Neoplasma 2023; 70(2): 294–299

doi:10.4149/neo_2023_220720N733

Allogeneic stem cell transplantation in patients with multiple myeloma-single center experience

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Received July 20, 2022 / Accepted January 23, 2023

The standard of care in multiple myeloma (MM) consists of induction chemotherapy followed by autologous stem cell transplant (autoSCT), but this setting doesn't present curative potential. Despite advances in new, efficient, and targeted drugs, allogeneic transplant (aloSCT) remains the modality with curative potential in MM. With the knowledge of high mortality and morbidity related to the treatment in comparison to treatment with novel drugs, there is no consensus in the indication of aloSCT in MM, also the choice of ideal patients profiting from this method is difficult. Therefore, we performed a retrospective unicentric study of 36 unselected consecutive patients transplanted for MM in the University Hospital in Pilsen between the years 2000-2020 in order to define possible variables influencing survival. The median age of the patients was 52 years (38-63) and the distribution of MM subtypes was standard. The majority of the patients were transplanted in the relapse setting, 3 (8.3%) patients in the 1st line setting, and in 7 (19%) patients elective auto-alo tandem transplant was performed. 18 patients (60% of patients with available cytogenetics (CG) had high-risk disease. 12 (33.3%) patients were transplanted with chemoresistant disease (at least PR not reached). With a median follow-up of 85 months, we observed median overall survival (OS) of 30 months (range 10-60) and median progression-free survival (PFS) of 15 months (11-175). 1- and 5-year Kaplan Meier survival probabilities for OS were 55% and 30.5% respectively. During the follow-up, 27 (75%) patients died, 11 (35%) due to treatment-related mortality (TRM), and 16 patients (44%) due to a relapse. 9 (25%) patients were still alive, 3 (8.3%) of them with complete remission (CR), and 6 (16.7%) patients with relapse/progression. Altogether 21 (58%) of the patients relapsed/progressed with a median of 11 months (3-175). Incidence of clinically significant acute graft versus host disease (aGvHD gr. >II) was low (8.3%) and extensive chronic GvHD (cGvHD) developed in 4 patients (11.1%). Univariant analysis proved marginal statistical significance in disease status before aloSCT (chemosensitive × chemoresistant) for OS, favoring patients with the chemosensitive disease (HR 0.43, 95% CI 0.18-1.01, p=0.05), there was no significant impact of high-risk cytogenetics (CG) on survival. No other analyzed parameter was found to be significant. Our findings support the conclusion that aloSCT is able to overcome high-risk CG and that aloSCT still remains a valid treatment choice with acceptable toxicity in well-selected high-risk patients with curative potential, even though often with active disease, but not derogating the quality of life significantly.

Key words: multiple myeloma; allogeneic HCT; prognostic factors; survival; indication

Multiple myeloma (MM) is a malignant proliferation of plasmocytes with a very variable aggressive or indolent chronic course, typically with frequent relapses of the disease. The standard of care in transplant-eligible patients with newly diagnosed MM consists of induction chemotherapy followed by autoSCT. This setting isn't curative and just more or less controls the disease and relapses are inevitable (even with the use of modern drugs). The plateau phase is not reached [1–3], so the disease is considered non-curable by definition. With aloSCT, in some patients, survival rates over some time reach the plateau phase and in some high-risk patients can provide longer OS and PFS in comparison with standard protocols [4], from where aloSCT remains modality with curative potential in MM. Because biological and clinical prognostic/predictive factors for aloSCT outcome in MM are still lacking, the indication of aloSCT in the treatment protocols is not well defined, and the choice of patients clearly profiting from this therapeutic modality is difficult. The society guidelines-for example The European Society for Blood and Marrow Transplantation (EBMT) or American Society for Transplantation and Cellular Therapy (ASTCT) are relatively unspecific and not very well usable for clinical practice [5, 6]. According to EBMT guidelines from 2019 [5], aloSCT is presented as a standard or possible clinical option

in case of high-risk disease, then in patients with first chemosensitive relapse after autoSCT or in case of early relapse after primary treatment which included autoSCT. Highly accented is the careful consideration of the risk/benefit ratio.

