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Efficacy and Outcome of Allogeneic Transplantation in IgD and Nonsecretory Myeloma. A Report on Behalf of the Myeloma Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation

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A B S T R A C T

We have recently reported on the outcome of autologous transplantation in the rare myelomas (IgD, IgE, IgM, and nonsecretory [NS]) but there is no real information on the outcome of these conditions after allogeneic transplantation. We used the European Group for Blood and Marrow Transplantation myeloma database to compare the outcomes after allogeneic transplantation of 1354 common myelomas (IgG, IgA, and light chain myeloma) with the outcome in 26 IgD myelomas and 52 NS myelomas. There was little difference between common and the IgD and NS myeloma patients with respect to prognostic factors although the IgD group had a higher beta 2 microglobulin at diagnosis, shorter time to transplantation, and more T cell depletion. IgD and NS patients had a significantly greater achievement of complete remission at conditioning but this did not translate into equivalent progression-free survival and overall survival for the IgD patients although the NS outcome was very similar to that of common myeloma. The PFS and OS of IgD, common, and NS myelomas appear similar after allogeneic transplantation, despite a tendency for higher early relapse rate in IgD myeloma. Allogeneic transplantation may, therefore, be an option to investigate in prospective observational studies.

INTRODUCTION

There have been a number of recent reports of the outcome of autologous transplantation for the rare myelomas (IgD, IgE, IgM, and nonsecretory myeloma [NS]) [1-4]. In the largest report [1], we have suggested that IgD, IgE, and IgM myelomas have a worse outcome after autologous transplantation than common myelomas (IgG, IgA, and light

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Table 1
Patient Characteristics at Diagnosis, Transplantation Characteristics, and Outcome Data

Characteristic	Common Myelomas (n = 1354)	% Data Available	IgD Myelomas (n = 31)	% Data Available	NS Myelomas (n = 52)	% Data Available
Patient Characteristics	IgG 794 (55%) IgA 275 (19%) BJ 285 (20%)	100	IgD 26 (1.8%)	100	NS 52 (3.6%)	100
Gender						
Male, %	810 (59.8%)	100	544 (71.0%)	100	33 (63.5%)	100
Age at Tx, Yr	47.0	100	44.8*	100	45.7*	100
β_2m						
mg/L	2.8	30.6	6.7†	38.7	2.6	30.8
Stage at diagnosis						
Salmon Durie I	11.3	84.0	3.7	87.1	7.5	76.9
II	19.8		14.8		17.5	
III	69.0		81.5		75.0	
Graft source						
BM, %	45.2	100	51.6	100	34.6	100
PB, %	54.8		48.4		65.4	
Conditioning						
MAC	70.1	100	67.7	100	63.5	100
RIC	29.9		32.3		36.5	
Time to transplantation, mo	11.7	100	10.9	100	11.6	100
T cell depletion						
No	69.1	91	51.9†	91	65.2	88
Yes – in vivo	7.8		25.9		10.9	
Yes – ex vivo	14.3		11.1		21.7	
Yes – both	8.8		11.1		2.2	
Gender mismatch female -> male						
% of all transplantations	24.4	100	29.0	100	23.1%	100
Disease response at conditioning						
CR	16.3	82	28.0‡	78	42.5	77
PR	62.3		52.0		45.0	
No change	16.1		12.0		7.5	
Relapse/progression	5.3		8.0		5.0	
Use of TBI	60.3	98	61.3	100	42.0§	96
Outcome Data						
CR after transplantation at 12 months						
Cumulative incidence	.32	92	.33	100	.34	100
Median OS, mo (95% CI)	30.6 (25.2-36.7)		16.2 (13.9-NA)		45.0 (13.2-NA)	
Survival at 36 months (95% CI)						
Survival	.47 (.44-.50)	442 patients	38 (.24-0.61)	9 patients	54 (.41-.71)	19 patients
Median PFS, mo (95% CI)	13.6 (11.9-15.1)		16.2 (5.6-NA)		14.9 (8.0-41.4)	
PFS at 36 months (95% CI)	.30 (.28-.33)	296 patients	.38 (.24-.61)	9 patients	.34 (.23-.52)	12 patients

