IgD subtype but not IgM or non-secretory is a prognostic marker for poor survival following autologous hematopoietic cell transplantation in multiple myeloma: results from the EBMT CALM (collaboration to collect autologous transplant outcomes in lymphomas and myeloma) study

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Original Study

IgD Subtype But Not IgM or Non-Secretory Is a Prognostic Marker for Poor Survival Following Autologous Hematopoietic Cell Transplantation in Multiple Myeloma. Results From the EBMT CALM (Collaboration to Collect Autologous Transplant Outcomes in Lymphomas and Myeloma) Study

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Abstract

The rare myelomas, immunoglobulin (Ig)D, IgM, and non-secretory, have been associated with poorer outcomes following treatment than the common myelomas (IgG, IgA, and light-chain only). We show that even with "novel" therapies, augmented with autologous transplantation, this remains true for IgD myeloma. In contrast, IgM and non-secretory myelomas have a prognosis similar to the usual myelomas.

Background: The Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study has provided an opportunity to evaluate the real-world outcomes of patients with myeloma. The aim of this study was to compare the outcome according to the different subtypes of myeloma using CALM data. **Patients:** This study compared overall survival (OS), progression-free survival (PFS), and complete remission (CR) and the impact of novel versus non-

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novel drug containing induction regimens prior to autologous hematopoietic cell transplantation (HCT) of 2802 patients with "usual" and "rare" myelomas. **Results:** Our data suggest that IgM and non-secretory myeloma have superior PFS and OS compared with IgD myeloma and outcomes comparable to those for usual myeloma. Patients who received novel agent induction had higher rates of CR prior to transplant. Non-novel induction regimens were associated with inferior PFS but no difference in OS. Although not the primary focus of this study, we show that poor mobilization status is associated with reduced PFS and OS, but these differences disappear in multivariate analysis suggesting that poor mobilization status is a surrogate for other indicators of poor prognosis. **Conclusion:** We confirm that IgD myeloma is associated with the worst prognosis and inferior outcomes compared with the other isotypes.

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Introduction

Myeloma cells normally secrete immunoglobulin (Ig)G, IgA paraproteins, and/or kappa or lambda light chains). Rare myeloma isotypes—namely, IgD, IgM, IgE, and non-secretory (NS)—constitute only a small proportion of any study population.[1] Due to their infrequent incidence, limited information is available regarding the prognosis of these rare isotypes; however, they have been associated with a more aggressive course and worse outcomes, particularly IgD myeloma.[2]

The Collaboration to Collect Autologous Transplant Outcomes in Lymphoma and Myeloma (CALM) study is a non-interventional prospective study conducted in 49 centers in 19 countries by the European Society for Blood and Marrow Transplant (EBMT) to collect details of treatment and in particular the effects of mobilizing stem cells with plerixafor.[3]

This study has provided an opportunity to examine the real-world outcomes of patients with myeloma, to compare usual myeloma (IgG, IgA, and light-chain) and rare myeloma (IgD, IgM, and non-secretory), and to establish if the advent of novel agents has altered the prognosis for these small subsets of myeloma. As the purpose of the CALM study was to identify if plerixafor mobilization constituted a hazard in terms of mobilizing myeloma stem cells (and adversely influencing the outcome of autologous transplantation), we hypothesized that the requirement for plerixafor to assist in mobilizing sufficient stem cells for successful transplantation would identify a subset of patients with poor prognosis, as has been suggested by Brioli et al[4] and Moreb et al.[5]

Materials and Methods

The CALM database was used to identify patients with newly diagnosed myeloma undergoing first autografts between 2008 and 2012. Patients with plasma cell leukemia, plasmacytoma, amyloid light-chain amyloidosis, or POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) were excluded from this database. The database identified 2803 patients who were divided into usual myeloma (IgG, IgA, and-light chain) and rare myeloma (IgD, IgM, IgE, and NS). As there was only one case of IgE myeloma, inclusion in this analysis was inappropriate, and this patient was excluded, thus reducing the analysis to 2802 patients. Patients from 49 participating centers were reported to the EBMT registry using Med-A and Med-B forms, with the addition of a Med-C form to capture data about plerixafor usage. Factors known to affect the outcome of transplantation from previous EBMT studies were also analyzed. The number of patients that could be evaluated for each parameter was noted, and the proportion of evaluable patients was included in the results. The impact of induction regimens, containing either novel or non-novel drugs, prior to autograft was examined. We defined a novel drug as the use in the induction regimen of bortezomib and/or an immunomodulatory drug (IMiD) such as thalidomide or lenalidomide. Poor mobilizers were defined as patients who had either a failed prior mobilization attempt or had failed to achieve the center-defined target level of peripheral blood cluster of differentiation 34 (CD34)-positive cells in a prior or the current mobilization attempt. Predicted poor mobilizers were defined by centers based on factors including prior skeletal radiotherapy or high exposure to drugs that damage stem cells.[3]

