Role of autologous and allogeneic stem cell transplantation in myeloma

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ABSTRACT

The treatment of multiple myeloma (MM), a largely incurable B-cell hematologic malignancy, is changing dramatically. Autologous stem cell transplantation (SCT) and the approval of 2 new classes of drugs, immunomodulators and proteosome inhibitors, have resulted in improved response rates and increased overall survivals. Thalidomide, bortezomib, and lenalidomide have been combined with corticosteroids, alkylators, and anthracyclines in front-line MM treatment. Phase 2 and preliminary phase 3 studies have reported very high response rates and complete response (CR) rates formerly only seen with SCT. When patients with MM who have received these new drugs then proceed to transplant, major response rates are further increased. Due to limited follow-up, it is unclear whether these higher response rates translate into increased survival.

Despite these improvements, the disease remains incurable for all but a small fraction of patients. Allogeneic SCT is potentially curative, due in part to a graft-versus-myeloma effect but is limited by mortality. Mortality can be reduced through the use of lower intensity conditioning regimens but this comes at a cost of higher rates of disease progression and relapse. Strategies to improve outcomes of allogeneic transplants include more intensive, yet non-myeloablative conditioning regimens, tandem transplants, peripheral blood cells, graft engineering, post transplant maintenance, and targeted conditioning therapies.

Keywords: multiple myeloma, autologous stem cell transplantation, allogeneic stem cell transplantation.

Multiple myeloma (MM) is a clonal plasma cell tumor that responds to alkylating agents, corticosteroids, radiation therapy, and several new agents including thalidomide, lenalidomide, and bortezomib. New agents used in combinations with established drugs such as dexamethasone have shown impressive response rates, both in newly diagnosed and relapsed patients. [1-4] Despite the abundance of therapeutic agents, cure is almost never achieved with conventional chemotherapy. Success in the management of refractory hematologic malignancies with stem cell transplantation (SCT) led to the exploration of this treatment for patients with MM. [5-8]. SCT from autologous or syngeneic donors allows the intensive use of chemotherapy +/- radiation to eradicate disease in the patient, since the most common dose-limiting toxicity, marrow ablation, can be overcome by infusing stem and progenitor cells which accelerate marrow recovery. SCT from an allogeneic donor provides an additional immunologic graft-versus-myeloma effect resulting in more frequent and durable responses.

Several prospective, randomized trials have been conducted comparing conventional chemotherapy to high dose therapy (HDT) using autologous SCT (ASCT) for patients with MM [9-13] The French intergroup study demonstrated that high dose melphalan and total body irradiation (TBI) followed by ASCT, when applied as consolidation therapy after conventional chemotherapy induction, resulted in higher response rates, longer disease-free intervals, and better overall survival compared to continued conventional chemotherapy. [9,14] The Medical Research Council Myeloma VII trial compared combination chemotherapy to combination chemotherapy followed by single agent high dose melphalan and ASCT. [10] This large trial, with 407 patients randomized, demonstrated a 12-month improvement in the median survival ($p=0.04$) and a similar improvement in event-free survival. Several other trials that allowed salvage ASCT in the conventional dose arm have shown higher response rates and longer progression-free intervals but survival benefits equivalent to up-front transplant. [15,16] Survival

benefits are similar because most patients who undergo ASCT will relapse and salvage transplants benefit patients who progress after only conventional chemotherapy.

As a result of these studies, ASCT has become a standard of care with more than 5900 ASCT performed in patients with MM in the United States reported to the Center for International Bone Marrow Transplant Registry in 2005; more than any other disease. Unfortunately, despite HDT and ASCT, the majority of patients with MM will relapse and die of recurrent disease. Relapses occur due to failure to eradicate disease in the patient or due to the reinfusion of malignant cells contained in the progenitor cell graft. One randomized study, which evaluated the effect of removing myeloma cells from autologous stem cell grafts on outcome, found no improvement in responses, overall or progression-free survivals. [17] [18] These results occurred even though the purging technique removed 3-4 logs of tumor cells from the grafts. One possible explanation that may account for this contradiction would be that despite the removal of 3-4 logs of tumor cells from the stem cell graft, there remained enough residual MM cells in the graft to lead to relapse. Alternatively, residual disease in the patient could be the major contributor to relapse. In that case, purging, even if 100% effective at removing malignant cells from the graft, will not have much impact on response rates or disease-free survival until improvements are made in the ability to eradicate residual host disease. Syngeneic donor transplant data could provide some insights into the relative contributions of infused tumor cells as a cause of relapse. A recent registry comparison of 43 syngeneic transplants compared with 170 autologous transplants suggested lower rates of relapse. This suggests that either infused tumor cells contribute to relapse or that a syngeneic graft versus myeloma effect can control residual disease. [19]

