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# Allogeneic transplantation in multiple myeloma – How, when or at all?

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ABSTRACT

Allogeneic transplantation (allo) of patients with multiple myeloma is a controversial treatment due to high transplant related mortality (TRM) with myeloablative conditioning before the transplant. However, using reduced intensity conditioning (RIC) and previous autologous transplantation (auto) has dramatically reduced TRM. This, in combination with a lower relapse/progression rate, has in two out of six prospective studies resulted in prolongation of both progression free survival (PFS) and overall survival (OS) as compared to auto. No prospective study has proven auto – single or tandem – to be better than the auto/RICallo modality. The rapid development of relatively effective drugs in multiple myeloma has made most centers reluctant to use upfront RICallo. Considering the initial TRM of 12–16% with this treatment, it is now mainly used after progression-relapse following auto. New studies including more effective GVHD prevention and combination of allo with new drugs in the conditioning and as maintenance therapy are ongoing or in planning. Until clear advantageous results have been shown it seems reasonable to use the auto/RICallo procedure mainly in relapsed patients or upfront in patients with poor prognostic parameters such as del17p, del8p or gain 1q. The prospects for long-term survival or perhaps cure for a fraction of patients seem highest following some kind of allo.



## Introduction

Based on a few initial promising case reports indicating possible cure with allogeneic transplantation (allo) of multiple myeloma the EBMT (the European Group for Blood and Marrow Transplantation) started to perform allo in the early 1980th, and results of the first large series of patients were published in 1987 [1] and 1991 [2]. A fraction of patients entered complete hematologic remission (CR) and CR was demonstrated to be the most important prognostic factor for long-term survival [3]. However, the high-dose myeloablative

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conditioning was associated with high transplant-related mortality (TRM) – up to 40% after upfront treatment [3]. In attempts to reduce the TRM the Seattle Group started a program using very low conditioning dosages – down to 200 cGy total body irradiation (TBI), the idea being to utilize the well documented graft-versus-myeloma (GVM) effect [4–6] for tumor cell killing. Recent prospective trials have mainly used variants of this nonmyeloablative, reduced intensity conditioning (RIC) approach, but preceded by an autologous transplant (auto) for tumor cell reduction. Until recently these studies used the VAD (vincristine + adriamycine + dexamethasone) or similar regimens for induction. Ongoing studies and those in planning are including novel drugs like thalidomide, bortezomib and lenalidomide in attempt to improve results.

## How to perform an allogeneic transplantation in multiple myeloma

### *Myeloablative conditioning*

Myeloablative conditioning has mainly been abandoned due to the high TRM. The primary goal of myeloablative conditioning is to eradicate the disease and rescue the patient with the normal cells in the allogeneic graft. However, in addition, a GVM effect is well documented [4–6]. The most common myeloablative conditioning regimens are TBI 10–12 Gray fractionated or unfractionated with lung shielding [2, 3]. Many other conditioning regimens including high dose melphalan, and cyclophosphamide have been used as well [7–9]. Myeloablative conditioning allo is associated with lower relapse rate as compared to both RICallo and high dose conditioning auto but the TRM is higher and amounted to of 30–40% in earlier studies, mainly due to severe graft-versus-host disease (GVHD). Despite the lower relapse rate the progression-free survival (PFS) and overall survival (OS) [3, 10] were therefore generally poorer with myeloablative conditioning allo. However, there were subgroups of patients who did better, e.g. females with a female donor [11, 12], but still the TRM was high. Thus, despite improvement in results with time due to better supportive treatment [13], high CR rate of 50–60% [3, 14], higher rates of molecular remissions than after auto [15] and comparatively low relapse/progression rate, the high TRM has discouraged from the use of myeloablative conditioning.