The study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Chronic Malignancies Working Party of the EBMT, a non-profit scientific society representing more than 600 transplant centers mainly located in Europe. Data reported to the EBMT are entered, managed, and maintained in a central database with internet access that is housed in Leiden University Medical Centre, The Netherlands. Each EBMT center is represented in this database, and all patients whose transplant data are reported by participating centers provide informed consent for transplant-related data to be used for research purposes in an anonymous way.

Comparisons among the four myeloma isotypes (usual, IgD, IgM, and NS) were made using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous data. Overall survival (OS) was defined as the time from transplantation to death from any cause. Patients still alive were censored at their last follow-up. Progression-free survival (PFS) was defined as the time between transplantation and progression of disease or death, with patients being censored who did not develop an event. The Kaplan–Meier estimator was used to compute the probability of OS and PFS, and the comparisons were made using the log-rank test. The incidence of complete remission (CR) after transplant was analyzed in the competing risk framework, considering relapse or death without prior CR as the competing event. The probability of being in CR was calculated using the proper non-parametric estimator for outcomes with competing risk and compared by Gray's test.

Adjusted effects on outcomes were estimated in terms of hazard ratios using the Cox model. The roles of the following factors were assessed: International Staging System (ISS) stage at diagnosis (I vs. II or III), pre-treatment induction agents (novel vs. non-novel agents), status of disease at transplant (CR/very good partial response [VGPR] vs. partial response or lower), age at transplant, mobilization status, gender, and the calendar year of the transplant. Age was dichotomized with a cut-off of 65 years for comparability with other studies, considering that Martingale residuals analysis did not suggest other cut-off points (data not shown). The robustness of the results was assessed as characteristics; PFS and OS were very similar in cases with known information and in those with missing data. In particular, for known and missing cases, respectively, OS at 60 months after transplantation was 63.7 months (95% confidence interval [CI], 61.2-66.2) and 66.0 months (95% CI, 62.4-69.6; $P = .66$), whereas PFS at 60 months was 23.3 months (95% CI, 21.1-25.5) and 23.4 months (95% CI, 20.1-26.6; $P = .86$).

In order to make the analysis homogeneous, the same factors were selected in the adjusted final model for all outcomes.

All P values shown are from two-sided tests, and the reported confidence intervals refer to 95% boundaries. $P < .05$ was regarded as statistically significant.

Results

Patient Characteristics

The number of patients with each isotype of myeloma is shown in Table 1. Usual myeloma accounted for 96.15% of the study population. Rare myeloma isotypes accounted for 3.81%, with non-secretory being the most common (2.18%), followed by IgD (1.03%) and IgM (0.6%). (The one IgE patient received a bortezomib and an immunomodulatory induction regimen and achieved a partial response prior to their autograft; the patient was followed up for 41.1 months and relapsed at 32.8 months.)

The patient characteristics are shown in Table 1. There was a male predominance within all isotypes, particularly in IgM (76.5%). The median age at time of transplant was 59.25 years, although IgD myeloma patients were younger, with a median age of 55.6 years; these differences were not significantly different. ISS was strongly associated with the isotype, as IgD had significantly more patients in ISS II or III (68%) and NS had more ISS I (61%) ($P = .047$). The majority of the patients achieved at least a partial response before transplant. The proportion of CR/VGPR was lowest within the IgM subgroup (35.3%), but the differences shown in Table 1 were not significantly different. There were no significant differences between the different isotypes with respect to interval between diagnosis and transplant and Karnofsky status, with similarly non-significant differences between groups in the number of cells collected and infused and transplant conditioning.

Information on mobilization status was available for 2793 patients (97.8%). Among these, 446 patients (16.3%) were poor mobilizers. Within the poor mobilizer group, 218 patients (49%) received plerixafor; however, it should be noted that a small percentage of patients (24 of 2293; 1%) within the non-poor mobilizer group also received plerixafor.