One way of dealing with minimal residual disease (MRD) in the patient after ASCT is to perform a second transplant utilizing HDT and ASCT or a reduced-intensity conditioning regimen

followed by SCT from an allogeneic donor (see below). In randomized trials tandem ASCT can improve overall survival by about 10% compared to single ASCT. [20] [21] This effect is small because patients who relapse after a single ASCT can receive a salvage ASCT, although there is controversy about the benefits of a salvage transplant. [22] Almost paradoxically, however, two studies have shown that the survival benefit of a second ASCT occurs mainly in patients who do not achieve a major response to their first transplant, while patients who are already in CR do not benefit from a second ASCT. It should be noted, however, that neither study was planned to perform such subgroup analyses and that both trial were conducted prior to the availability of new, more effective drugs now used for induction therapy. This suggests that patients in CR after ASCT continue to harbor highly resistant residual MM cells. In addition, studies have determined that disease biology has a powerful impact on outcomes after ASCT. Several studies have shown that patients with cytogenetic abnormalities detected by fluorescence in-situ hybridization (FISH), specifically deletion 13, translocation 4:14 and deletion 17p, have significantly shorter progression-free and overall survivals than patients without them. [23] [24] More recently it was shown that deletion 13 as a sole abnormality does not have the same prognostic significance in the absence of the 4:14 or 17p abnormalities. [25] Maintenance and consolidation therapy after ASCT has been explored as another way to improve responses, event-free and overall survivals. [26] At the present time there are conflicting data on the value of these strategies, although one study suggested thalidomide maintenance after ASCT is superior to a second ASCT. [27] [28] [29]

Another way to improve outcomes after transplant is to utilize more effective induction regimens with the goal of improving overall responses after ASCT. These novel drugs may also overcome some of the high-risk cytogenetic features in some patients. There are a large number of combinations incorporating novel drugs into induction regimens for patients with newly diagnosed MM. Relatively few trials, however, have reported comparisons of combinations

incorporating thalidomide and bortezomib with more traditional drug combinations such as vincristine, adriamycin and dexamethasone (VAD) in patients proceeding to transplant (table 1). The French myeloma intergroup is comparing induction therapy with bortezomib and dexamethasone (BT) with VAD followed by ASCT. [30] This trial has completed accrual with 480 patients and preliminary results indicate a substantially greater major response rate (≥VGPR) after BT compared to VAD. Following ASCT, the groups receiving BT or VAD induction had a further improvement in responses, but the advantage of BT remained. Survival, with a median of 18 months of follow-up is not different between the BT and VAD groups. The Italian consortium compared bortezomib, thalidomide and dexamethasone (BTD) to thalidomide and dexamethasone (TD). [31] The BTD regimen was substantially more effective that TD in producing major responses. Following transplant there was a further increase in major response rates for both regimens, but, again, the advantage for BTD remained. This would argue for a re-examination of the relative merits of single v. tandem ASCT.

The ECOG group compared lenalidomide plus either high-dose dexamethasone (480 mg/cycle) (RD) or low-dose dexamethasone (160 mg/cycle) (Rd). [32] After initial induction, 102 patients proceeded to ASCT at patient or physician preference while 91 remained on RD and 120 remained on Rd. At 2 years, the projected overall survivals were 94% for ASCT, 80% for RD and 91% for Rd. In a trial reported in 2006, among 204 patients who received induction with TD or VAD followed by ASCT, the major response rates after induction were 25% and 7% for TD or VAD, respectively. [33] Following transplant, however, the advantage for TD disappeared with major response rates of 44% and 41% for TD and VAD, respectively. It thus appears from preliminary data that some novel induction regimens result in a higher frequency of major responses than more traditional regimens and that ASCT further improves major response rates. It will require further follow-up to ascertain whether this translates into improved survival

and it is important to emphasize that there are currently no data suggesting that long-term treatment with any novel drug combination is superior or even equivalent to ASCT.