## Reduced intensity (nonmyelablative) conditioning (RIC)

The idea of using nonmyeloablative reduced intensity conditioning (RIC) is to take advantage of the GVM effect for tumor killing and reduce TRM by lowering the irradiation and/or cytotoxic drug dose. Experimental canine transplant studies [16] by the Seattle Group showed that allogeneic engraftment [17] was possible with only 200 cGy irradiation and GVHD prophylaxis with mycophenylate moffetil and cyclosporine [18]. In a clinical study of 18 patients with refractory disease or failed prior autologous transplantation 2 entered CR and 3 further patients had a partial response with this approach. It was assumed that the response was mainly due to the GVM effect.

Since these crucial results appeared numerous phase I and II RICallo studies have been performed [7, 18–28]. In addition there are six prospective upfront studies with somewhat different design comparing the combination auto/RICallo to auto or auto/auto (Table I). All of them were based on the availability of an HLA matched sibling donor [29–37]. In four of the studies TBI 200 cGY was used for the RICallo conditioning as in the Seattle study. One – the EBMT study – used as well fludarabin 30 mg/m$^2$ × 3 before irradiation. The IFM study used a combination of fludarabine, low dose busulfan and ATG and the PETHEMA group Melphalan 140 mg/m$^2$ plus fludarabine. In five of the studies, the control group was tandem autologous transplantation in those patients who lacked a donor, while in one of the studies – the EBMT study – either single or tandem autologous transplantation was used. The induction treatment was VAD (vincristine + adriamycin + dexamethasone), thalidomide and dexamethasone, or similar combinations in all studies, and the conditioning for the initial autologous transplant was 200 mg/m$^2$ melphalan.

The IFM study [31, 32] included 219 patients without (tandem auto group) and 65 with an identical sibling donor (auto/RICallo group). All patients had high risk disease as defined by beta$_2$-microglobulin of more than 3 mg/L, and deletion of chromosome 13. On an intention to treat basis the median event-free survival was 19 versus 22 months and the OS 34 versus 48 months in the auto/RICallo and auto/auto groups respectively, i.e. a trend for inferior OS in the auto/RICallo group ($p = 0.07$). The use of antithymocyte globulin – Imtix Genzyme (2.5 mg/kg/day during 5 days) for GVHD prevention – and busulfan and fludarabine for conditioning might have played a role for the trend for poorer outcome with auto/RICallo.

The Italian study [33, 37] comprised 245 patients enrolled at time of diagnosis. Eighty out of 162 patients who underwent HLA typing had an HLA-identical sibling donor and 58 out of these 80 patients underwent the auto/RICallo procedure. They were compared to 46 patients without and HLA identical sibling who received auto/auto. On an intention to treat analysis the median event-free survival in the auto/RICallo group was 35 months, as compared to 29 months in the auto/auto group ($p = 0.02$). The median OS was 80 months versus 54 months, respectively ($p = 0.01$). Long-term intent to treat analysis with patients more than seven years from diagnosis continue to demonstrate an OS benefit for auto/RICallo with median survival not reached versus 4.2 years in the auto/auto arm ($p = 0.001$) [37].

The Spanish PETHEMA study [35] – was relatively small in that it included only 25 patients in the auto/RIC arm compared to 85 receiving auto/auto. Patients less than seventy who failed to achieve a CR or nCR after the initial autologous transplant were eligible for second transplant. The median time for PFS and OS had not been reached in the auto/RICallo group, while it was 31 months ($p = 0.08$) and 58 months ($p = 0.9$), respectively, in the auto/auto group. Thus, this study indicated a trend toward superior outcome with the auto/RICallo procedure in patients who did not reach CR after initial auto.