The following induction regimens were compared: bortezomib plus immunomodulatory agent (plus steroid, $n = 664$), thalidomide (plus steroid $n = 671$), lenalidomide (plus steroid, $n = 51$), bortezomib (with no immunomodulatory agent, $n = 987$), and non-novel (including steroid, $n = 430$). Within these groups, the bortezomib plus IMiD group had the lowest proportion of patients transplanted within 12 months and the lowest proportion of patients with Karnofsky score of >80. The bortezomib and IMiD group also had the lowest proportion of patients achieving cell collection of CD34+ cells $> 5 \times 10^6$/kg; thus, the proportion of poor mobilizers was highest in this group. Patients not receiving any novel agent in induction had the lowest proportion of patients achieving CR/VGPR ($P < .001$).

Progression-Free Survival and Overall Survival

Univariate Analysis.. IgD myeloma was associated with the worst PFS and OS (Figures 1, 2). The median PFS rates for usual, IgD, IgM, and NS myeloma were 27.0 months, 19.9 months, 40.8 months, and 38.7 months, respectively ($P = 0.0374$). The median overall survival for usual versus IgD myeloma was 81.7 months versus 48.5 months ($P = .002$), whereas the median OS for the IgM and NS groups had not been reached at the time of analysis. The significantly better PFS for NS myeloma ($P = .0013$) may not have converted into an improvement in OS.

PFS with a non-novel agents was shown to be inferior to induction with a novel agent ($P = .0088$). At 36 months, PFS was 32.8% (95% CI, 28.3-37.4) for non-novel agents, and it was 40.9% (95% CI, 38.9-43.0) for novel agents. However, the difference in OS was not statistically significant ($P = .376$) (Figure 3).

ISS I patients had a significantly better OS (median OS not reached vs. 73.9 months; $P < .001$) and PFS (median PFS 31.4 vs. 24.6 months; $P = .004$) than ISS II or III.

The median OS for patients defined as poor mobilizers was 70.7 months compared with 84.9 months in patients who were not poor mobilizers ($P = 0.011$), whereas the median PFS was 24.6 months vs. 27.7 months, respectively ($P = .0108$).

Multivariate Analysis.. Although only showing a trend to worse PFS (hazard ratio [HR] = 1.46; 95% CI, 0.94-2.27; $P = .095$), IgD myeloma was confirmed as having the worst OS, with HR = 2.86 (95% CI, 1.73-4.70; $P < .001$) compared with usual myeloma (Table 2). IgD myeloma had also inferior PFS compared with IgM and NS, with HR = 0.50 (95% CI, 0.21-1.19; $P = .120$) for IgM versus IgD and HR = 0.39 (95% CI, 0.20-0.76; $P = .006$) for NS versus IgD. A significant PFS advantage for NS myeloma compared with usual myeloma (HR= 0.56; 95% CI, 0.34-0.94; $P = .028$) failed to translate into an OS advantage (HR = 0.72; 95% CI, 0.36-1.45; $P = .360$). Although there was an increase in PFS for the novel induction agent group (HR = 0.86; 95% CI, 0.73-1.00; $P = .051$), there was no OS advantage for the novel induction agent group (HR = 1.03; 95% CI, 0.83-1.28; $P = .796$). It can also be seen, as would be expected, that being transplanted with less than CR/VGPR affected PFS and OS adversely, and ISS of II or III at diagnosis was an adverse factor for PFS and OS. When mobilization status was included in a multivariate analysis, there was no significant impact on OS ($P = .315$) and PFS ($P = .206$) (Table2). The analysis also shows a significant advantage for female sex in PFS but this does not convert into a significant OS advantage.

