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ORIGINAL REPORT

Tandem Autologous/Reduced-Intensity Conditioning Allogeneic Stem-Cell Transplantation Versus Autologous Transplantation in Myeloma: Long-Term Follow-Up

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ABSTRACT

Purpose
Results of allogeneic stem-cell transplantation (allo) in myeloma are controversial. In this trial autologous stem-cell transplantation (auto) followed by reduced-intensity conditioning matched sibling donor allo (auto-allo) was compared with auto only in previously untreated multiple myeloma.

Patients and Methods
In all, 357 patients with myeloma up to age 69 years were enrolled from 2001 to 2005. Patients with an HLA-identical sibling donor were allocated to the auto-allo arm (n = 108) and patients without a matched sibling donor were allocated to the auto arm (n = 249). Single (n = 145) or tandem (n = 104) auto was optional. Conditioning for the auto arm was melphalan 200 mg/m^2; conditioning for the allo arm was total-body irradiation 2 Gy plus fludarabine 30 mg/m^2/d for 3 days. Median follow-up time was 61 months. Primary end point was progression-free survival.

Results
Progression-free survival at 60 months was significantly better with auto-allo than with allo alone (35% *v* 18%; $P = .001$), as was the risk of death and of relapse in the long term ($P = .047$ and $P = .003$, respectively). Overall survival at 60 months was 65% versus 58%, and relapse incidence was 49% versus 78%. Complete remission rates were 51% and 41%, respectively ($P = .020$). Nonrelapse mortality at 24 months was 12% after auto-allo compared with 3% in the auto group ($P < .001$). The incidence of grade 2 to 4 acute graft-versus-host disease (GvHD) was 20%, and the incidence of limited and extensive chronic GvHD was 31% and 23%.

Conclusion
In patients with previously untreated multiple myeloma, long-term outcome with respect to progression-free survival, overall survival, and relapse rate is superior after auto-allo compared with auto only. Nonrelapse mortality is at a reasonable level in both groups.

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INTRODUCTION

Multiple myeloma is considered an incurable malignancy, even though some patients attain long remissions after high-dose (chemo)therapy (HDT).[1,2] HDT with autologous stem-cell transplantation (ASCT) is part of the first-line standard treatment in patients up to the age of 65 years on the basis of the results of randomized trials.[3,4] Allogeneic stem-cell transplantation (alloSCT) with myeloablative conditioning has been used in myeloma since the mid-1980s,[5] but it is hampered by severe toxicity and a high incidence of treatment-related mortality (TRM) in the range of 30% to 50%.[6] In a case-control trial,[7] ASCT was demonstrated to be superior to myeloablative alloSCT despite a lower relapse rate. Reduced-intensity conditioning (RIC) alloSCT is associated with less toxicity, and the combination of HDT/ASCT followed by RIC alloSCT has reduced TRM to 15% or less.[8,9] However, the role of RIC alloSCT in relation to ASCT—the gold standard—is not yet defined, and previous direct comparative studies have yielded diverging results.[10-12]

In this prospective study of a large number of patients with previously untreated multiple myeloma, patients were selected for treatment with ASCT followed by RIC alloSCT (auto-allo) or with ASCT (auto) alone on the basis on the availability of an HLA-identical sibling. The time of follow-up is long,