Tx indicates treatment; β_2m, beta 2 microglobulin; BM, bone marrow; PB, peripheral blood; PR, partial response; NA, not available.
* $P = .020$.
† $P = .017$.
‡ $P = .001$.
§ $P = .34$.

chain only) in keeping with their responses to conventional chemotherapy (with NS having an outcome similar to the common myelomas), although 2 other reports suggest an outcome similar to the common myelomas for all rare myelomas. As allogeneic transplantation in myeloma is only about 8.6% of all transplantations in the European Group for Blood and Marrow Transplantation (EBMT) registry of 1997 to 2009 and rare myeloma constitutes <6% of all myeloma, there is little information published on the outcome of allogeneic transplantation in rare myeloma. In this study, we used the myeloma database of the EBMT to study the outcome of allogeneic transplantation in IgD and NS myeloma and have compared the result with that of 1354 common myelomas.

MATERIALS AND METHODS

A retrospective study of 1437 patients with multiple myeloma who underwent first allogeneic transplantation from HLA-identical sibling donors between 1985 and 2009 with complete data for age, sex, and type of myeloma was undertaken. Patients with no follow-up, missing type of conditioning regimen, missing male-female match (<1%), and missing or combined source of cells (<2%) were also excluded. One half of the patients underwent transplantation after 1999. The number of patients with each type of myeloma is shown in Table 1. Five IgM patients were identified but not included in the analysis. Patients with IgG, IgA, and Bence Jones (BJ) myeloma were collectively described as common myeloma. Patients with plasma cell leukemia were analyzed in a concurrent analysis. Solitary plasmacytoma and amyloidosis were also excluded. All patients were reported to the EBMT registry using MED A (limited data set) or MED B (for extensive data set) forms. All 1432 allografted patients (IgM excluded) were included in the study regardless of availability of complete MED A or MED B data. The number of patients who could be evaluated for each parameter was noted and the proportions of evaluable patients are included in the results. Factors known to affect transplantation outcomes from previous EBMT studies were also analyzed [5]. Response criteria were those used by the centers that were in current use at the time of reporting. On account of differences in follow-up, the analysis of outcomes is restricted (artificial censoring) to the first 4 years after transplantation, a figure equivalent to the lowest median follow-up for the 3 groups.

Statistical Methods

Overall survival (OS) and *progression-free survival* (PFS) were defined, respectively, as time from transplantation to death and to the first event among relapse, progression, or death; observations were censored at the time of last follow-up in case of no failure. OS and PFS curves were produced using the Kaplan-Meier estimator. PFS curves were compared by the log-rank test, whereas for OS that presented crossing curves, we tested the