In Hematology-Oncology Department at University Hospital in Pilsen, we have been performing aloSCT in patients with MM since the year 2000. In order to identify the best candidates for aloSCT and to determine potential factors affecting outcomes of aloSCT in MM, we performed a retrospective analysis of these patients transplanted in Pilsen between the years 2000–2020.

Patients and methods

Patients. This is a retrospective analysis of all consecutive patients transplanted for MM between 2000–2020 at the University Hospital in Pilsen, 36 patients met the inclusion criteria. Pre-transplant, transplant data, and post-transplant information were sourced from the local transplant database and from the hospital information technology (IT) system.

Table 1. Patients' characteristics.

Characteristics	Patients (N=36)
Male/female	26/10
Median age at transplant - years (range)	52 (38–63)
Myeloma type	
IgG kappa/lambda (%)	22 (61)
IgA kappa/lambda (%)	7 (19.5)
ISS value-median (range)	2 (1–3)
Free light chains (%)	7 (19.5)
ISS 1	10 (28)
ISS 2	9 (25)
ISS 3	14 (39)
ISS ND	3 (8)
Poor cytogenetics (% of patients with available CG)	18
Induction	
Without novel drugs (%)	20 (56)
With novel drugs (Imids, PIs) (%)	16 (44)
Number of previous lineages- median (range)	2 (1–5)
1 and 2	28 (78)
3 a more	8 (22)
Auto/alo tandem (%)	7 (19)
Stage of the disease at transplant (%)	
CR	2 (5.6)
VGPR	3 (8.3)
PR1	7 (19.4)
PR2+	12 (33.3)
REL1	6 (16.7)
REL2+	6 (16.7)
Chemosensitive disease (%)	24 (66.7)
Chemoresistant disease (%)	12 (33.3)
Period of transplant (%)	
2000–2010	19 (52.8)
2011–2020	17 (47.2)

All patients signed consent with the anonymous use of personal data for research purposes.

Study definitions and endpoints. The cytogenetic evaluation was obtained at the time of diagnosis in all patients. Treatment response was evaluated in periodical intervals according to International Myeloma Working Group (IMWG) criteria [7]. OS was defined as an interval between transplantation and death or the last known visit. PFS was defined as the interval between transplantation and relapse/progression or death of the patient. Risk stratification was evaluated according to the cytogenetic profile when we divided patients into three groups by the CG risk: poor (t(4,14), t(14,16), t(16,20), tp53/del 17 or complete aberration), good (t(11,14) or hyperdiploidy), and group with intermediate risk. In all patient's diseases, the stage was evaluated according to International Staging System (ISS) [8]. Evaluation of aGvHD (st.I–IV) was realized according to Glucksberg evaluation [9].

Statistics. Statistical evaluation was performed with the use of GraphPadInStat – Statistical Software and basic statistic tests – Mann-Whitney, Fisher's Exact Test, and t-test. The probability of survival curves and TTP were processed by Kaplan-Meier methods, and the evaluation of statistic importance of statistical differences was made with a long-rank test (software MedCalc). Differences between specific groups were evaluated on a level of importance of 95% and values lower than 0.05 were considered statistically significant.

Results

Patient characteristics. A total of 36 patients were included. The group consisted of 26 men and 10 women with a median of age 52 years (38–63), data were evaluated in terms of the whole group. The main characteristics are summarized in Table 1.

Myeloma types. IgG kappa 17× (47.2%), IgA kappa 6× (16.7%), IgG lambda 5× (13.9%), kappa free 4× (11.1%), lambda free 3× (8.3%), IgA lambda 1× (2.8%).