Table 1 Patient Characteristics

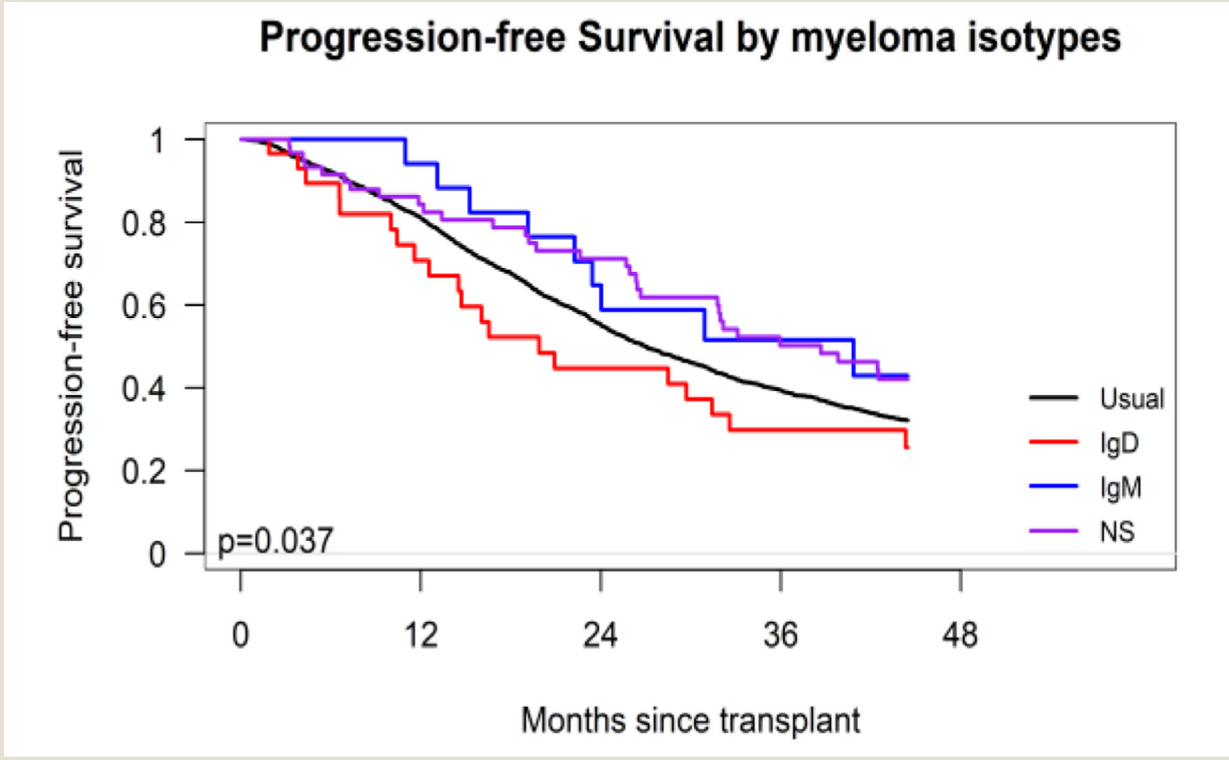
Characteristic	Usual	IgD	IgM	NS	*P*
Isotype, *n* (%)	2695 (96.2)	29 (1.00)	17 (0.60)	61 (2.20)	—
Age at ASCT (y), median (range)	59.5 (23-76)	55.6 (40-66)	59.3 (41-70)	59.2 (33-76)	.430
Gender, *n* (%)					.271
Male	1562 (58)	18 (62.1)	13 (76.5)	31 (50.8)	
Female	1133 (42)	11 (37.9)	4 (23.5)	30 (49.2)	
ISS at diagnosis, *n* (%)					.047
I	719 (39.0)	8 (32.0)	4 (33.3)	22 (61.1)	
II or III	1123 (61.0)	17 (68.0)	8 (66.7)	14 (38.9)	
Missing ($n = 887$; 32)	853 (31.7)	4 (13.8)	5 (29.4)	25 (41)	
Induction treatment, *n* (%)					.785
Non-novel agents	414 (15.4)	3 (10.3)	2 (11.8)	11 (18.0)	
Novel agents	2281 (84.6)	26 (89.7)	15 (88.2)	50 (82.0)	
Interval from diagnosis to transplant, *n* (%)					.331
≤12 mo	2140 (79.4)	27 (93.1)	14 (82.4)	48 (78.7)	
>12 mo	555 (20.6)	2 (6.9)	3 (17.6)	13 (21.3)	
Poor mobilizer, *n* (%)					.431
No	2206 (83.6)	21 (75)	15 (88)	53 (88)	
Yes	430 (16.3)	7 (25)	2 (12)	7 (12)	
Missing ($n = 61$; 2%)	59 (2.2)	1 (3.4)	0 (0)	1 (1.6)	
Karnofsky score, *n* (%)					.696
>80	1664 (67.5)	18 (62.1)	11 (64.7)	42 (73.7)	
≤80	801 (32.5)	11 (37.9)	6 (35.3)	15 (26.3)	
Missing ($n = 234$; 8%)	230 (8)	0 (0)	0 (0)	4 (6)	
Disease status at transplant, *n* (%)					.758
CR/VGPR	1198 (45.0)	15 (51.7)	6 (35.3)	25 (45.5)	
PR or lower	1464 (55.0)	14 (48.3)	11 (64.7)	30 (54.5)	
Missing ($n = 39$; 1.4%)	33 (0.4)	0 (7)	0 (0)	6 (10)	
Number of cells collected, *n* (%)					.489
$<3 \times 10^6$/kg	209 (12.1)	4 (21.1)	1 (14.3)	7 (18.4)	
3-5 $\times 10^6$/kg	342 (19.7)	6 (31.6)	1 (14.3)	6 (15.8)	
$>5 \times 10^6$/kg	1182 (68.2)	9 (47.4)	5 (71.4)	25 (65.8)	
Missing ($n = 1005$; 36%)	962 (35.7)	10 (34.5)	10 (58.9)	23 (37.7)	
Number of cells infused, *n* (%)					.608
$<3 \times 10^6$/kg	649 (28.9)	8 (30.8)	2 (12.5)	15 (34.1)	
3-5 $\times 10^6$/kg	902 (40.1)	11 (42.3)	6 (37.5)	18 (40.9)	
$>5 \times 10^6$/kg	697(31.0)	7 (26.9)	8 (50.0)	11 (25.0)	
Missing ($n = 468$; 17%)	447 (16.6)	3 (10.3)	1 (5.9)	17 (27.8)	