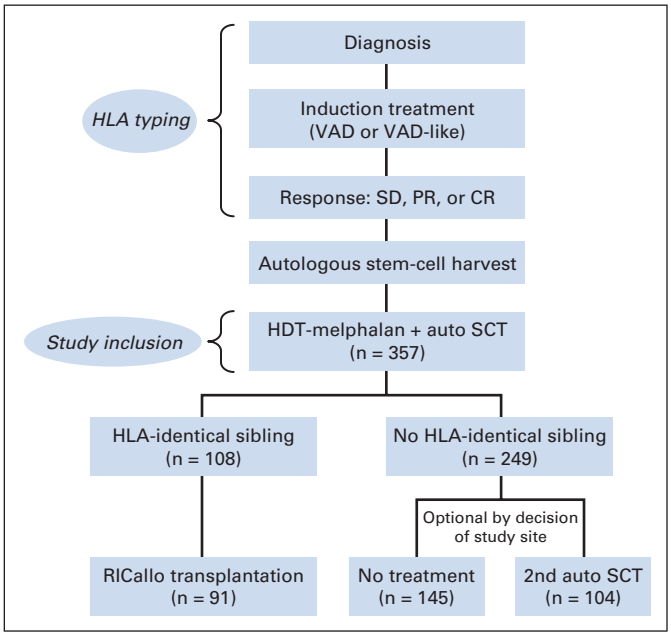

Fig 1. Design of the trial. CR, complete response; HDT, high-dose chemotherapy; PR, partial response; RICallo, reduced-intensity conditioning allogeneic stem-cell transplantation; auto SCT, autologous stem-cell transplantation; SD, stable disease; VAD, vincristine, doxorubicin, and dexamethasone.

and over time, the patients in the auto-allo treatment arm had a better outcome with respect to survival and freedom from progression.

PATIENTS AND METHODS

Patients

From February 2001 through January 2005, 357 patients up to the age of 69 years who had complete response (CR), partial remission (PR), or stable disease (SD) on first-line treatment were enrolled in 23 European Bone Marrow Transplantation (EBMT) centers. All patients had undergone HLA typing. One-hundred eight patients had an HLA-identical sibling and were assigned to the auto-allo treatment arm, while the other 249 without a matched sibling were treated in the auto arm. Single or tandem ASCT was optional by decision of each study center before starting the study. Two patients in the auto-allo arm did not have an HLA-identical donor but did have a sibling donor with one HLA mismatch; they were mistakenly treated according to the auto-allo arm protocol and were included in this arm in the intention-to-treat (ITT) analysis. The study design is illustrated in Figure 1. The time point for enrollment in the trial was at ASCT, after completion of induction treatment. Patients with substantial renal failure (glomerular filtration rate < 50 mL/min), liver impairment with bilirubin more than $2\times$ upper limit of normal, severe cardiac failure (left ventricular ejection fraction $< 40\%$), or other major organ system dysfunction were considered ineligible for inclusion. Baseline characteristics (Table 1) were evenly distributed between the two cohorts, with the exception of age at diagnosis, which was slightly higher in the auto group (median 57 years *v* 54 years in the auto-allo group). Median time of follow-up after inclusion (ie, the first ASCT) was 61 months (range, 21 to 91 months) for patients alive at last follow-up.

Analysis of Chromosomal Aberrations

Cytogenetic analysis with respect to chromosome 13 deletion—del(13q14)—was performed in 214 patients by fluorescent in situ hybridization as previously described.[13] The del(13) aberration was present in 92 patients, 29 of whom were in the auto-allo group and 63 of whom were in the auto group. Of the 214 patients, 122 were negative for del(13), with 34 and 88 patients in the auto-allo and auto treatment arms, respectively.

Table 1. Patient Characteristics

Characteristic	Auto-Allo No.	Auto-Allo %	Auto No.	Auto %	*P*
Sex					.784
Male	65		146		
Female	43		103		
Age, years					< .001
Median	54		57		
Range	34-66		31-69		
Subtype					.323
IgG	71	67	139	57	
IgA	17	16	46	19	
Light chain	15	14	45	18	
Other Ig	1	1	5	2	
Nonsecretory	2	2	10	4	
Durie-Salmon stage					.285
I	14	13	30	12	
II	22	21	35	14	
III	71	66	182	74	
β_2-microglobulin at diagnosis, mg/L					.977
< 4	58	67	129	67	
> 4	29	33	64	33	
Del(13)					.562
Present	29	46	63	42	
Absent	34	54	88	58	
Response status at inclusion					.527
CR	7	6	20	8	
PR	83	77	199	80	
SD	18	17	30	12	
Time from diagnosis to transplantation, months					.599
0-6	37	34	72	29	
> 6-12	57	53	141	57	
> 12	14	13	36	14	

Abbreviations: Auto, autologous stem-cell transplantation; allo, allogeneic stem-cell transplantation; CR, complete response; IgA, immunoglobin A; IgG, immunoglobulin G; PR, partial response; SD, stable disease.

