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A B S T R A C T

Before the introduction of "new drugs," we designed a trial in which 162 newly diagnosed myeloma patients were biologically randomized to receive either an autologous stem cell transplant (auto-SCT) followed by a nonmyeloablative allogeneic stem cell transplant (allo-SCT) or a double auto-SCT. Fifty-eight patients in the allo-SCT arm and 46 in the double auto-SCT arm completed the assigned treatment. At a median follow-up of 12.3 years from allo-SCT and 12.1 years from second auto-SCT, median overall survival (OS) was 11.4 in the allo-SCT arm and 3.9 years in the auto-SCT -arm ($P = .007$), whereas event-free survival was 3.6 and 1.5 years ($P < .001$), respectively. A subset of allo-SCT patients showed persistent molecular remission. Two-year cumulative incidence of chronic graft-versus-host disease was 67.2%. At 5 years, 39% of these patients were alive, disease-free, and off immunosuppression; 36.6% had relapsed and 12.2% were still on immunosuppres- sion. Thirty-three of 58 patients (allo-SCT arm) and 39 of 46 (auto-SCT arm) relapsed at least once and were rescued with new drugs. In the allo-SCT arm, 2 patients in biochemical relapse did not reach clinical criteria for treatment. Overall 28 (90%) were treated with new drugs and 14 (45%) received donor lymphocyte infu- sions (DLIs). In 28 of 31 patients (90%) DLIs were given with new drugs. Median OS from first relapse was 7.5 years in the allo-SCT arm and 2 years in the auto-SCT arm ($P = .01$). Patients who received DLI showed sig- nificantly longer OS (hazard ratio, .38; $P = .042$) as compared with auto-SCT patients. This difference was slightly lower when only allo-SCT patients who did not receive DLIs were considered (hazard ratio, .56; $P = .154$). In summary, long-term disease-free survival and survival outcomes after treating relapse with new drugs with or without DLIs were better in allo-SCT patients.

Key Words: Allogeneic transplant Multiple myeloma New drugs Long-term follow-up
Chronic graft-versus-host diseaseow-up Chronic graft-versus-host disease

INTRODUCTION

Before the introduction of "new drugs," prospective studies where newly diagnosed myeloma patients were "biologi- cally randomized" in the presence or absence of a suitable HLA identical donor were conducted [1-6]. Moreover, the concept of temporally splitting myeloablation and immuno- therapy was explored through a tandem approach with a standard autologous stem cell transplant (auto-SCT) after melphalan 200 mg/m^2 followed by an allogeneic stem cell transplant (allo-SCT) after nonmyeloablative 200 cGy total body irradiation [1,4-8]. The aim was that of reducing tox- icity while sparing the graft-versus-myeloma (GVM) effect. Reported clinical outcomes were discordant partly due to dif- ferences in study design, patient selection, conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, and donor availability. Moreover, prolonged follow-up was needed to detect differences in clinical outcomes between patient cohorts [7,8]. Here, we report the impact of new drugs on the long-term follow-up of a comparison of allografting with autografting for newly diagnosed myeloma designed in the late 1990s.

METHODS

Study Population and Treatment Assignment

Study design and clinical outcomes were previously published [1]. Between September 1998 and July 2004, 162 consecutive patients with newly diagnosed myeloma and at least 1 sibling were enrolled at 5 centers. In- duction therapy included vincristine adriamycin dexamethasone-based regimens and a standard autograft. Then, patients received either a nonmyeloablative allograft or a second autograft in the presence or absence of a suitable donor. At diagnosis, after HLA typing patients were divided into 2 groups: "donor" (n = 80) or "no donor" (n = 82). In the donor group 60 of 80 patients (75%) were eligible and gave their written consent to high- dose chemotherapy and tandem auto–allo-SCT and 58 of 60 patients (dropout rate, 3%) completed treatment. In the no donor group 59 of 82 patients were eligible and assigned to receive high-dose chemotherapy and tandem auto- SCT, and 46 of 59 (dropout rate, 22%) completed treatment. No maintenance or consolidation was allowed. There were no per-protocol indications for treatment at relapse.