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; IgD = immunoglobulin D; IgM = immunoglobulin M; ISS = International Staging System; NS = non-secretory; PR = partial response; VGPR = very good partial response.

Complete Response After Transplant

Univariate comparisons did show superior outcomes for NS myeloma; 24 months after the transplant, the incidence of CR was 49.5% for usual, 50.2% for IgD, 29.4% for IgM, and 70.0% for NS, respectively ($P = .004$). Multivariate analysis confirmed the univariate results (Table 2). Patients with NS myeloma were more likely to be in CR after transplant (HR = 2.99 for NS vs. IgM; $P = .046$), whereas patients transplanted in PR or lower stage response were less likely to be in CR (HR = 0.33; $P < .001$). Female gender was beneficial (HR = 1.21 for female vs. male; $P = .002$), whereas the use of novel agents did not significantly affect achievement of CR after transplant. Being poor mobilizers positively affected the outcome (HR= 1.24; 95% CI, 1.05-1.47; $P = .013$), but this difference was not reflected in PFS or OS. Poor mobilizers were found to have been transplanted >12 months since diagnosis, unlike those mobilizing normally and more often in a status lower than CR or VGPR after having being treated with novel agents, specifically with bortezomib and IMiDs. In the later years of the study, CR was

Figure 1 Progression-Free Survival by Myeloma Group.
Abbreviations: IgD = immunoglobulin D; IgM = immunoglobulin M; NS = non-secretory.



observed significantly more frequently after transplant, but this did not translate into a PFS or OS difference, possibly as the HR was small.

Discussion

The EBMT CALM project was initiated in response to a European Medicines Agency requirement for additional safety data on plerixafor and ran from the start of 2008 to the end of 2012. This period covers the switch from conventional drug induction prior to mobilization and transplant to the widespread use of novel agents for induction therapy, including proteosome inhibitors and IMiDs. The study has analyzed excellent follow-up data on PFS and OS; furthermore, this study, although not involving all EBMT centers, commenced in 2008 and our previous study reported the EBMT experience to the end of 2007.[2]

This CALM data confirm our earlier EBMT studies indicating that IgD myeloma is associated with the worst prognosis and inferior outcomes compared with other isotypes (although the outcomes continue to be better than without transplantation) and also confirm that IgD myeloma is associated with a younger age of presentation and an advanced clinical stage.[2,6] It appears that IgD myeloma is more common in Eastern Asian populations. A number of single-center studies from this region also suggest worse outcomes for IgD myeloma.[7-10] A multi-center review from this region using the least absolute shrinkage and selector operation technique confirmed these results,[11] as did a systematic review on an overlapping population.[12] Kang et al[13] reported a dramatic improvement for IgD myeloma over a 20-year period, but this was driven by novel agents and transplantation. In contrast, the only other large transplant study, conducted by the Center for International Blood and Marrow Transplant Research, reported similar outcomes for IgD myeloma compared with usual myelomas.[14] A number of other studies examining IgD myeloma in which some patients were transplanted also gave an outcome more similar to usual myeloma.[15-17] The current study is consistent with our previous study and suggests that the use of novel agents while generally beneficial does not benefit IgD myeloma more than the other isotypes.