Treatment

All patients had received induction chemotherapy with vincristine, doxorubicin, and dexamethasone (VAD), or similar treatment: VAD was used in 73% of patients in the auto-allo arm and in 67% in the auto arm. The remaining patients received a variety of mixed regimens, of which the majority were cyclophosphamide- or dexamethasone-based. No patients were treated with novel drugs such as thalidomide, lenalidomide, or bortezomib. Autologous peripheral-blood stem cells were mobilized and collected according to the standards in each single center. Patients with at least stable disease (CR, PR, or SD) after induction chemotherapy and with a successfully collected autologous stem-cell graft were included in the study after giving informed consent.

All 357 patients received HDT with melphalan 200 mg/m^2 followed by the infusion of autologous stem cells. Supportive care, use of granulocyte colony-stimulating factor, and so on was given according to the routines of each center.

Of the 108 patients allocated to the auto-allo arm, 91 received an RIC alloSCT according to the protocol. Seventeen patients did not receive their planned allogeneic transplantation for the following reasons: disease progression (seven patients), patient declined transplantation (four), died before allogeneic transplantation (one), renal failure (one), failure to mobilize donor stem cells (one), and donor ill or unavailable for other reason (three; in one of the latter cases in which the donor declined, the patient received a matched

unrelated donor RIC alloSCT). All these 17 patients are analyzed as auto-allo in the ITT analysis. Median time between autograft and allograft was 4.2 months (range, 1.3 to 22.2 months). The RIC regimen consisted of fludarabine 30 mg/m^2/d for 3 days plus total-body irradiation (TBI) 2 Gy.[9] Prophylaxis against graft-versus-host disease (GvHD) with cyclosporine and mycophenolate mophetil was administered after transplantation (cyclosporine 6.5 mg/kg orally twice per day from day −1 or 1.5 mg/kg intravenously twice per day and continued until oral cyclosporine could be given; mycophenolate mophetil 15 mg/kg orally twice per day from day 0 to day 24). Allo patients without GvHD and who had not reached CR at least 3 months after transplantation were offered treatment with donor lymphocyte infusions in escalating doses; two patients in PR were treated accordingly.

Patients without a matched sibling donor received either no further treatment (n = 145) or, at the discretion of the center, a second ASCT as part of a tandem transplantation program (n = 104). After progression, treatment was optional. The pretransplantation conditioning for the second autograft was the same as for the first (ie, melphalan 200 mg/m^2).

Response Criteria

The EBMT criteria for response and progression were applied as previously described.[14]

Statistical Methods

The primary end point was progression-free survival (PFS) from the time of inclusion in the study (ie, from the date of the first ASCT). Secondary end points were overall survival (OS), relapse rate, CR rate, and nonrelapse mortality (NRM) incidence. Relapse/progression and NRM incidence were analyzed as competing risks, and relapse/progression and death were considered as competing risks for CR achievement. The main analysis followed an ITT principle, that is, treatment arms defined at enrollment (on the basis of the availability of a donor) were compared regardless of future administration of a second transplantation. Thus, all patients enrolled contributed to the analyses of outcomes since first ASCT (108 auto-allo; 249 auto); five patients could not be analyzed when considering CR achievement because of missing date of response assessment. An explorative ITT analysis was conducted in two subgroups defined on the basis of the presence of del(13). Outcomes were also compared after the second transplantation, including only patients who got the type of transplantation planned according to protocol (91 auto-allo; 104 tandem auto).