**Table I – Conditioning and timing of RIC allogeneic transplantation in multiple myeloma**

| Reference | Conditioning for RICallo | Transplant procedure number of allo patients (or donor available) | Time of transplant | NRM/TRM per cent at year (y) | PFS Median months (m) or per cent at year (y) | OS Median months (m) or per cent at year (y) |
|---|---|---|---|---|---|---|
| Garban et al., 2006 and Moreau et al., 2008 [31, 32] | Flu 25 mg/m$^2$ × 5 days + BU 2 mg/kg × 2 days + ATG 2.5 mg/kg × 5 days | Auto/RICallo 65 | Prospective upfront | 11% | 19 m | 34 m |
| Bruno et al., 2007 [33] | TBI 2 Gy | Auto/RICallo 80 | Prospective upfront | 16% 6.5 y | 35 m | Median not reached |
| Lokhorst et al., 2012 [34] | TBI 2 Gy | Auto/RICallo 138 | Prospective upfront | 11% 1 y | 28% 6 y | 55% 6 y |
| Krishnan et al., 2011 [36] | TBI 2 Gy | Auto/RICallo 189 | Prospective upfront | 11% 3 y (standard risk) | 43% 3 y (standard risk) | 77% 3 y (standard risk) |
| | | 37 | | 22% 3 y (high risk) | 40% 3 y (high risk) | 59% 3 y (high risk) |
| Björkstrand et al., 2011 and Gahrton et al., 2013 [29, 30] | Flu 30 mg/m$^2$ × 3 d + TBI 2 Gy | Auto/RICallo 108 | Prospective upfront | 12% 2 y | 43% 3 y | 71% 3 y |
| | | | | 15% 5 y | 22% 8 y | 49% 8 y |
| Rosinol et al., 2008 [35] | Flu 25 mg/m$^2$ × 5d + Mel 70 mg/m$^2$ × 2d | Auto/RICallo 25 | Prospective failing CR or nCR following auto | 16% | Median not reached | Median not reached |
| Crawley et al., 2007 [7] | Flu + TBI Flu + Mel Flu + Bu ± T-cell depl | Auto/RICallo or RICallo alone 516 (RIC 62%) Progressive 28% | Retrospective | 24% 2 y | 19% 3 y | 38% 3 y |
| Michallet et al., 2014 [73] | Myeloablative and RIC | Myeloablative and RIC (%) | Retrospective from 2004 (<PR %) | No information | | Per cent surviving at 5 years |
| | | 1934 (22%) | Upfront (25%) | | 43% | 39% |
| | | 1997 (79%) | <8 m post 1 auto (15%) | | 42% | 53% (median RIC/MAC 76 m versus 45 m) |
| | | 1588 (71%) | >8 m post 1 auto (29%) | | 26% | 33% |
| | | 588 (84%) | <8 m post 2 auto (17%) | | 28% | 31% |
| | | 930 (68%) | >8 m post 2 auto (31%) | | 24% | 29% |
| | | 296 (71%) | After 3 auto (27%) | | 15% | 23% |
| Kröger et al., 2010 [19] | Mel 140 mg/m$^2$ + Flu 30 mg$^2$ × 3d + ATG 20 mg/kg × 3d | RICallo 49 | Prospective – relapse Phase II | 25% (Sibling 10%) | 20% | 26% |
| Efebere et al., 2010 [69] | Mel 90–140 mg/m$^2$ + Flu 90–120 mg/m$^2$ ± ATG | RICallo 55 | Prospective Relapse | 25% | 19% 2 y | 32% 2 y |
| Shimoni et al., 2010 [71] | Mel + Flu based | RICallo 50 | Retrospective Refractory/Relapse | 26% | 26% 6.4 y | 34% 6.4 y |
| Patriarca et al., 2012 [39] | Flu + Mel + Thiotepa (41%) Flu + TBI 2 Gy (35%) Flu + Treosulfan (9%) Other RIC (15%) | RICallo 75 | Retrospective Relapse | 22% | 42% 2 y | 52% 2 y |
| Karlin et al., 2011 [70] | TBI 2 Gy | Auto/RICallo 23 | Retrospective Relapse | 17% | 36.8 m | 60 m |

RIC = reduced intensity conditioning; NRM = non relapse mortality; TRM = treatment related mortality; PFS = progression free survival; OS = overall survival; Flu = fludarabine; Bu = busulphan; TBI = total body irradiation; ATG = antithymocyte globulin; CR = complete remission; nCR = near complete remission.