IgM myeloma has been reported in the literature as <0.5% of all myeloma.[1] The CALM data suggest that the incidence of IgM myeloma in patients undergoing autologous transplantation is higher than previously reported (0.6%) and double that in our previous study.[2] This reflects the increased recognition of IgM myeloma as a distinct entity and an improvement in the ability to differentiate between IgM myeloma and Waldenstrom's macroglobulinemia.[18]

In contrast to our previous study, our data suggest that IgM myeloma receiving induction therapy and autologous transplantation has survival superior to that for IgD and comparable to usual myeloma. This is surprising, given that IgM myeloma had the smallest proportion of patients in CR/VGPR prior to transplantation. Early reports of IgM myeloma indicated a poor OS.[19,20] We previously reported that the proportion of patients with IgM myeloma achieving complete remission prior to transplantation was the lowest

Figure 2 Overall Survival by Myeloma Group.
Abbreviations: IgD = immunoglobulin D; IgM = immunoglobulin M; NS = non-secretory.

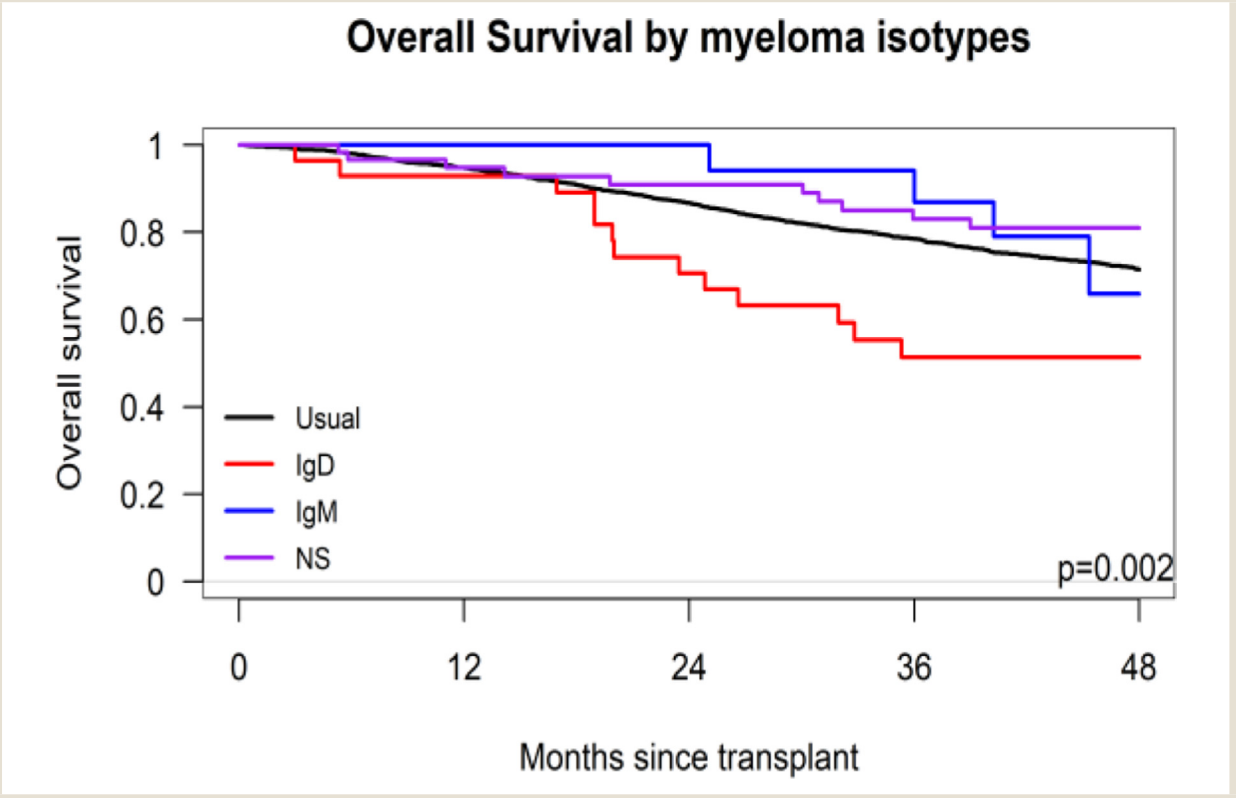


Figure 3 Overall Survival (a), and Progression-Free Survival (b) by Agent.