All nominal and continuous characteristics were described with the usual tables and indexes; comparisons were done by using standard nonparametric tests (χ^2 or Fisher's exact test for categorical variables; Mann-Whitney U test for continuous variables). Among the outcomes, only NRM could be compared by the Gray test, while the proportionality assumption at the basis of the standard methods for survival (log-rank test and Cox model) and competing risks (Gray test and Fine and Gray model) was violated (with crossing effects) for all other end points. The regression models were amended to include a linear time-varying effect identified from the analysis of Schoenfeld residuals. It was thus possible to assess the amount of and significance of the improvement in time of the auto-allo arm. These models were adjusted by age, since the auto-allo patients were slightly younger both at diagnosis and at first transplantation. To assess differences in the long term—when they where expected (ie, after 2 years, except for OS, 3 years)—the landmark log-rank test was used, applying the Z-OLS correction[15] for PFS and OS. Differences in terms of survival probabilities at 60 months were tested according to the cloglog transform.[16]

RESULTS

ITT Analysis of All Patients

The ITT analysis is illustrated in Figures 2 and 3. At 60 months after the first ASCT, actuarial PFS was significantly better for the patients in the auto-allo group: 35% compared with 18% in the auto group (P = .001) by ITT analysis. This benefit for the auto-allo group was emerging after 2 years of follow-up because of significantly lower relapse/progression risk (P = .003). At 60 months, the incidence of relapse/progression was 49% and 78% for the auto-allo and auto