The HOVON-50 study [34] – comprised 260 HLA typed patients of whom 122 had an HLA identical sibling donor. Of these 122 patients, 99 received an HLA-identical sibling transplant, while those without a donor received further treatment with thalidomide maintenance or a second auto. No significant difference in PFS or OS was seen when analyzed on an intention to treat basis. However, the relapse rate was significantly lower in the donor group. Although not significant, the six-year PFS was 28% in the donor group and 22% in the no donor group ($p = 0.19$). On an as treated analysis, when those patients who had really received a RICallo transplant ($n = 99$) were compared to those who continued maintenance or received a second auto transplant, there was a significant advantage in PFS for the RICallo patients.

The American BMT CTN 0102 study [36] – comprised 710 patients (625 standard risk and 85 high risk). Patients <70 years, between 2 and 10 months of initiation of myeloma therapy were eligible for enrollment and assigned to either auto/auto with high dose melphalan (200 mg/m$^2$) or auto/RICallo with single dose 2 Gy total body irradiation conditioning. Standard risk myeloma was defined as beta$_2$-microglobulin <3.0 and absence of deletion 13 by classic karyotyping. By intent to treat analysis there was no significant difference in three year PFS between the auto/auto and auto/RICallo at 46% versus 43% ($p = 0.671$) respectively. Three year OS was 80% with auto/auto versus 77% with auto/RICallo ($p = 0.19$). A subgroup analysis was done on high risk patients to assess if these patients who had a higher risk of relapse would benefit from the auto/allo approach. No significant difference was seen with a three year PFS of 40% with auto/RICallo versus 33% with auto/auto ($p = 0.74$) and OS of 59% versus 67% ($p = 0.46$) respectively.

The EBMT study [29, 30] – comprised 357 myeloma patients from 23 centers. Patients up to age 69 with an HLA-identical sibling were allocated to the auto/RICallo group ($n = 108$), and those without to auto ($n = 249$), either as a single or tandem transplant. The study was originally published in 2011 [30] and was updated in 2013 [29] with the median follow-up now 96 months. At this time, both PFS and OS were significantly superior in the auto/RICallo group as compared to the auto group. On an intention to treat analysis, PFS with auto/RICallo was 22%, as compared to 12% with auto ($p = 0.012$), and OS was 49%, as compared to 36% with auto ($p = 0.020$). Despite the higher nonrelapse mortality of 13% at 36 months in the auto/RICallo group as compared to 3% in the auto group, the lower relapse rate of 60% at 96 months in the auto/RIC allo group versus 82% in the auto group translated into superior PFS and OS. However, at 36 months, there was no significant difference between the two groups, i.e. PFS was 43% versus 39% and OS 75% versus 68% in auto/RICallo and auto respectively. Thus, the conclusion was that long-term follow-up is necessary to see the benefits of the auto/RICallo procedure as compared to the auto procedure. In a subgroup analysis it was shown that CR was the important factor in achieving long-term PFS, in both groups, but a CR obtained with auto/RICallo was sustained longer than if obtained after auto/auto ($p = 0.008$) [38].

Although two of the six prospective studies show superior outcome with the auto/RICallo procedure as compared to auto or auto/auto the studies are not designed to give information about the impact of the type of conditioning regimen (Table I). However, in the four studies that used TBI 2 Gy [29, 33, 34, 36] with or without fludarabine, the results are initially similar. The three-year PFS/OS survival was not significantly different between auto/RICallo and auto (or auto/auto) in any of these studies. The six-year OS was very similar for both auto/RICallo and auto (auto/auto in the HOVON study) in the HOVON and EBMT studies, i.e. 61% versus 51% compared to 64% versus 57% respectively, however the difference in OS was only significant in the EBMT study. The long-term superior survival with auto/RICallo in the Italian study appears to be in the same range as in the EBMT study. A longer follow-up of the BMT CTN has not yet been published. Thus total body irradiation 200 cGy with or without fludarabine seems to be a reasonable conditioning for RICallo. Other regimens like low dose busulfan + fludarabine, low or intermediate dose melphalan + fludarabine or treosulfan + fludarabine may well be used. However no prospective comparison between different conditioning regimens has been performed.