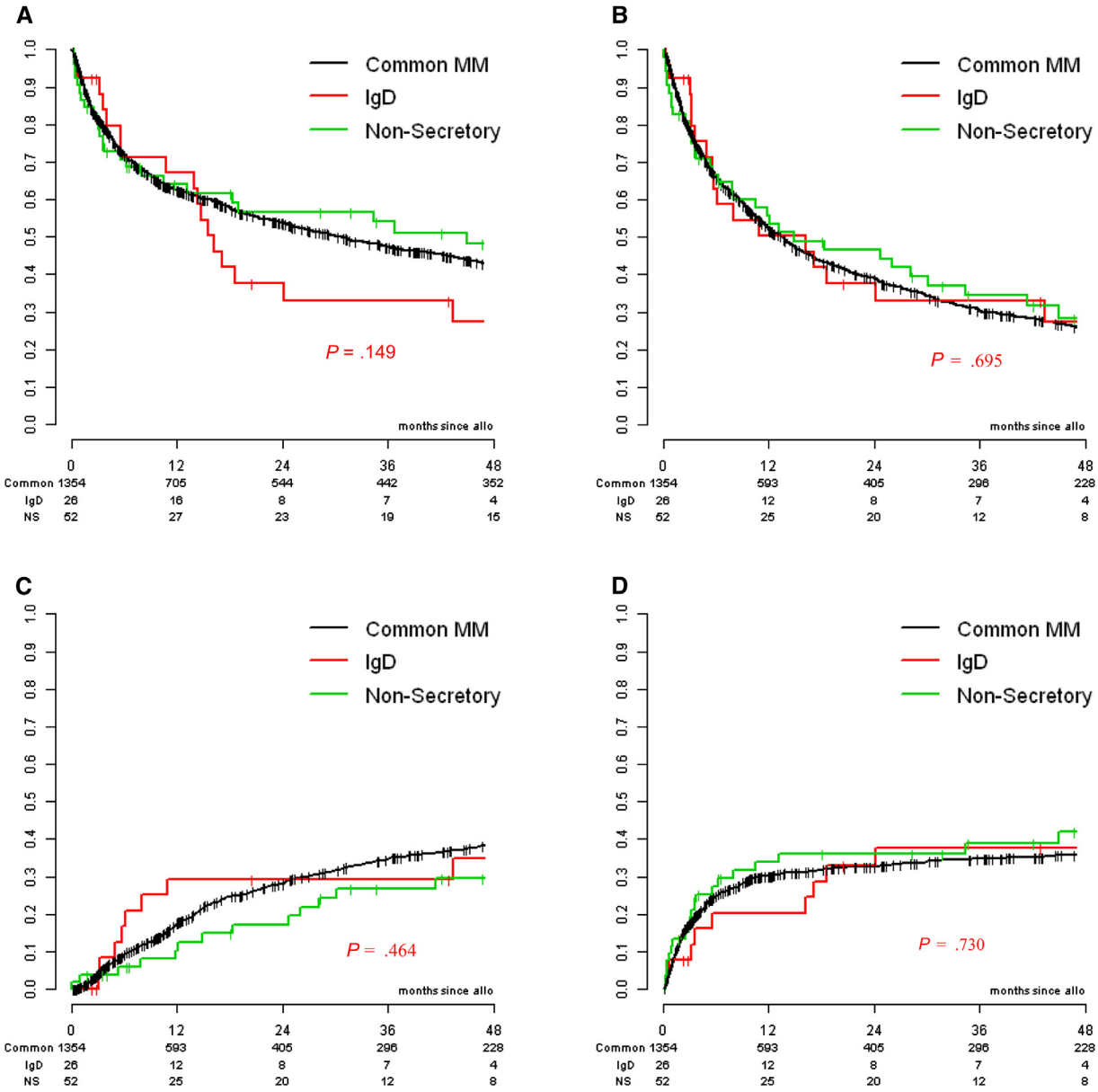

Figure 1. (A) Shows overall survival, (B) shows relapsed/progression-free survival, (C) shows relapse/progression, and (D) shows nonrelapse progression mortality for common, IgD, and NS myeloma. All differences are nonsignificant.

hypothesis that there was no difference at 36 months (an overall test is not meaningful in these situations, and the log-rank test is not suitable to detect differences at a specific point in time); this was done applying the method of the "cloglog" transformation proposed by Klein et al. [6]. The other time-to-event endpoints (relapse/progression incidence, nonrelapse mortality [NRM], achievement of complete remission [CR], occurrence of graft-versus-host disease [GVHD], and engraftment) were analyzed in a competing risks framework, applying the proper nonparametric estimator of the crude cumulative incidence curves and the Gray test for comparison [7]. Death was considered a competing risks in all analyses (except NRM); relapse/progression was a competing risk for NRM and for CR achievement; only patients surviving at 100 days were considered to be at risk of chronic GVHD. Conversely, acute GVHD was analyzed until 100 days. For the comparisons of characteristics in groups, the standard nonparametric tests were applied (chi-squared or Fisher exact test for categorical variables, Mann-Whitney/Kruskal-Wallis Test for continuous variables).

RESULTS

The patient characteristics at diagnosis are shown in Table 1 with percentage availability of results for each variable shown. There was little difference between the groups in respect of most variables (including albumin, calcium, creatinine, and hemoglobin; 39 g/L, 2.21 mmol/L, 71 μmol/L, and 9.0 g/dL, respectively, median values for the IgD patients) except that the IgD group had significantly higher beta 2 microglobulin ($P = .02$ overall). All 23 IgD patients reported had λ light chains. The lower median age of IgD and NS patients ($P = .02$ compared to common) would seem insufficient to be of biological importance.