The observation that induction regimens employing new drugs produce complete responses (CR) in a substantial fraction of patients has opened the question of whether ASCT might be necessary for such patients. Small, retrospective studies with VAD based regimens have shown similar outcomes among patients who achieve CR prior to ASCT and those who achieve CR only after ASCT. [34] This does not necessarily mean that ASCT is of no value for such patients. In fact a more recent retrospective review showed that while patients achieving CR before and after ASCT has similar survivals, patients who came to transplant in nearCR but converted to CR after ASCT had better survival. [35] Thus, in order to more definitely determine the value to ASCT, patients who achieve CR with induction would need to be enrolled in a randomized study comparing ASCT with no transplant.

Another strategy for improving response durability after ASCT is to employ vaccines in an effort to restore myeloma specific immunity in developing T and B cells. A variety of vaccines, dendritic cell infusions or activated T cell therapies are under study but as yet no solid data exist to suggest improvement in clinical outcomes. [36] [37] [38-40]

SCT from allogeneic donors is curative for 10-20% of patients with chemotherapy resistant, refractory hematologic malignancies and up to 80% of patients who are transplanted in remission. Much of the high response and curative potential of allografts is attributed to a “graft-versus-tumor” effect. In patients with multiple myeloma, this effect has been well-documented [41] [42] [43]. In contrast, SCT from autologous or syngeneic donors provides little or no immunologic effect against the myeloma cell. Long-term follow-up of recipients of ASCT indicate a continuing risk of disease recurrence after 5 years and arguably few, if any, patients are cured. In contrast,

allogeneic SCT with long-term follow-up appear to result in durable remissions and a lower risk of recurrence after 5 years. [44] Although treatment with high-dose chemoradiotherapy followed by allogeneic SCT is capable of producing remissions and long-term survival for patients with multiple myeloma, the transplant-related mortality of 25-50%, even in “good-risk” patients, limits the wider application of this approach.

The high intensity conditioning regimens customarily used before allogeneic transplants are designed to produce cytoreduction and immunosuppression sufficient to allow establishment of the donor graft. The demonstrated efficacy of donor lymphocyte infusions in relapsed allograft patients suggests that the allogeneic graft-versus-myeloma effect is important for cure. This has led to the exploration of reduced intensity conditioning regimens, designed more for immunosuppression rather than cytoreduction, with the aim of establishing consistent donor engraftment with while minimizing toxicity and damage to normal host tissues. Furthermore, reduced intensity immunosuppression should decrease the period of severe pancytopenia that always occurs after high intensity conditioning. This technique, in theory, allows the graft-versus-myeloma effect to operate while avoiding the high transplant-related mortality.

One of the more widely used reduced intensity regimens was developed in Seattle based on canine transplant studies where it was shown that reliable allogeneic donor peripheral blood stem cell engraftment could be achieved with a very low dose of total body irradiation of 2 Gy and a combination of 2 potent immunosuppressive drugs including mycophenolic acid and cyclosporine. [45] This strategy was applied to 18 patients undergoing allogeneic transplant for multiple myeloma. Seven patients had refractory disease and 6 had failed a prior autograft. Two patients of the first 4 rejected the donor graft leading to the addition of fludarabine, which provided additional immunosuppression. [46] There were no further occurrences of rejection following the addition of fludarabine to the regimen. Although only 1 of 18 patients died of

transplant related toxicities, complete responses occurred in only 2 patients and only 3 others achieved partial responses. None of the responses were durable. These results confirmed that in multiple myeloma, the graft-versus-myeloma effect is relatively modest and that additional cytoreduction would be required to improve the responses using a reduced intensity allograft. Several studies of reduced intensity allografts from family members or unrelated donors have confirmed that results are poor when patients have failed a prior autologous transplant or have chemotherapy-resistant disease. [47] [48] [49] Two German studies and a study from MD Anderson confirmed 2 year survivals of 26-50% for patients who had failed 1 or more autologous transplants. A study combining data from several centers including approximately 120 patients found that relapse from a prior autologous transplant was the most significant risk factor for transplant mortality (HR 2.80; p=0.02), relapse (HR 4.14; p<0.001), and death (HR 2.69; p=0.005). [50] A large EBMT registry trial found equivalent overall survival and inferior progression-free survival when reduced intensity allografts were compared with ablative allografts. [51] At least one trial comparing autologous to reduced intensity allografts following relapse from a prior autologous transplant found no differences in progression-free and overall survival. [52] A more recent study has demonstrated that a second ASCT performed only after relapse or progression can result in major responses with prolonged survival [53] Thus it remains to be determined whether or not an reduced intensity allograft or a second autograft is the best choice once patients have failed a prior autograft.