Statistical Analysis

Time-to-event endpoints were calculated from the date of diagnosis for the intention-to-treat analyses and from the date of second transplant (allo- SCT or auto-SCT) for the per-protocol indications. Overall survival (OS) and event-free survival (EFS) were estimated by the Kaplan-Meier method and compared by the Cox proportional hazard model. For analysis of OS after relapse, comparisons between groups were also adjusted for age, gender, IgG, Durie-Salmon stage, and for time from SCT to relapse. Cumulative in- cidences of nonrelapse mortality, chronic GVHD and discontinuation of immunosuppression (IS) were estimated accounting for competing deaths as described by Gooley et al [9] and by the Fine and Gray model [10].

RESULTS

At the time of this report, median follow-up in the allo- SCT group was 13.1 years (range, 8.3 to 16.3+) from diagnosis and 12.3 years (range, 7.7 to 15.3+) from the allo-SCT, whereas median follow-up in the auto-SCT group 12.8 years (range, 11.5 to 16.6+) from diagnosis and 12.1 years (range, 10.5 to 15.4+) from the second auto-SCT. Overall, 29 of 58 patients (50%) in the allo-SCT group and 35 of 46 patients (76%) in the auto-SCT group died. By intention-to-treat analysis (Figure 1), OS was 8.7 years (95% confidence interval [CI], 4.9 to 13.4) in the donor group and 4.2 years (95% CI, 3.3 to 5.8) in the no donor group (hazard ratio [HR], .51; 95% CI, .35 to .74; $P < .001$), whereas EFS was 2.9 years (95% CI, 2.3 to 4.3) in the donor group and 2.4 years (95% CI, 2.1 to 2.7) in the no

donor group (HR, .62; 95% CI, .45 to .87; $P = .006$).

Patients who completed the assigned treatments (Figure 1) showed a median OS from diagnosis of 12.1 years (95% CI, 6.6 to not reached) in the allo-SCT group (n = 58) and 5.2 years (95% CI, 3.2 to 8.9) in the auto-SCT group (n = 46), a median OS from the second transplant of 11.4 years (95% CI, 5.8 to not reached) in the allo-SCT group and 3.9 years (95% CI, 2.1 to 7.6+) in the auto-SCT group (HR, .51; 95% CI, .31 to .83; $P = .007$), and a median EFS from the second transplant of 3.6 years in the allo-SCT group and 1.5 years in the auto-SCT group (HR, .46; 95% CI, .29 to .74; $P < .001$). By multivariate analy- ses, independent of age, gender, myeloma protein isotype, and Durie-Salmon stage, the presence of an HLA-identical sibling was significantly associated with longer OS (HR, .49; 95% CI, .34 to .72; $P < .001$) and EFS (HR, .60; 95% CI, .43 to .85; $P = .004$). Similarly, patients who received allo-SCT showed improved OS (HR, .5; 95% CI, .3 to .84; $P = .01$) and EFS (HR, .41; 95% CI, .25 to .67; $P < .001$) compared with those who received a second auto-SCT.

The major cause of treatment failure and death was disease recurrence in both arms (18/29 [62%] in the allo-SCT arm and 33/35 [94%] in the auto-SCT arm). Five-year cumulative in- cidence of nonrelapse mortality was 17.2% (95% CI, 7.4 to 27.1) after allo-SCT and 4.3% (95% CI, 0 to 10.3) after auto-SCT ($P = .030$).

Chronic GVHD developed in 41 patients for a 2-year cu- mulative incidence of 67.2% (95% CI, 54.9 to 79.5). Discontinuation of IS after GVHD resolution and achieve- ment of immunotolerance is considered a surrogate of good quality of life. Notably, 39% (95% CI, 23.6 to 54.4) of the 41 patients who developed chronic GVHD were alive, relapse- free, and eventually off IS at 5 years (Figure 1), whereas 36.6% had relapsed and 12.2% were still on IS. At the time of follow- up no patient was on IS.