Transplantation-related Variables

Table 1 also shows transplantation-related variables, including graft source, intensity of conditioning, T cell depletion and type, the proportion of female donor to male recipient matches, disease response, and use of total body irradiation (TBI) in conditioning. Percentage availability is shown where appropriate. The most commonly used of the

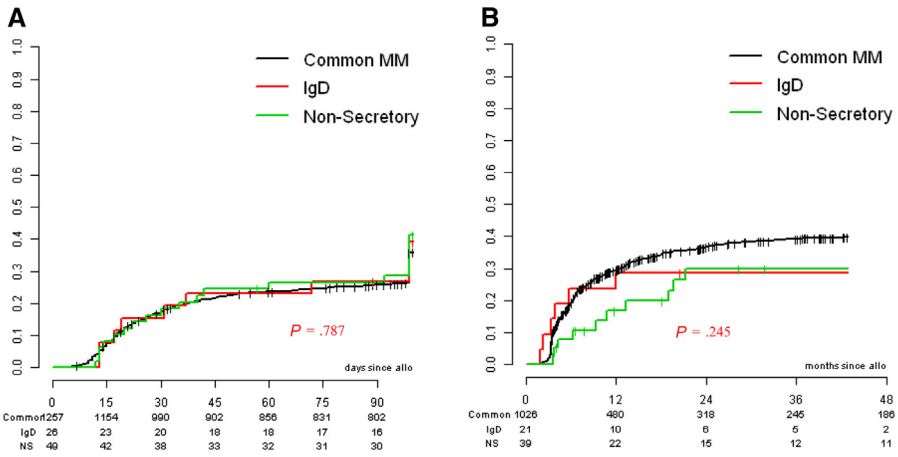

Figure 2. (A) Shows acute graft-versus-host disease and (B) shows chronic graft-versus-host disease for common, IgD, and NS myeloma. All differences are nonsignificant.

reported regimens was TBI/cyclophosphamide and TBI/melphalan, which account for 47% of reported regimens. There was less use of T cell depletion in the IgD group and differences in the type of T cell depletion used, but the subgroups (in vivo, in vitro, or combined depletion) were too small for separate analysis. IgD and NS patients also achieved a significantly higher proportion of CR before transplantation ($P = .001$). Response in NS myeloma was as defined by reporting institutions. There was no difference in time to engraftment of leukocytes, neutrophils, and platelets between groups.

Transplantation Outcomes

In a preparatory analysis, the OS and PFS of the IgG, IgA, and BJ myelomas were compared. Although the IgA group appeared to have had better outcomes than the IgG or BJ groups (OS median: 43 months versus 28 months and 26 months, respectively; PFS median: 17 months versus 12 months and 14 months, respectively), these differences do not reach statistical significance, even comparing IgA versus the other 2 groups combined (P values .096 and .249, respectively, for OS and PFS). Thus, the control group of usual myelomas was considered to be homogeneous.

Figure 1A-D show the data for OS, PFS, relapse/progression, and NRM, respectively. Although there were no significant differences in the achievement of CR between groups in Figure 1A, it appears that the patients with IgD myelomas may have a worse performance than the common and NS patients. Overall survival was 16.2 months (95% confidence interval [CI], 13.9 to >48), 30.6 (95% CI, 25.2 to 36.7), and 45 (95% CI, 13.2 to >48) respectively. However, statistical assessment of differences is difficult because of the IgD and common curves crossing in 2 points, whereas comparison at 36 months using the clog-log method shows a trend for poorer survival ($P = .149$) but with the small numbers surviving at 3 years, the comparison of IgD and NS is nonsignificant. Thus, there may be little difference in the outcome of rare and common myelomas.

Figure 1B shows the PFS for the 3 groups. PFS for common was 13.6 months (95% CI, 11.9 to 15.1), for IgD it was 16.2 months (95% CI, 5.6 to >48), and for NS it was 14.9 months (95% CI, 8.0 to 41.4). Although the values for OS and PFS are similar for the IgD group, it should be noted that the confidence intervals for both OS and PFS for this group are very wide because of the small number of cases. Figure 1C and D show IgD myelomas appear to have a higher rate of early relapse/progression (but about the same at 36 months) and correspondingly a lower NRM than NS (and common) myeloma; but, again it is about the same at 36 months and significance is not reached. Thus, it appears there is no significant difference between the groups.