In an effort to improve cytoreduction, patients with MM who had not received a prior high dose regimen first received HDT and ASCT followed by a reduced intensity allograft. Patients had autologous peripheral blood stem cells collected, followed by melphalan 200 mg/m^2 and reinfusion of autologous stem cells to provide cytoreduction and some immunosuppression. In this way the high dose therapy is separated in time from the introduction of the allograft. Two to 4 months later, after recovery from the first autologous stem cell transplant, patients received a

regimen of 200 cGy total body irradiation, mycophenolic acid and cyclosporine with allogeneic peripheral blood stem cells. Fifty-four patients ages 29-71 years, median age 52 years, received this tandem autologous, allogeneic transplant strategy. [54] All patients were stage II or III and 48% had refractory or relapsed disease. One patient died of cytomegalovirus pneumonia after the initial autologous stem cell transplant, 1 patient progressed after the autograft, and 52 proceeded to allogeneic stem cell transplant. All 52, except 1, achieved full donor chimerism with a single patient requiring donor lymphocyte infusions on day 84 for partial chimerism. The overall transplant mortality was 22% and the complete remission rate was 57%. Four patients developed severe acute GVHD (grades 3-4) and chronic GVHD developed in 60%. With a median follow-up of 60 months after allograft, the survival at 60 months was 69%, and the progression-free survival 40%. In a more recent update of this strategy, 102 patients have received this treatment with a median follow-up of 6.3 years. The estimated 5-year overall survival, progression free survivals and transplant-related mortality were 64%, 36% and 18% respectively. [55]

Planned tandem autologous, followed by reduced intensity allografting have been reported in studies containing approximately 120 patients (table2). Autologous transplant was performed approximately 2-6 months prior to planned allografting. The allograft regimens utilized melphalan 100-140 mg/m2 plus fludarabine or 2Gy TBI or cyclophosphamide plus fludarabine. These studies reported transplant-related mortalities of 18-24%, chronic GVHD of 7-60%, and survivals of 58-74% at 2 years, 86% at 3 years and 69% at 5 years. Complete response rates ranged from 28-73%. Chronic GVHD has been associated with a lower rate of disease recurrence, although this is controversial since only occasional studies have shown benefit. [56]

No prospective randomized trials have been published comparing ablative with non-ablative conditioning regimens for the transplant of patients with multiple myeloma. There are, however,

a number of studies reported or underway comparing tandem autologous transplants to a tandem autologous-non-ablative allograft approach. The randomization for these studies was "genetic," in that patients with available related donors were typed and if an HLA identical donor was identified, they were offered a non-ablative transplant as the second transplant. While not truly randomized, they provide some comparative data on the relative risks and benefits of the 2 techniques.

A French trial using 2 parallel studies compared outcomes in 284 patients with multiple myeloma who were high risk by virtue of elevated beta-2-micoglobulin and deletion of chromosome 13 by FISH. [57] All patients first had an autologous transplant with high dose melphalan. The 65 patients with HLA matched donors underwent an allogeneic transplant on one protocol after conditioning with busulfan, fludarabine and a high dose of anti-thymocyte globulin 12.5 mg/kg. They were compared to 219 patients without donors who were treated on another protocol with a second autologous transplant with melphalan 220 mg/m^2. Transplant mortality was 5% for the tandem auto group compared to 11% for the auto-allo group. The complete response and very good PR rates were 51% and 62% respectively for the tandem auto and auto-allo groups. With a relatively short follow-up of a median 2 years, the overall survivals and event free survivals were not statistically different, 35% v. 41%, and 25% v. 30% for the tandem auto and auto-allo studies, respectively. Although these results indicate that patients with high-risk features do not benefit from a tandem auto-reduced intensity allograft approach, the regimen utilized a high dose of ATG 12.5 mg/kg. This resulted in a low incidence of acute and chronic GVHD (7%) but a relatively low complete response rate (33% of evaluable patients). This study agrees with another report analyzing the outcome of RIC allografting in patients with or without del13. [58] This study demonstrated that del13 was an independent, adverse risk factor for overall survivals and progression free survivals after reduced intensity allografting due primarily to a greater risk of relapse. Whether or not any allograft procedure can

overcome this adverse risk factor remains to be determined, but a retrospective study of 101 patients who received reduced intensity allografts showed similar survivals between patients with normal cytogenetics or the 4:14 translocations, but worse outcomes in patients with 17p deletions. [59]