## Novel drugs as maintenance and at progression/relapse after allogeneic transplantation

The long-term prospective up front studies are hampered by not having included novel drugs in the conditioning regimen. In a few retrospective studies of RICallo for treatment of progression/relapse novel drugs have been included before or after the conditioning. However there has been no comparison between different conditioning regimens. Patriarca et al. [39] included 169 consecutive patients in a retrospective multicenter study comparing the outcome of salvage auto versus salvage RICallo. All patients received salvage treatment with thalidomide, lenalidomide and/or bortezomib. Seventy-five patients had an HLA matched donor of which 68 underwent RICallo transplantation including 24 from an HLA-identical sibling. The two-year NRM was 22% in the donor group and 1% in the no donor auto group. The two-year PFS was 42% in the donor group as compared to 18% in the no donor group, but there was no significant difference in the two-year OS between the two groups (54% and 53%, respectively). The impact of including new drugs in the regimen was not evaluated. Consolidation and maintenance treatment following auto is standard in many centers. However, in the allo setting studies on maintenance are scarce. The HOVON study used thalidomide for maintenance, as did the BMT CTN trial. In both trials the authors concluded that they could not see a significant effect of thalidomide in this setting. However, in the HOVON trial thalidomide was used in both treatment arms, therefore its efficacy could hardly be evaluated and in the BMT CTN trial over 80% of patients were unable to complete the planned thalidomide maintenance. In addition in all the upfront prospective trials the extent to which the new drugs were used at progression or relapse was not analyzed, since treatment after progression was optional.

Novel drugs have been used in phase II studies both at progression and for maintenance. In one study [40] low dose

thalidomide was used for treatment of 18 patients with progressive or residual disease after allo and before donor lymphocyte infusions (DLI). The overall response rate was 68% with 22% CR. In another study [41] thalidomide was used to treat 31 patients with progression after allo. Nine out of 31 patients responded, and three of these came with a very good partial response. These responses were interpreted as partly due to a GVM effect since they were associated with chronic GVHD. Thus thalidomide may have a place in treatment of relapse/progression after allo, but the value of its use as maintenance or in the conditioning is not known.

Bortezomib appears to be effective in association with allo, due to a GVHD preventive effect, while presumably still preserving the GVM effect [42–44]. Its additional antimyeloma effect makes the rationale apparent for using it upfront in the conditioning regimen and/or for consolidation and maintenance. In one study [43] 19 patients who had relapsed following RICallo were treated with bortezomib plus dexamethasone followed by DLI. Sixty eight % responded, including 10 of them with CR. The 3-year PFS and OS was 31% and 73% respectively and no severe aGVHD was seen. Due to its dual effect – preventing GVHD and preserving GVM – bortezomib should be ideal for inclusion in the conditioning as has been done in the autologous transplant setting [45]. Such studies are in progress within EMN (European Myeloma Network) and EBMT. Oral proteasome inhibitors such as ixazomib may also have a potential in the allo setting. Ixazomib has been tried as a single agent in relapse and in combination with lenalidomide in the frontline setting. Phase I/II trials are planned using this agent as maintenance therapy post allo for high risk or relapsed myeloma [46, 47].