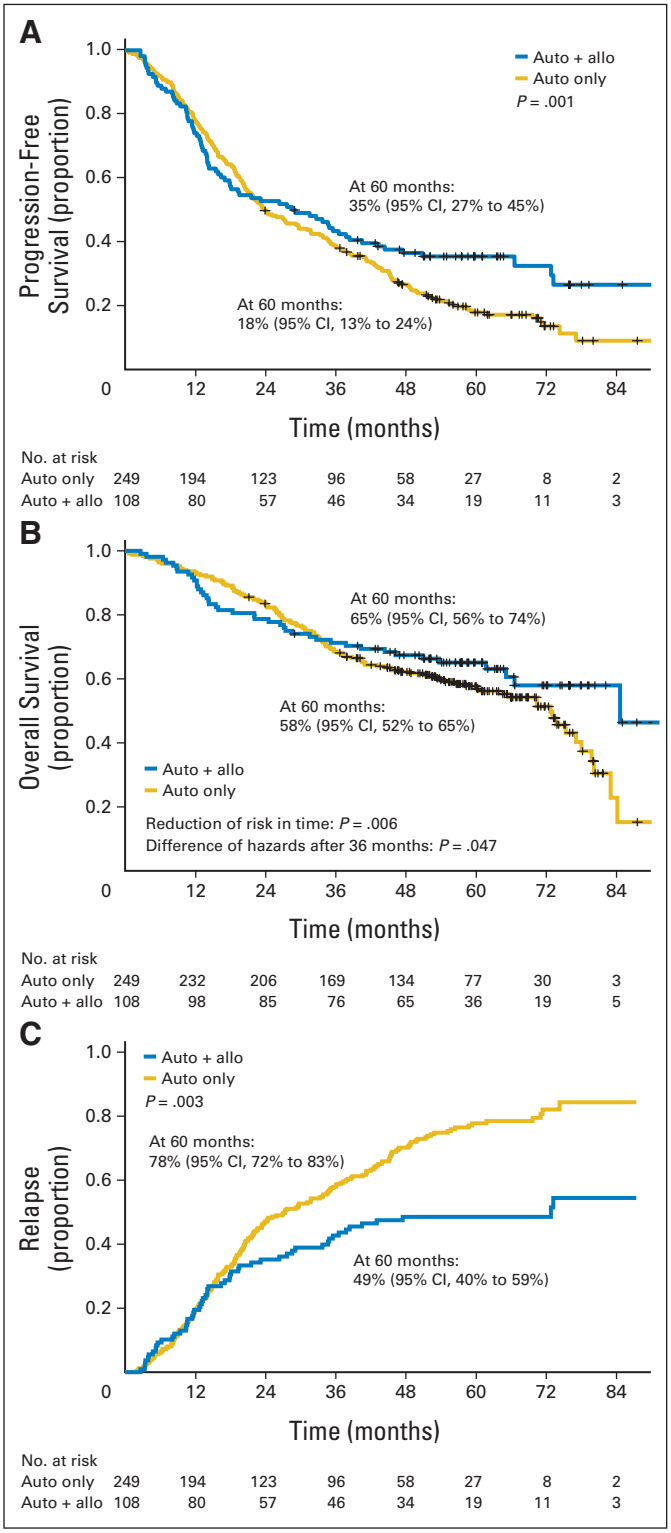

Fig 2. Intention-to-treat comparison of the two study arms (auto [autologous stem-cell transplantation] + allo [reduced-intensity conditioning allogeneic stem-cell transplantation] *v* auto). Rates are calculated from the time point of the first autologous transplantation. The numbers at the bottom of each plot indicate the number of patients at risk. (A) Progression-free survival; (B) overall survival; (C) relapse rate.

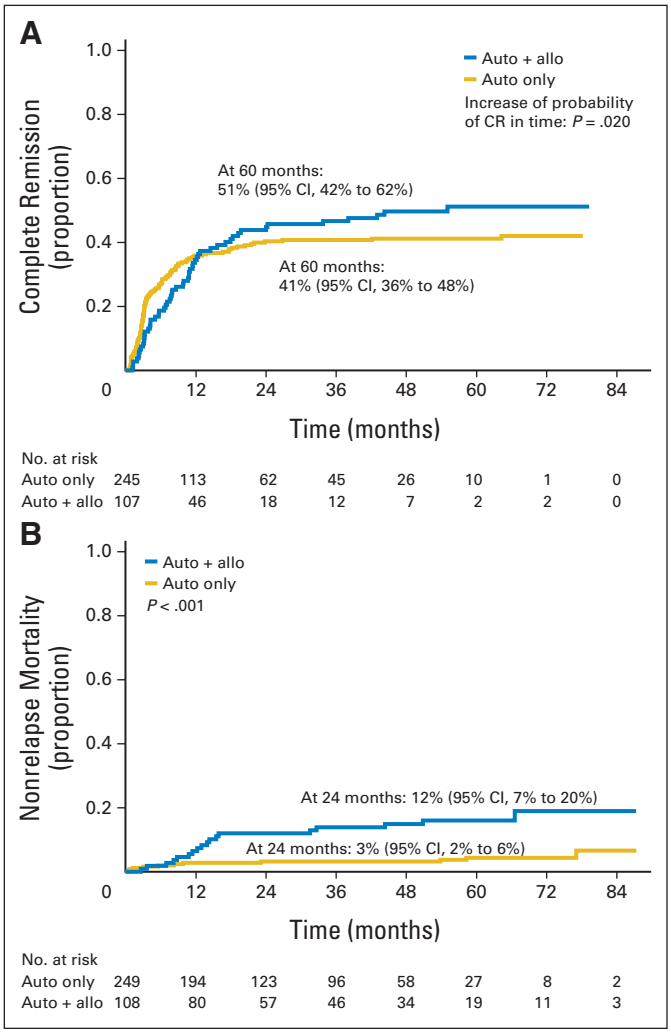

Fig 3. Intention-to-treat comparison of the two study arms (auto [autologous stem-cell transplantation] + allo [reduced-intensity conditioning allogeneic stem-cell transplantation] *v* auto). Rates are calculated from the time point of the first autologous transplantation. The figures at the bottom of each plot indicate patients at risk. (A) Complete remission (CR) rate; (B) nonrelapse mortality rate.

groups, respectively. Long-term OS was significantly superior in the auto-allo group since that group had a significant reduction of risk in time ($P = .006$) with lower hazard of death after 3 years ($P = .047$): OS at 60 months was 65% compared with 58% for the auto group. The CR rate within 60 months was 51% with the auto-allo and 41% with the auto group ($P = .020$ for trend of improvement in time). For the patients who did not attain CR, best response status for the auto-allo and auto groups was PR, 43% and 50%; no response, 3% and 5%; and progressive disease, 3% and 4%, respectively. Cumulative NRM at 24 and 60 months was 12% and 16% for the auto-allo group and 3% and 4% for the auto group ($P < .001$).