A more recent study prospectively assigned 162 patients with stage II or II multiple myeloma to induction with VAD for 2-3 cycles, followed by autologous peripheral blood stem cell collection following cyclophosphamide and granulocyte colony stimulating factor. [60] All patients then received high dose melphalan followed by autologous peripheral blood stem cells. Patients with an HLA-identical sibling (N=80) were assigned to receive a reduced intensity allogeneic transplant using the Seattle regimen, while patients without a matched sibling (N=82) were assigned to receive a second course of high dose melphalan and ASCT. Only 58 and 46 patients in the auto-allo and auto-auto groups completed their assigned treatments. The complete response rate was 26% with the tandem auto and 55% with the auto-allo group (p=0.004). The transplant mortality was 2% and 10% for the tandem auto and auto-allo groups, respectively, p=ns. Based on intention to treat, and with a 45-month median follow-up, the median overall survivals were 54 months and 80 months, for the tandem auto v. auto-allo groups, respectively, p=0.01. The progression-free survivals were 29 months v. 35 months for the auto-auto and auto-allo groups respectively, p=0.02. An important strength of this trial is the treatment assignment based solely on donor availability and analysis on intention to treat. These results suggest a possible advantage for the auto-allo approach, although longer follow-up is needed. One concern in this study was that high lactate dehydrogenase and low platelet count at diagnosis were both independent predictors of survival and progression-free survival. This would suggest that allogeneic transplant may not be able to overcome some high-risk prognostic factors.

In another strategy, a Spanish cooperative group reported on 114 patients who received ASCT after a melphalan or busulfan-melphalan regimen and achieved less than a near CR. [56] Eighty-eight patients with no donors received a second ASCT after a regimen of cyclophosphamide, carmustine and etoposide, while 26 patients with donors received a reduced intensity allograft after a fludarabine, melphalan regimen. The TRM, and CR rates for the ASCT and allo SCT groups were 5% and 16% and 11% and 33%, respectively. With a relatively short follow-up of 19-26 months, there were no survival differences, but a trend in EFS favoring the allografts.

It is clear that reduced intensity allogeneic transplant regimens can result in reliable donor engraftment with a relatively low mortality compared to high dose regimens. The immunologic effect of the allograft is, however, relatively modest resulting in a reduced rate of CR and a higher rate of progression compared to ablative regimens. Thus, it appears that substantial cytoreduction pre-allografting is required in order to facilitate the success of a reduced intensity allograft. Preliminary results suggest the tandem auto/reduced intensity allogeneic strategy can result in CR in over 50% of patients with multiple myeloma; similar to what can be achieved with a high dose conditioning regimen. Reduced intensity regimens are a promising strategy to ensure reliable engraftment, low mortality and high response rates, as well as the ability to expand this technique to older patients or patients with co-morbid conditions. It will be important, however, to have longer follow-up of patients transplanted with non-ablative regimens in order to document the durability of these remissions since most studies to date do not demonstrate a plateau in disease free survival.

In summary there has been important progress in the treatment of MM including new drugs and combinations, ASCT, and reduced intensity allografts. Most studies point to the achievement of at least a VGPR or better as a surrogate for survival. Despite these advances MM remains an incurable disease for the majority of patients. The challenge at present is how to integrate the

best combinations of new and old drugs used for initial induction, followed by ASCT and possibly an RIC allograft in order to achieve long term disease control. The availability of novel drug combination for induction will likely improve the overall survival of patients proceeding to ASCT. It will likely require completely novel strategies such as radioisotope targeting as part of the conditioning regimen to cure patients proceeding to ASCT.

