortality risks related to alloSCT does not seem to be justified, even considering a potential additional survival benefit. Although a small proportion of patients may benefit from myeloablative alloSCT, this treatment is associated with high TRM rates, even when implemented as frontline therapy. While TRM after RIC alloSCT tends to be lower, this treatment is also associated with higher risk of relapse or progression. Further, we still do not have enough evidence for the superiority of alloSCT over ASCT [55], and even if it was the case, the applicability of allotransplantation as the first line treatment still might raise controversies considering already proven efficacy of novel agents, such as proteasome inhibitors and immunomodulators.

AlloSCT still may be an option in patients with high-risk MM and poor long-term prognosis. In this group, allotransplantation may be considered as a frontline therapy or as a salvage treatment after the failure of the first-line chemotherapy, but only when the risk of the disease progression outweighs the transplant-related threats.

The International Myeloma Working Group clearly stated that RIC alloSCT should only be recommended in the context of clinical trials. Future studies of allotransplantation in MM should be aimed at strengthening of the GVM effect with a simultaneous decrease in morbidity and mortality associated with GVHD [13]. This recommendation stays in agreement with the National Comprehensive Cancer Network guidelines on the treatment of myeloma.

Abbreviations

aGVHD — acute graft-versus-host disease
alloSCT — allogenic stem-cell transplantation
ASCT — autologous stem-cell transplantation
ATC — anti-thymocyte globulin
cGVHD — chronic graft-versus-host disease
CR — complete response
EBMT — European Bone Marrow Transplantation
EFS — event-free survival
GVM — graft-versus-myeloma
GVHD — graft-versus-host disease
IMWG — International Myeloma Working Group
MAC — myeloablative conditioning
MM — multiple myeloma
OS — overall survival
PFS — progression-free survival
RIC — reduced intensity conditioning
TBI — total body irradiation
TRM — treatment-related mortality
VGPR — very good partial response

Conflict of interest: none declared

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Received & Accepted: 19 Jun 2018

Based on a presentation at the VI Annual Conference of the *Nowotwory Journal of Oncology*, 'Oncological Debates', held in Warszawa, 6–7th April 2018.

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