ITT Analysis of Patients With Poor-Prognosis Chromosomal Aberrations

For patients with del(13), PFS at 60 months was 31% (95% CI, 18% to 53%) in the auto-allo group and 11% (95% CI, 5% to 22%) in the auto group ($P = .002$). OS was 69% (95% CI, 54% to 88%) in the auto-allo group and 55% (95% CI, 44% to 69%) in the auto group with a significantly better improvement in time ($P = .003$) in the auto-allo group. The relapse/progression risk after 2 years was significantly lower in the auto-allo group ($P = .004$), in which the rate at 60 months was 55% (95% CI, 39% to 77%) versus 86% (95% CI, 78% to 96%) for the auto group.

For patients who were negative for del(13), PFS at 60 months was 44% (95% CI, 30% to 64%) in the auto-allo group and 20% (95% CI, 12% to 32%; $P = .017$) in the auto group. OS was 70% (95% CI, 56% to 88%) and 61% (95% CI, 51% to 73%; $P = .363$), and relapse/progression rate was 39% (95% CI, 25% to 60%) and 76% (95% CI, 67% to 87%; $P = .005$ for the hazard after 2 years) in the auto-allo and auto groups, respectively. Thus, a tendency for better outcome was found in both del(13) and non-del(13) patients, which corroborates the findings in the total cohort patients.

Per Protocol Analysis Comparing Auto-Allo With Tandem ASCT

In the comparison between patients who actually received their RIC alloSCT according to protocol (n = 91) and patients who received a second ASCT in a planned tandem transplantation program (n = 104), outcome was superior with auto-allo (Fig 4): PFS at 60 months after the second transplantation was 39% (95% CI, 30% to 50%) and 19% (95% CI, 12% to 29%) for the auto-allo and auto groups, respectively ($P = .004$). The corresponding figures for OS at the same time point were 63% (95% CI, 53% to 74%) and 60% (95% CI, 51% to 71%; $P = .753$) but with a highly significant trend of reduction of risk in time ($P < .001$), and for relapse/progression rate 43% (95% CI, 34% to 55%) for auto-allo compared with 78% (95% CI, 70% to 87%) for auto ($P = .001$ for the hazard after 2 years). The CR rate within 60 months was 56% (95% CI, 47% to 68%) and 44% (95% CI, 35% to 55%) for the auto-allo and auto groups, respectively ($P = .007$ for improvement in time). For the patients who did not attain CR, response status for the auto-allo and auto groups was PR 35% and 51%, no response 6% and 3%, and progressive disease 3% and 2%, respectively. Cumulative NRM was similar to the ITT analysis, namely 18% (95% CI, 11% to 28%) in the auto-allo arm versus 3% (95% CI, 1% to 10%) in the auto arm at 60 months ($P < .001$).

GvHD

Among the 91 patients who received the RIC alloSCT, acute GvHD (aGvHD) occurred as follows: grade 1 in 10 (11%), grade 2 in eight (9%), grade 3 in eight (9%), and grade 4 in two patients (2%). Sixty patients (67%) had no aGvHD. Forty-nine patients (54%) developed chronic GvHD (cGvHD) which was limited in 28 (31%) and extensive in 21 patients (23%). GvHD information was missing in three patients, and four died before day 100. In a landmark analysis of the evaluable patients alive after day 100, long-term outcome was inferior in patients with aGvHD: At 60 months, OS was 74% (95% CI, 62% to 89%) in patients without aGvHD compared with 32% (95% CI, 15% to 69%) for patients with aGvHD ($P = .0012$). This was based on a higher cumulative NRM from day 100 in the aGvHD patients (36% *v* 4% at 60 months; $P < .001$). With respect to the effect of cGvHD, a landmark analysis was done to compare the outcomes from 12 months after the alloSCT. The basis of the landmark analysis was whether the patient had cGvHD before 12 months (n = 30) or not (n = 37) and was restricted to the 67 patients who were surviving after month 12. There was no significant difference in OS, PFS, relapse incidence, or NRM between the study arms.