Table 1 Ongoing Trials of Novel Drug Combinations in Patients Proceeding to Autologous Stem Cell Transplantation

Reference	No Patients	Induction Regimens	Major Response After Induction%		Major Response After Autograft %		Survival at (yr)
			≥nCR	≥VGPR	≥nCR	≥VGPR	
Harousseau [30]	240	Bortezomib, dex[1]	21	47	35	62	92% (1.5)
	242	Vincristine, dex, adriamycin	8	19	24	42	89% (1.5)
Cavo [31]	74	Bortezomib, thalidomide, dex	36	60	57	77	nr[2]
	79	Thalidomide, dex	9	27	28	54	
Rajkumar [32]	102	Lenalidomide, low or high dex->ASCT					94% (2)[4]
	91	Lenalidomide, high dex	4[3]	52	nr	nr	80% (2)
	120	Lenalidomide, low dex	2[3]	44			91% (2)
Macro [33]	100	Thalidomide, dex	nr	25	nr	44%	nr
	104	Vincristine, dex, adriamycin		7		41%	

[1]dex=dexamethasone
[2]nr=not reported
[3]bone marrows were not required on study for confirmation of CR
[4]Only these patients received stem cell transplant (not randomized); others remained on induction regimen. High dex=480 mg/cycle, low dex=160 mg/cycle

Table 2. Phase 2 Trials of Tandem Autologous-Reduced Intensity Allogeneic Transplantation from Related and Unrelated Donors for the treatment of Multiple Myeloma

Reference	**No**	**Regimen**	**# Tandem Auto**	**Proph GVHD**	**AGVHD %, 2-4**	**CGVH %**	**TRM %**	**CR %**	**%Survival at (yr)**
Maloney [54]	54 (0)	TBI 2Gy, Flu	54	CSA Mmf	45	60	22	57	69 (5)
Lee [61]	45[1] (12)	HDM 100 (TBI2Gy,Flu)	12	CSA	58	13	38 10 t	64	36 (3) 86 t
Kroger [62]	17 (8)	HDM100, Flu, ATG	17	CSA, Mtx	38	7	18	73	74 (2)
Kroger [63]	21 (21)	HDM100-140, Flu, ATG	9	CSA, Mtx	38	12	24	40	74 (2)
Galimberti [64]	20 (0)	TBI 2Gy,Flu (10) Cy, Flu (10)	20	CSA Mmf	25	30	20	35	58 (2)
Perez-Simon [65]	29 (nr)	Mel,Flu	10	CSA Mtx	41	51	21	28	60 (2)
Vesole [66]	23 (0)	Flu Cyclophos	23	CSA steroid	17[2]	39	9	33	78 (2)

Notes: No.=total number of patients (number from matched unrelated donors); Regimen HDM=high dose melphalan, TBI=total body irradiation, Flu=fludarabine, Cy=cyclophosphamide, ATG= anti-thymocyte globulin; # Tandem Auto-planned prior autologous transplant; ProphGVHD graft-versus-host disease prophylaxis, CSA=cyclosporine, , Mtx=methotrexate, Mmf=mycophenolic acid, AGVHD=acute graft-versus-host-disease; CGVH=chronic GVHD; TRM=transplant related mortality rate; CR=complete response rate

[1] 14 patients given DLI, t TRM or survival for tandem patients

[2] Only grade 3-4 GVHD reported

Table 3_ Comparison Trials of Tandem Autologous Transplant with Tandem Autologous - Reduced Intensity Allografting

Author	**Regimens**	**Number**	**TRM**	**Response CR/VGPR**	**DFS (f/u yr)**	**OS (f/u yr)**
Garban[1] [57]	Auto mel 200/220	219	5%	33%/18%	0% 5yr	44% 5yr
	Auto mel200 Allo bu,flu,ATG	65[2]	11%	33%/29%	0% 5yr	33% 5yr
Bruno [60]	Auto mel 200	80[3]	4%	26%/nr[7]	20% 4yr	53% 4 yr
	Auto mel200 Allo 2Gy TBI	82[4]	10%	55%/nr	42% 4yr[5]	75% 4 yr[5]
Rosinol[6] [56]	Auto BuMel-Mel, Auto CBV	85	5%	11%/6%	Med 31mo	Med 58 mo
	Auto BuMel-Mel Allo FluMel140	25	16%	40%/nr	"not reached"	"not reached"

[1] high risk patients with elevated B-2M or deletion 13 by FISH.
[2] 19/65 patients did not receive the reduced intensity allograft
[3] 46/80 patients completed the tandem autograft
[4] 58/82 patients received the reduced intensity allograft
[5] statistically significant
[6] only patients not in ≥ nCR after autograft
[7] nr = not reported

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