Overall, 31 of 58 patients (53%) in the allo-SCT group and 39 of 46 patients (85%) in the auto-SCT group relapsed. In the allo-SCT group 2 additional patients experienced bio- chemical relapse from complete remission without reaching clinical criteria for treatment and were alive at 11 and 13 years, respectively, from diagnosis, suggesting prolonged effective GVM; of 31 patients, 14 (45%) received donor lym- phocyte infusions (DLIs) and 28 (90%) received "new drugs" (Table 1). Moreover, 2 patients received a second allo-SCT from the same donor: 1 patient in first relapse died of progression 2 years later and the other patient in second relapse is alive 11.5 years from the allo-SCT. Four patients developed GVHD after DLI (1 limited, 3 extensive). In the auto-SCT arm, 35 of 39 patients (90%) received new drug– based regimens (Table 1). Three of 39 patients (8%) received an allo-SCT from an unrelated donor: 2 patients, in first and second relapse, died 6 and 11 years after allo-SCT for pro- gression, and 1 patient in third relapse was alive at last follow-up, 3 years after allo-SCT.

Complete remission was achieved in 16% (5/31) of the allo-SCT patients and in 8% (3/39) of the auto-SCT patients at first relapse, in 14% (3/22) and 5% (1/20) at second relapse, and in 6% (1/16) and 11% (2/17) at third relapse, respectively (Table 1). After a median follow-up of 9.7 years from first relapse, OS was 7.5 years in the allo-SCT arm versus 2.0 years in the auto-SCT (HR, .47; 95% CI, .26 to .84; $P = .01$) (Figure 1). Notably, although the occurrence of chronic GVHD did not impact on relapse incidence (HR, 1.01; 95% CI, .46 to 2.2; $P = .989$), relapsed patients with previous chronic GVHD had a survival advantage (HR, .38; 95% CI, .12 to 1.19; $P = .097$) com- pared with patients who relapsed after allo-SCT without chronic GVHD. Furthermore, after adjusting for age, gender, IgG, Durie-Salmon stage, and time from SCT to relapse, allo- SCT patients who received DLIs at relapse showed significantly longer OS (HR, .38; 95% CI, .15 to .97; $P = .042$) as compared with auto-SCT patients. Interestingly, this difference was slightly lower when allo-SCT patients who did not receive DLI were considered (HR, .56; 95% CI, .25 to 1.24; $P = .154$).

DISCUSSION

After prolonged follow-up, intention-to-treat and per- protocol analyses reinforced the advantage in clinical outcomes of allo-SCT observed in the original report [1]. Im- portantly, a subset of allo-SCT patients showed persistent molecular remission [11]. Current treatment strategies combining auto-SCT with new drug–based induction and consolidation or maintenance allow extended 5-year OS rates up to higher than 60% [12]. Our trial was designed almost 20 years ago; therefore, no patients en- rolled could benefit from new drugs upfront. However, most relapsed patients were rescued with agents that became available over the following years. The efficacy of the combination of new drugs and GVM was highly remarkable as shown by the advantage in postrelapse OS observed in allo-SCT patients compared with auto-SCT patients. Importantly, the efficacy of DLI with new drugs reinforced the concept that GVM and new drugs are not mutually exclusive. Unfortunately, patients were mainly treated outside the context of clinical trials. It is therefore not possible to detect a potentially different efficacy of a given class of antimyeloma drugs between the 2 patient cohorts. The "immunoescape" seen at relapse after allo-SCT was likely overcome by the antimyeloma effects of new agents that potentiated GVM. In fact, synergism between new compounds and allo-SCT was suggested not only in myeloma [6,8] but also in other hematologic malignan- cies [13].

The cumulative incidence of chronic GVHD was high in our cohort (67.2%). However, this was not completely detrimental because it conferred survival advantage in case of disease relapse and was observed, at 5 years, in only 12% of nonrelapsed patients.

Despite recent improvement in OS after auto-SCT, in a subset of patients OS and EFS are very poor even in the era of new drugs [12]. The negative impact of high-risk cytoge- netics appeared to be partly neutralized by GVM in reports [14,15]. At the time our study was designed, in the late 1990s, cytogenetic analysis was not routinely performed. Kröger et al. [14] evaluated the impact of molecular remission and high- risk cytogenetics after tandem auto–allo-SCT. Five-year progression-free survival after allo-SCT was 17% in patients in partial remission, 41% in those in complete remission, 57% in molecular remission, and 85% in sustained molecular re- mission. There was no statistically significant difference in clinical outcomes between patients with del(17p13)/t(4;14) and those without [14]. In another study, Roos-Weil et al. [15] compared patients carrying cytogenetic abnormalities in- cluding t(4;14), del(17p), or t(14;16) (n = 53) and those without (n = 32). No differences in outcomes were ob- served. In both studies the authors concluded that allo-SCT may be of benefit to high-risk patients.