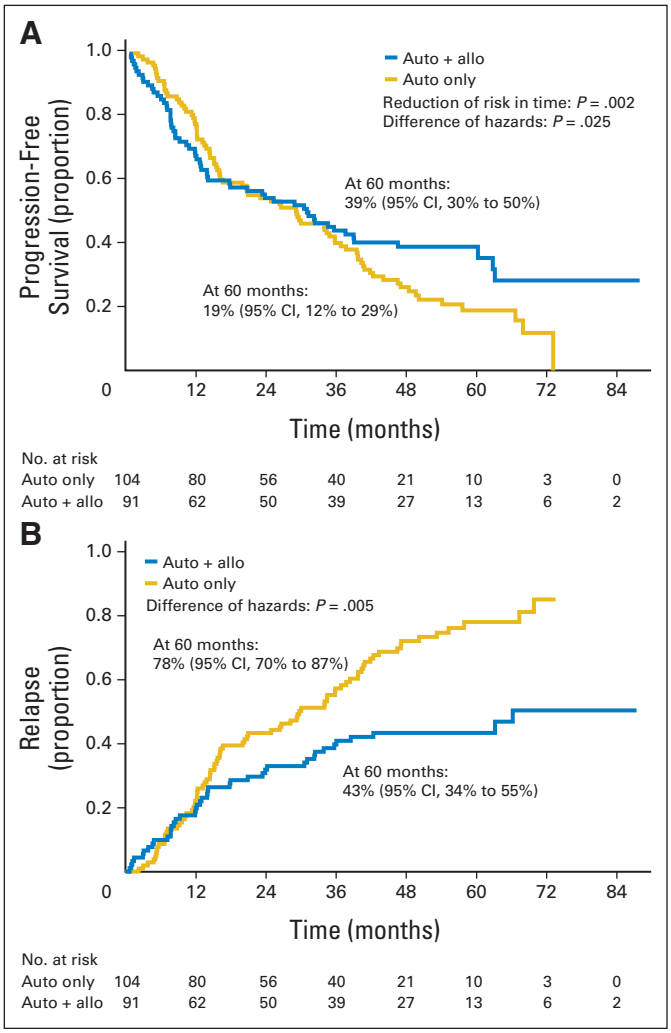

Fig 4. Per-protocol comparison of the two study arms (auto [autologous stem-cell transplantation] + allo [reduced-intensity conditioning allogeneic stem-cell transplantation] *v* auto) of patients who actually received a second transplantation (allo or planned auto). Rates are calculated from the time point of the second transplantation (allo and second auto, respectively). The figures at the bottom of each plot indicate patients at risk. (A) Progression-free survival; (B) relapse rate.

DISCUSSION

Our study demonstrates the long-term efficacy of RIC alloSCT and illustrates the importance of prolonged follow-up in this type of trial, since during the first 1 to 2 years the allo patients did worse, and the difference favoring this group did not emerge until after 2 to 3 years. It seems clear that remissions can be induced by the allogeneic antitumor effect[17,18] in a manner that is not achieved by HDT alone. The allogeneic antitumor effect after RIC alloSCT is more important for the outcome than the adverse effect of procedure-related deaths, since these are on a relatively low level, in contrast to myeloablative alloSCT in which the efficacy is overshadowed by the high rate of TRM.[6] This and similar studies in previously untreated patients have required HLA-matched sibling donors, which naturally substantially limits the applicability of the method in the clinical setting. Study data with RIC alloSCT that uses matched unrelated donors are scarce and mainly limited to patients with relapsed disease,[19] but if a treatment safety similar to that with matched sibling transplantations could be developed, availability would be increased to include the majority of patients in need of a transplantation.