Cytogenetics (CG), disease status, and other prognostic factors. In this cohort of patients, 18 patients (60% of all patients with available CG) had high-risk disease, in 6 patients the cytogenetic evaluation was not available due to low mitosis rate or other processing obstacles. The median ISS at the time of diagnosis was 2 (1–3).

Timing of aloSCT in the treatment petting. The median of previous lineages was 2 (1–5), 92% of patients underwent autoSCT after induction therapy. The median of autoSCT before aloSCT was 2 (1–3), elective auto-alo tandem transplant was performed in 7 patients (19%). In 3 cases (8.3%) aloSCT was performed upfront, all of them with mobilization failure and high-risk disease.

Disease status before aloSCT. In 24 patients (66.7%) the disease was chemosensitive (2× complete remission (CR), 3× very good partial remission (VGPR), 7× partial remission

(PR)1, 12× PR2), 12 patients presented with chemoresistant disease (6× relapse (REL)1, 6× REL2).

Time of aloSCT, novel drugs. In 19 cases (52.8%) aloSCT was performed between years 2000–2010 including, in 17 cases (47.2%) after the year 2010. 16 patients (44.4%) were pre-treated by modern drugs (Immunomodulatory drugs (Imids), proteasome inhibitors (PI)) before aloSCT.

Donor, source of hematopoietic stem cells (HSC), pretransplant regimen, GvHD prophylaxis. Transplant data are summarized in Table 2. In 20 cases (55.6%) donor was unrelated (14× (38.9%) full match, 6× (16.7%) 1 mismatch), in 16 cases (44.4%) the donor was related (14× (38.9%) HLA identical, 2× (5.5%) haploidentical. The source of HSC was in 34 (94.4%) cases peripheral cells (PBSC), in 2 patients (5.6%) the source was bone marrow (BM). 33 patients (91.7%) underwent a pretransplant regimen with reduced intensity (RIC), 3 patients (8.3%) were prepared with a myeloablative regimen (MAC). GvHD prophylaxis was based on calcineurin inhibitors in 35 cases (97.2%) (usually Cyclosporine A/MTX (CSA/MTX)), in 1 case (2.8%) cyclophosphamide regimen was used in a patient with a haploidentical donor. In 11 patients (30.6%) *in vivo* T-lymphodepletion by antithymoglobulin antigen (ATG) was performed.

Acute and chronic GvHD. Acute GvHD developed in 20 patients (55.6%), clinically significant stages III and IV only in 3 cases (8.3%), chronic form of GvHD developed in 12 patients (33.3%), from which extensive cGvHD developed in 4 cases (11.1%).

Survival, relapse rate. With a median follow-up of 85 months (8–178), 27 patients died (75%), 11 (31%) of them due to treatment-related mortality (TRM), 16 (44%) patients due to relapse. TRM in 100 days (TRM 100) was 15% in a group of patients transplanted until the year 2010, in patients transplanted in 2011 and later TRM 100 was 6.25%. TRM in 1 year was 35% in the group transplanted until 2010, and 18.75% in the group transplanted in 2011 and later. The main cause of death by TRM was infectious/septic complications (63.6%). In total 21 patients (58%) progressed or relapsed with a median of 11 months (3–175). Out of 9 living patients, 6 of them live with relapse/progression, 3 of them with remission of the disease. Medians of OS/PFS are 30 months (10–60), respectively 15 months (11–175). The probability of survival in 1 and 5 years are 55% and 30.3% respectively.

Prognostic factors of survival. Using univariate data analysis, we detected statistically significantly better OS in patients who were transplanted without the chemoresistant disease (HR 0.43, 95% CI 0.18–1.01, p=0.05), this was not proved in the case of PFS (HR 0.75, 95% CI 0.25–2.21, p=0.57) (Figure 1). All of the other compared variables (cytogenetics, age, number of treatment lines, use of modern drugs, period of transplantation) did not affect survival outcomes, results are summarized in Table 3.

Table 2. Transplant data.