Lenalidomide has been used for maintenance following allo [48–50], but more frequently for treatment of relapse. Its use as maintenance is controversial because of induction of GVHD. In the HOVON 79 study [48] 47% of the patients had to stop treatment after 2 cycles due to development of acute GVHD. In another study by Wolschke et al. [49] GVHD was the main reason to discontinue treatment in 29% of the patients. In a US trial [50] lenalidomide was used following allo for high risk myeloma. Patients started lenalidomide at a dose of 10 mg at a median of 96 days post transplant, but acute GVHD remained an issue with 37% of patients discontinuing therapy. One year PFS was 68%, which was encouraging in this high risk group. Lenalidomide has also been used for treatment of progression, both in the NMAM2000-EBMT study and in the HOVON study, but its impact on outcome was not analyzed. In the EBMT study the survival following relapse was significantly better after auto/RICallo than after auto/auto [29] perhaps associated with better response to lenalidomide treatment following relapse/progression after allo. This would corroborate with a recent study by Coman et al. [51] showing impressive response rates and a significant association with the development of cGVHD after lenalidomide treatment of relapse following allo. Bensinger et al. [52] showed that lenalidomide is highly effective in treating relapse/progression after allo and may be used without inducing severe GVHD if started later than 6–12 months after transplantation. Thus, lenalidomide may be particularly valuable following allo both in the maintenance and relapse setting.

Other drugs that may be of value in combination with allo are the proteasome inhibitor carfilzomib, the immunmodulator pomalidomide and elotuzomab, an antibody against CS1 that may have effect in combination with lenalidomide [53]. These drugs have been proven to be effective in myeloma and in association with auto, but have not been used in trials with allo. Defibrotide is another potentially useful drug, a polydisperse oligonucleotide with anti-ischemic and anti-thrombotic properties that has been used to prevent veno-occlusive disease (VOD) associated with auto and allo and treatment with thalidomide [54–56]. Experimental results suggest that defibrotide has antimyeloma effects by preventing tumor angiogenesis [56, 57], however its clinical antimyeloma efficacy is far from clear.

The EBMT and the European Myeloma Network (EMN) have recently started a phase II allo trial including relapsed/progressive myeloma patients and using novel drugs both in the conditioning and as maintenance.

## Source of stem cells

Originally bone marrow was used as the graft source, but has practically entirely been substituted for peripheral blood stem cells since the late 1990th. Peripheral blood cells seem to engraft more rapidly and induce somewhat more chronic GVHD, but similar PFS and OS as with bone marrow [58]. The number of stem cells should exceed $2 \times 10^6\ kg^{-1}$ to ensure engraftment. The target dose is $4 \times 10^6\ kg^{-1}$.

## Other cell therapies

Donor lymphocyte transfusions (DLI) are effective in about 30% of patients relapsing or progressing following allo with response lasting more than two years [59–61]. Attempts have also been made to use DLI to improve the quality of the response. Escalating dosages of DLI were used in a European multicenter study of 63 patients with refractory or relapsed disease after RICallo [62]. Twenty-four patients responded, 12 with CR. The treatment was associated with acute GVHD in 38%, and chronic GVHD in 43%. In another study [63] 32 patients who had obtained only partial remission after allo received DLI. Eight of these patients obtained hematologic CR and 7 of them a molecular remission. DLI associated with chronic GVHD seemed in one study to improve PFS and OS [43]. Thus, DLI is effective in treatment of relapse and progression, but the risk of inducing severe GVHD has to be considered.

NK cells are innate cells that have anti-myeloma effect [64–66]. It has been shown that treatment with expanded NK cells together with IL-2 significantly improves survival in a mouse myeloma model [65]. NK cells have with some success been tried in patients with acute leukemia who have received allo with haploidentical T-cell-depleted cells [67] and in a phase I study in terminal cancer, among them chronic lymphocytic leukemia [68]. Some responses have been documented. Thus, it is possible that NK cells included

in the allo setting may improve outcome in multiple myeloma.