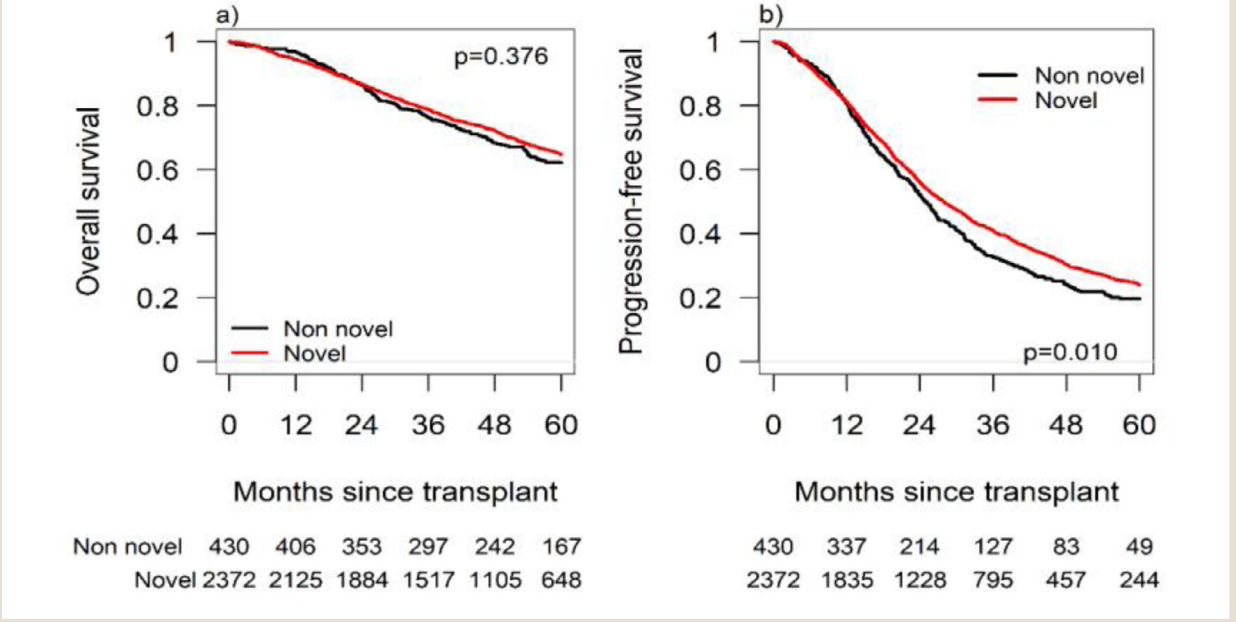


Table 2 Multivariate Analysis for PFS, OS, and CR After Transplant

	PFS			OS			CR After Treatment		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
IgD vs. usual	1.46	0.94-2.27	.095	**2.86**	**1.73-4.70**	**<.001**	1.28	0.74-2.22	.379
IgM vs. usual	0.74	0.35-1.55	.419	0.84	0.27-2.63	.770	0.50	0.19-1.33	.166
NS vs. usual	**0.56**	**0.34-0.94**	**.028**	0.72	0.36-1.45	.360	1.49	0.96-2.31	.073
IgM vs. IgD	0.50	0.21-1.19	.120	**0.30**	**0.09-1.02**	**.053**	0.39	0.31-1.20	.100
NS vs. IgD	**0.39**	**0.20-0.76**	**.006**	**0.25**	**0.11-0.59**	**.002**	1.17	0.58-2.34	.666
NS vs. IgM	0.77	0.31-1.89	.562	0.85	0.23-3.24	.817	**2.99**	**1.02-8.76**	**.046**
PR or lower vs. CR/VGPR	1.29	1.15-1.45	<.001	1.25	1.06-1.48	.007	0.36	0.31-0.41	<.001
ISS, II or III vs. I	1.19	1.06-1.33	.002	1.50	1.27-1.78	<.001	1.00	0.88-1.13	.959
Poor mobilizers, yes vs. no	1.10	0.95-1.27	.206	1.11	0.91-1.36	.315	1.24	1.05-1.47	.013
Age (y), >65 vs. ≤65	1.02	0.89-1.17	.798	1.30	1.07-1.57	.009	0.94	0.80-1.10	.430
Novel vs. non-novel agents	0.86	0.73-1.00	.051	1.03	0.83-1.28	.796	1.13	0.93-1.38	.226
Gender, female vs. male	0.88	0.79-0.99	.028	0.86	0.74-1.01	.072	1.21	1.07-1.38	.002
Year of transplant, +1 year	1.02	0.98-1.07	.310	0.97	0.90-1.04	.387	0.92	0.87-0.97	.001