Characteristic	Patients (N=36)
Donor (%)	
Related	16 (44.4)
HLA identical	14 (38.9)
Haploidentical	2 (5.6)
Unrelated	20 (55.6)
Full match	14 (38.9)
1 mismatch	6 (16.7)
Source of HSC (%)	
Peripheral cells (PBSC)	34 (94.4)
Bone marrow (BM)	2 (5.6)
Pretransplant conditioning (%)	
RIC (fludarabine/melphalan (FLU/MEL) ± antithymocyte globulin (ATG))	33 (91.7)
MAC (busulfan/cyclophosphamide (BU/CY2) ± ATG)	3 (8.3)
GVHD prophylaxis (%)	
Csa/MTX	34 (94.4)
Cy/Csa/mycophenolate mofetil (MMF)	1 (2.8)
Post-transplant cyclophosphamide (PTCY)/MMF	1 (2.8)
In vivo T-lymphodepletion (ATG) (%)	11 (30.6)

Table 3. Prognostic factors for OS and PFS, univariant analysis.

Prognostic factor	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Poor cytogenetics	0.67	0.31–1.46	0.32	0.52	0.21–1.30	0.16
Use of novel drugs	1.30	0.59–2.90	0.51	0.81	0.35–1.88	0.63
Patients age (>50 years vs. <50 years)	0.51	0.23–1.16	0.11	0.89	0.36–2.21	0.80
Year of treatment (2000–2009 vs. 2010–2020)	1.11	0.50–2.46	0.79	0.91	0.40–2.11	0.83
Number of previous lineages (<3 vs. >3 and more)	2.14	0.69–6.60	0.19	1.94	0.50–7.49	0.34
Stage of the disease before SCT (Sensitive vs. resistant)	0.43	0.18–1.01	0.05	0.75	0.25–2.21	0.57

Discussion

Despite the advent of highly effective new therapeutic modalities in MM (proteasome inhibitors, immunomodulant, monoclonal antibodies) and promising preliminary data in immunotherapies (CAR-T, bispecific antibodies), aloSCT still remains the method with curative potential. Regarding high mortality and morbidity in aloSCT compared to modern drugs, aloSCT is usually chosen as the last option of treatment.

In our group of patients, we proved the curative potential of aloSCT in high-risk patients (plateau phase reached). The incidence of clinically significant GvHD (i.e., grade III–IV) was low (8.3%) and didn't participate in transplant mortality.

With a median of 11 months (3–175), the majority (58%) of our patients progressed/relapsed.

Comparing our cohort with the literature we observed similar survival data. For example, Greil et al. [4] report a median OS of 39 months and a median PFS of 14.2 months in their group of patients. An extensive study from Auner et al. [10], which included 413 myeloma patients transplanted after RIC preparative regimen reports medians of OS and PFS of 24.7 months and 9.6 months respectively. Finally, a large European study from Sobh et al. [11] reports a range of medians for OS and PFS of 16–26 months and 7–11 months, respectively, in the cohort of patients with late aloSCT. In our patients, with a median follow-up of 85 months, we show a median OS of 30 (10–60) months and median PFS of 15 (11–175 months), which are figures comparable to the above-mentioned results.

In an effort to identify prognostic factors of aloSCT in MM, we demonstrated, in accordance with prior studies [12, 13], statistically longer OS in patients without resistant disease before aloSCT, however, PFS remains unaffected. When analyzing other parameters, there were no other variables significantly affecting the outcomes. No significant difference in survival outcomes also in patients with high-risk cytogenetics may, in accordance with previous studies [14, 15], reflect the ability of aloSCT to overcome the high-risk cytogenetic profile of the disease. Trying to show a decrease of TRM due to the onset of new supportive therapy, we compared TRM ratios in patients transplanted until 2010 and in 2011 and later. Even though the trend was obvious, still there wasn't a statistical difference between these two groups.