In summary, in this follow-up study, long-term disease- free survival and postrelapse survival outcomes were significantly better after allo-SCT than after auto-SCT. The role of the combination of new drugs and allo-SCT should pro- spectively be explored in high-risk patients, in particular in those with early relapse, where prognosis remains poor also in the era of new drugs.

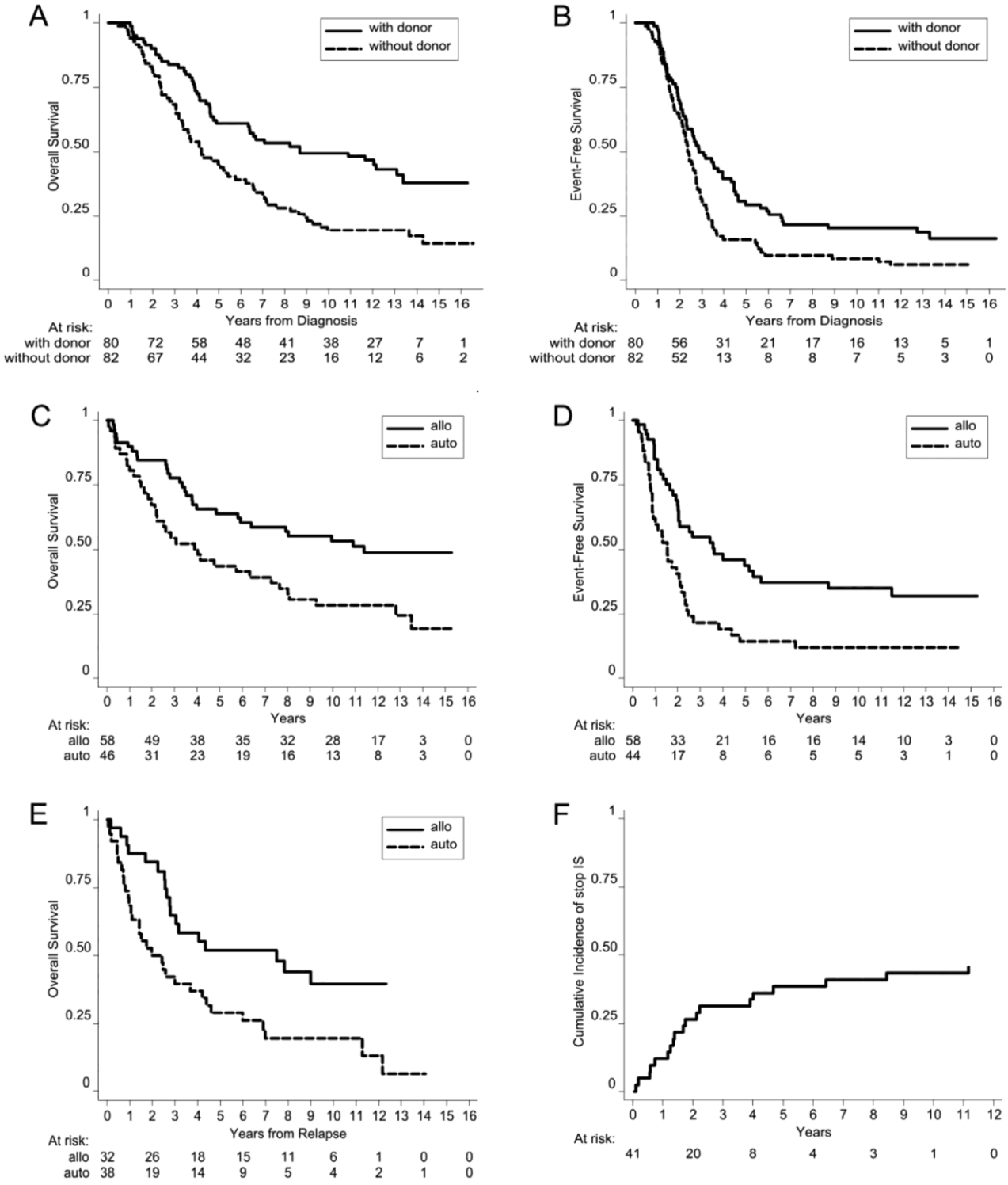

Figure 1. Patient survival. OS (A) and EFS (B) of the "donor" and "no donor" groups from diagnosis by intention-to-treat. OS (C) and EFS (D) from second transplant of the "donor" and "no donor" groups by per-protocol analysis. (E) OS from first relapse in the allo-SCT arm and auto-SCT arm. (F) Cumulative incidence of IS discontinuation (death and relapse were considered as competitive events).