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; IgD = immunoglobulin D; IgM = immunoglobulin M; ISS = International Staging System; NS = non-secretory; OS = overall survival; PFS = progression-free survival; PR = partial response; VGPR = very good partial response.
*Significant results hi-lighted in bold print.

of all the myeloma isotypes. Autologous transplant appeared to have a beneficial effect, with the percentage of patients achieving complete remission rising to 34% and a similar improvement in the proportion of partial remissions, although OS was similar to IgD myeloma and worse than in usual myelomas.[2] Although the proportion of IgM patients achieving CR was improved compared with our previous findings, it remains lower than the other isotypes, although OS now appears at least as good as usual myelomas. Other more recent reports of IgM myeloma are in keeping with our findings. In a multi-center retrospective study of 134 IgM myeloma cases, 23 patients were transplanted and outcomes were considered to be similar to those for usual myelomas.[21] Furthermore, a recent study[22] of 17 cases of IgM myeloma observed an OS of 67 months for patients receiving bortezomib before autologous transplantation.

The proportion of NS myeloma in this study is almost exactly half that found previously. As in many other reports,[2,23-25] NS status was not an adverse factor and auto-HCT may improve OS, although not always significantly. One recent matched-care control report of a stringently selected group of NS patients suggests these patients may fare slightly less well than secretory patients.[26] In contrast two recent large studies from the Swedish Myeloma Registry[27] and the Mayo Clinic[28] suggest that in the era of proteasome inhibitors and IMiDs the outcomes for NS patients is superior to usual myelomas. The advantage for NS patients in terms of superior PFS and CR rate in the current study does not appear to have converted into a significantly superior OS (although the median OS for the NS group had not yet been reached). We accept that establishment of CR in NS myeloma is less reliable than secretory myelomas, but we have worked with the available data. This may explain why the significant improvement in PFS does not appear to convert into a significantly improved OS.

The time period of this study has allowed a real-world comparison of pre-transplant induction regimens, including regimens containing no novel agents. Novel agent induction was associated with a higher rate of CR both before and after transplant. Although non-novel induction regimens were associated with inferior PFS (P= .0088 and P= .059 in univariate and multivariate analysis, respectively) (Table 2), there was no difference in OS among the different induction regimens. We postulate that patients who did not receive a novel agent at induction would have received a novel agent at relapse, leading to longer PFS and thus OS similar to patients receiving novel agents at induction.

Although not the primary focus of the CALM study, we nevertheless found that, although poor mobilization was associated with reduced PFS and OS, these differences disappeared in the multivariate analysis. Poor mobilization status has been associated with more aggressive disease biology and worse outcomes.[5] Brioli et al[4] reported significantly shorter times to progression, PFS, and OS in poor mobilizers versus standard mobilizers among patients who had received either bortezomib, thalidomide, and dexamethasone or thalidomide and dexamethasone induction. However, the multivariate analysis of the CALM data indicates that it does not significantly affect OS or PFS, suggesting that poor mobilization status is a surrogate for other indicators of poor prognosis.

In conclusion, the CALM data reinforce the poor outcome of patients with IgD myeloma but reveal that IgM and NS myelomas have outcomes comparable to those for usual myeloma.

Clinical Practice Points

- The size of most clinical trials in multiple myeloma means that there will be insufficient numbers of IgD, IgM, and NS myeloma for meaningful conclusions to be drawn. In this large post-marketing EBMT study, carried out to confirm the safety of plerixafor used to mobilize stem cells prior to autologous transplantation, the numbers were sufficient to overcome this problem.
- Despite the use of proteasome inhibitors and/or IMiDs in the induction regimen prior to transplantation, IgD myelomas continue to have poor PFS and OS (despite having a

good incidence of achieving CR). In contrast, IgM myelomas demonstrated the lowest levels of CR after transplant but have PFS and OS similar to those for the common myelomas. NS myelomas have outcomes at least as good as the common myelomas.

- We suggest that, although being a poor mobilizer is associated with a poor prognosis, this may be an indicator of an accumulation of other poor prognostic factors and not an independent indicator. Additional strategies for the better management of IgD myeloma are needed.

Disclosure

The authors have stated that they have no conflicts of interest.

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