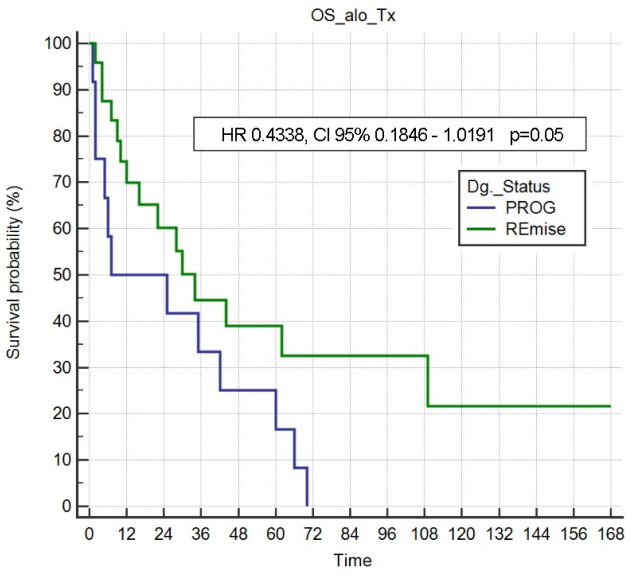

Figure 1. OS according to disease chemosensitivity.

In terms of aloSCT timing, the majority of our patients were transplanted in relapse after standard induction therapy and usually also after autoSCT. Only a minority of patients were transplanted in the first-line therapy (tandem auto-alo or first line without autoSCT). The indications for the first-line elective tandem auto-alo transplant included ultra-high-risk cytogenetics, age less than 55, good performance status, the unfavorable clinical course of the disease, and eventually suboptimal harvest of CD34 autologous cells. Therefore, we can't evaluate the benefit of aloSCT in the first-line setting. The benefit of elective tandem auto-alo- transplantation was not supported by recent studies [15–17]. AloSCT with RIC regimen after standard pretreatment (induction, autoSCT) and the second-line therapy still remain the most explored and used setting.

When compared to other therapeutic modalities (except for CAR-T), the Graft versus Myeloma effect (GvM), in other words, the direct, immunologically provided the antimyeloma effect of the donor cells, shows to be very essential and unique. GvM by its continuous antimyeloma effect could, even in a subsequent relapse of MM, enhance efficacy of upcoming modern therapy. GvM effect was first directly proved by Tricot et al. [18] showing the direct effect of the application of fresh donor mononuclear cells to a patient with by the time progressive MM after aloSCT. After this work, the principle of GvM was confirmed repeatedly in many ways. For example, proving survival benefit in patients with mild or moderate GvHD [19], clinically meaningful GvM by donor lymphocytes infusion (DLI) in patients relapsed after aloSCT [20], or reaching CR after immunosuppression withdrawal in transplanted patients [21]. This is supported also by the relatively long survival of our patients after relapse, who were further treated.

Our data are representative in terms of a single-center experience but still with a relatively small and heterogeneous group of patients, which does not allow us to draw strong clinical conclusions. Most of the patients were heavily pretreated and aloSCT was usually the last treatment option. These facts limit our transplant outcomes but the trends that we observed correlate well with the outcomes known from the literature.

In conclusion, our data support the opinion that aloSCT is still a valid and effective treatment modality with accept-

able toxicity in some selected high-risk patients. We show the curative potential of aloSCT and prolonged survival in some high-risk patients, even with the knowledge of the possibility of active disease after transplant, but without significant deterioration of quality of life in many cases. The Graft versus Myeloma effect shows up as a very good platform for the upcoming therapy in the case of relapse after aloSCT. Unfortunately, we still cannot precisely define the group of patients clearly benefiting from this method.

Acknowledgments: This study was supported by the grant SVV–2020-2022 No 260 540 and by the grant of the Ministry of Health of the Czech Republic – Conceptual Development of Research Organization (Faculty Hospital in Pilsen – FNPl, 00669806). Support was also provided by The Bone Marrow Transplant Foundation.

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