## When to perform an allogeneic transplantation

Upfront allo in myeloma has been manly abandoned due to relatively high TRM. Despite the encouraging results in two out of six upfront studies using combination auto/RICallo the TRM amounting to about 12–16 per cent is considered too high despite the higher CR rate and lower relapse/progression rate as compared to auto or auto/auto. Also, since the lower relapse progression rate only translated into better PFS and OS in two of the six prospective studies the possible cure of a limited fraction of patients is not considered reason to perform upfront allo. Allo is therefore presently performed mainly in progression/relapse and only occasionally upfront in the auto/RICallo setting in high risk patients (Table I).

Efebra et al. [69] included 51 patients with heavily pretreated relapsed multiple myeloma in a study of RICallo transplant using a conditioning of melphalan 90–140 mg/m$^2$ + fludarabin 90–120 mg/m$^2$. ATG was added to patients who received a transplant from unrelated donors. Transplant-related mortality at one year was 25% and PFS and OS at two years 19% and 32%, respectively. A retrospective study by Karlin et al. [70] of 23 patients treated in first relapse with auto/RICallo (conditioning 2 Gy before RICallo) showed an NRM mortality at one year of 17%. The median event-free survival and OS were 37 and 60 months, respectively. A significant advantage was seen in these patients as compared to pair matched patients selected from 142 not allografted ones during the same time period ($p = 0.027$). In a study by Shimoni et al. [71] of fifty refractory or relapsed patients transplanted between 2001 and 2004 with melphalan–fludarabine based conditioning the estimated seven-year PFS and OS after a median follow-up of 6.4 years were 26% and 34% respectively.

It seems clear that allo should not be performed without previous induction therapy, preferably a previous auto, particularly if considered for upfront therapy. In a retrospective EBMT study [72] 472 patients who received a planned auto/RICallo were compared to 173 matched patients who received RICallo without previous auto between the years 1996 and 2013. After a median follow-up of 93 months the PFS was 34% versus 22% and OS 60% versus 42% respectively at 5 years from transplant. Thus the auto before the RICallo was important.

In a recent retrospective study of allotransplants in the EBMT registry Michallet et al. [73] found 7333 allotransplants performed between 1990 and 2012. An analysis of those 4726 patients transplanted from 2004 made it possible to divide the material into 6 groups based on the time of transplantation. The best results were found if the transplant was performed <8 months after an auto (PFS 42% at 5 y OS 53% at 5y) and particularly if RIC had been used (median OS 76 m with RIC). However even after several autos and relapses PFS and OS from allotransplant were 15% and 23% respectively.

## Should allogeneic transplants be performed at all – conclusions

Allo has the potential to cure a fraction of patients with multiple myeloma. Still, high-dose myeloablative conditioning has mainly been abandoned due to high TRM. RIC before allo has significantly lower TRM in the range of 12–16 percent in upfront treatment and is an option for some high risk patients. Two prospective studies with large numbers of patients treated with tandem auto/RICallo have shown superior results after long-term follow-up compared to auto or auto/auto. The auto/RICallo approach may overcome poor risk cytogenetic factors in some patients. Also, in relapsed/progressive patients auto/RICallo may be a treatment possibility. However, effective induction and/or maintenance therapy with the novel drugs, like proteasome inhibitors and immunomodulators, have not been included in most of the allo studies. Therefore, bortezomib, lenalidomide, carfilzomib and pomalidomide should be included in the conditioning and/or consolidation and maintenance in future trials. Prospective studies using these drugs in all phases are needed and planned. New cell therapies, such as with NK cells, that have shown encouraging results in experimental animals, should be tried. Auto/RICallo transplantation should preferentially be used in clinical trials, but could also be considered outside such trials in high risk patients (del17p, del8p and gain 1q) and in progression or relapse following auto. Allo trials for treatment of multiple myeloma in these new settings are in progress in a joint venture between EMN and EBMT as well as in other groups.

## Conflict of interest/Konflikt interesu

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None declared.

## Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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