Table 1
Salvage Treatments at Relapse

	First Relapse				Second Relapse				Third Relapse			
	Allo-SCT Arm (n = 31)	Response	Auto-SCT Arm (n = 39)	Response	Allo-SCT Arm (n = 22)	Response	Auto-SCT Arm (n = 20)	Response	Allo-SCT Arm (n = 16)	Response	Auto-SCT Arm (n = 17)	Response
DLI alone	1 (<1%)		—		—		—		1 (6%)	1 CR	—	1 PR
With chemotherapy	4 (13%)	6 SD			1 (4.5%)		—		—		—	
With IMiDs	2 (6.5%)	4 PR			—	1 SD	—		—		1 (6%)	
With bortezomib	6 (19%)	3 CR			—							
Radiotherapy alone	4 (13%)	2 SD 1 PR 1 CR	—	—	—		—		1 (6%)	1 UK	—	
Chemotherapy alone	2 (6.5%)	1 SD 1 CR	3 (8%)	2 PR 1 PD	2 (9%)	1 SD 1 PR	1 (5%)	1 SD	6 (37%)	4 SD 2 UK	2 (12%)	2 SD
IMiDs	6 (19%)	3 SD 3 PR	17 (44%)	9 SD 6 PR 1 CR 1 PD	7 (32%)	3 SD 2 PR 1 CR 1 UK	12 (60%)	7 SD 4 PR 1 PD	5 (25%)	3 SD 2 PR	5 (29%)	2 SD 3 PR
Bortezomib	4 (13%)	2 SD 1 PR 1 UK	7 (18%)	4 SD 2 PR 1 PD	10 (45%)	3 SD 4 PR 2 CR 1 PD	3 (15%)	1 SD 2 PR	2 (12%)	2 PR	4 (23%)	2 SD 1 CR 1 PD
Allograft	—		1* (2%)	1 PR	1† (4.5%)	1 PR	1* (5%)	1 CR	1† (6%)	1 PR	1† (6%)	1 PR
Autograft (with new drugs)	—		7‡ (18%)	1 SD 4 PR 2 CR	—		3 † (15%)	1 SD 2 PR	—		2§ (12%)	1 SD 1 UK
Daratumumab/vorinostat	—		—	—	—		—		—		1 (6%)/1 (6%)	CR/PD
Palliative care	2 (6.5%)	—	2 (5%)	—	1 (4.5%)	—	—		—		—	
Unknown	—		2 (5%)		—		—		—		—	

Dash means none.
CR indicates complete remission; PR, partial remission; SD, stable disease; IMiDs, immunomodulatory drugs; UK, unknown; PD, progressive disease.
* Thalidomide given pretransplant.
† Bortezomib given pretransplant.
‡ Thalidomide and bortezomib given pretransplant in 1 and 3 patients, respectively.
§ Bortezomib given pretransplant in 3 patients.

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Mundipharma, Bristol MSD, and Janssen. The remaining authors declare no conflicts ofinterest.

Authorship statement: All authors gave substantial contributions to research design, acquisition, analysis, or interpretation of data; drafted the paper or revised it critically; and approved the submitted and final versions. B.B. and M.B. designed the research study. L.G. and B.B. wrote the paper.
B.B. supervised the clinical conduction of the study and data analysis. B.B., L.G., and P.O. supervised data collection, analyzed data, and reviewed and assisted in writing the manuscript. A.E. and G.C. analyzed the data and did the statistical analysis. L.G., F.P., R.S., M.P., F.C.-S., M.F., L.B., F.Z., S.B., N.M., E.M., R.F., and B.B. performed the research.

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