GVHD

Figure 2A and B show the incidence of acute and chronic GVHD. Ninety-three percent of cases were evaluable for acute GVHD and 99% for chronic GVHD. There is no difference between the groups (Gray test, $P = .787$ and $P = .245$, respectively).

Myeloablative versus Reduced-intensity Conditioning

Only 10 patients in the IgD/NS subpopulation had reduced-intensity conditioning (RIC); too low for meaningful statistical analysis by usual methods. As the majority of patients had myeloablative (MAC), the NRM overall is high. Nevertheless, we looked for any sign of differences depending on RIC or MAC (interactions); the interaction terms were highly nonsignificant, suggesting that they are not affected by the inclusion of the RIC group.

DISCUSSION

The rare myelomas have intrigued hematologists and biochemists ever since their first identification. One factor that has consistently been noted (with occasional exceptions) is the poor survival for patients with rare myelomas compared with patients with common myelomas with conventional therapy. Compared with the reported survival for IgD myeloma, Wechalekar et al. [2], found survival was better for 11 IgD patients who received autologous transplantation, but survival was inferior to common myeloma. Sharma et al. [3] (17 patients) and Reece et al. [4] (36 patients) showed considerable improvement in survival after autologous transplantation with OS similar to common myeloma. In our series [1], consisting of 379 IgD patients, OS after autologous transplantation was significantly less than for common myeloma patients (43.5 months and 62.3 months, respectively). This overall improvement in survival for all myelomas after autologous transplantation, still keeping a clear difference between rare and common myelomas, was obtained

even before the use of new drugs, although patient selection may account for part of this apparent improvement in survival for rare myeloma due to autologous transplantation. In contrast, little information has been published on the outcome of allogeneic transplantation in rare myelomas.

In the present study of allogeneic transplantation, performed retrospectively with mainly MAC conditioning and HLA-identical sibling donors and mostly before the use of the novel drugs (proteosome inhibitors and immunomodulatory drugs), the difference in outcome between common and rare myelomas is not obvious. The small proportion of patients undergoing RIC allogeneic conditioning is a reflection of the period of data collection, which ended in 2010 when RIC allogeneic transplantations started to be performed much more frequently. Although there is a tendency for an early higher relapse rate in rare myelomas, it is no longer significantly different at 36 months. The PFS is similar. OS tends to be somewhat inferior in the beginning, but at 36 months there is no difference. Although numbers are small, the lack of significant difference could be an indication that allogeneic transplantation partly overcomes the poorer prognosis in rare myelomas, also seen in allogeneic transplantation of patients with other poor prognosis parameters [8,9]. In a separate analysis (not shown), adding data from the 5 IgM patients to the IgD group gave very similar results. As this survey covers a wide time period, it seems probable that the improved outcome measures noted in successive time cohorts [10] and confirmed in recent randomized clinical trials [11,12] could apply to the rare myelomas, but the number of cases is too small for this analysis.

It should be noted that NS myeloma should be considered separate from IgD myeloma. Better techniques are showing that only a small proportion of NS myeloma cannot be shown to have any Ig or light chain specificity. Although monitoring response is more difficult, on account of the lack of easily measured biomarker, OS is very similar to that for common myelomas [1,13,14] and our study once again confirms this view.

Although confining our report to patients with reasonably complete data sets at initial reporting (consistent with our report on autologous transplantation), follow-up reporting is modest, resulting in truncation of the follow-up to 4 years after transplantation. Obtaining reliable long-term follow-up for myeloma patients has proved challenging for EBMT, but this is being addressed for future studies. It may also account for the unusual similarity between OS and PFS (both 16.2 months) in the IgD group, where the wide confidence intervals are a factor and (in an analysis not shown) there is joining of the PFS and OS plots just before the median is reached.

Our results highlight the difficulty of obtaining a meaningful understanding of how to manage rare conditions such as IgD and other rare myelomas. We suggest that allogeneic transplantation may be an effective modality in the condition, but as many of the patients were treated in the era before the use of novel drugs, further evaluation is required. As randomized controlled clinical trials are not practical for this group, and although inclusion of IgD patients into poor prognosis studies might be considered, the best approach to understanding how to treat such patients may be through the use of prospective observational studies, possibly after an overall plan of management.

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