Three trials with a similar design have previously been undertaken by the French Myeloma Intergroup (IFM [Intergroupe Français du Myélome]),[10] an Italian collaborative group,[11] and the Spanish Cooperative Group for Hematological Malignancies Treatment of the Spanish Society of Hematology (PETHEMA).[12] Our trial is the largest of these trials and has the longest time for follow-up, and there are also some other differences in the design and outcome of these studies. The Italian trial[11] enrolled 162 patients (80 allo; 82 auto), but all patients in the auto group were candidates for tandem autografting. As in our trial, PFS and OS were significantly better in the allo treatment arm. No subgroup analysis with respect to cytogenetic prognostic factors was undertaken. The IFM[10] (n = 284) and the PETHEMA[12] (n = 110) trials did not demonstrate any significant differences in the outcome of the two treatment arms, although in the latter trial there was a trend for better PFS with alloSCT. In a long-term follow-up analysis of the IFM trial (median follow-up, 56 months), outcomes were essentially unchanged but showed a trend for better OS favoring the tandem auto transplantation group.[20] The discrepancies in the results of the four trials cannot readily be explained, but there are some important differences and similarities between the studies that may have played a role. The Italian trial used an RIC protocol similar to that in our study with TBI 2 Gy but no fludarabine; the IFM trial used fludarabine, busulphan, and antithymocyte globulin; and the PETHEMA trial used fludarabine and high-dose melphalan. What particularly stands out is the heavier immunosuppression in the IFM trial, and there may be a relationship between the relatively lighter immuno- and myelosuppression in our trial and the Italian trial, and the fact that the outcome after RIC alloSCT was better in these studies compared with the other two trials. The inclusion criteria in the IFM trial allowed enrollment only of patients with high-risk criteria in terms of del(13) and high β_2-microglobulin; the other three trials, including our own, were not restricted to high-risk patients.

The choice of del(13) as a marker for poor prognosis was based on knowledge that was current when the study was planned[21,22] and seemed natural and logical at that time. Later research demonstrated other karyotypic changes (eg, del(17p) and t(4;14)) as more important and that del(13) is a surrogate marker for these changes.[23] However, studies[24] have suggested a crucial role for chromosome 13 in the clonal expansion of tumors, and recent data still identify del(13) as an aberration associated with inferior survival after ASCT.[25]

Tandem ASCT was an option according to the decision in each individual center; the purpose of the study was not to compare single and tandem ASCT, and no such comparison has been made. Notably, however, the outcome after tandem ASCT in the per-protocol analysis was almost identical to that in the whole ASCT cohort according to ITT. In the alloSCT group, the results of the ITT and per-protocol analyses were quite similar, probably reflecting the fact that the number of dropouts (ie, patients who did not fulfill the second transplantation) was low.

The induction chemotherapy consisted of the chemotherapy that was standard at the time, primarily the VAD regimen.[26] With the introduction of novel agents such as bortezomib, thalidomide, and lenalidomide before and after ASCT, outcome for patients with myeloma has improved.[27,28] In particular, response rates have improved,

which could argue against the validity of this study. However, our view is that including the new drugs in the same way in the auto-allo setting may improve the outcome even further with this approach.

We conclude that RIC alloSCT using fludarabine and low-dose TBI is an effective treatment for patients with multiple myeloma who are eligible for this type of therapy with respect to age, comorbidity, and performance status. Our study demonstrates the long-term superiority of a treatment program with sequential ASCT and RIC alloSCT over therapy comprising ASCT alone. While the survival curves after ASCT continuously drop, the level after alloSCT stabilizes with time. The possibility that a fair number of patients might be cured can justify the TRM and GvHD morbidity. It is likely that freedom from progression and survival will further increase with the introduction of more effective drugs as part of induction treatment, and post-transplantation consolidation with donor lymphocyte infusion, other cell therapy approaches, or novel agents.[29-31] We suggest that all patients who are eligible for HDT and have an HLA-identical sibling should be considered as candidates for RIC alloSCT as part of first-line treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Bo Björkstrand, Roche (C) **Consultant or Advisory Role:** Gösta Gahrton, Fujimoto Pharmaceutical (C), Avaris (C) **Stock Ownership:** None **Honoraria:** Gösta Gahrton, Celgene Sweden **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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