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Outcome of Patients With IgD and IgM Multiple Myeloma Undergoing Autologous Hematopoietic Stem Cell Transplantation: A Retrospective CIBMTR Study

Donna E. Reece¹, David H. Vesole², Smriti Shrestha³, Mei-Jie Zhang³, Waleska S. Pérez³, Angela Dispenzieri⁴, Gustavo A. Milone⁵, Muneer Abidi⁶, Harold Atkins⁷, Asad Bashey⁸, Christopher N. Bredeson⁹, Willem Bujan Boza¹⁰, César O. Freytes¹¹, Robert Peter Gale¹², James L. Gajewski¹³, John Gibson¹⁴, Gregory A. Hale¹⁵, Shaji Kumar⁴, Robert A. Kyle⁴, Hillard M. Lazarus¹⁶, Philip L. McCarthy¹⁷, Santiago Pavlovsky⁵, Vivek Roy¹⁸, Daniel J. Weisdorf¹⁹, Peter H. Wiernik²⁰, and Parameswaran N. Hari³

¹Princess Margaret Hospital, Ontario, Canada

²Hackensack University Medical Center, Hackensack, NJ

³Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

⁴Mayo Clinic, Rochester, MN

⁵Fundaleu, Buenos Aires, Argentina

⁶Karmanos Cancer Institute, Wayne State University Hospital, Detroit, MI

⁷Ottawa General Hospital, Ottawa, Canada

⁸The Blood and Marrow Transplant Group of GA, Atlanta, GA

⁹Froedtert Memorial Lutheran Hospital, Milwaukee, WI

¹⁰Hospital Mexico, San José, Costa Rica

¹¹South Texas Veterans Health Care System, University of Texas Health Science Center, San Antonio, TX

¹²Celgene Corporation, Summit, NJ

¹³Oregon Health and Science University, Portland, OR

¹⁴Royal Prince Alfred Hospital, Camperdown, Australia

¹⁵All Children's Hospital, St. Petersburg, FL

¹⁶University Hospitals Case Medical Center, Cleveland, OH

Address for correspondence: Donna E. Reece, MD, Princess Margaret Hospital, 610 University Avenue, Ste 5-207, Toronto, Ontario, M5G 2M9, Canada, Fax: 416-946-6546; donna.reece@uhn.on.ca.

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¹⁷Roswell Park Cancer Institute, Buffalo, NY

¹⁸Mayo Clinic, Jacksonville, FL

¹⁹University of Minnesota Medical Center, Minneapolis, MN

²⁰New York Medical College, New York, NY

Abstract

Introduction—Immunoglobulin D (IgD) and IgM multiple myeloma represent uncommon immunoglobulin isotypes, accounting for 2% and 0.5% of cases, respectively. Limited information is available regarding the prognosis of these isotypes, but they have been considered to have a more aggressive course than the more common immunoglobulin G (IgG) and IgA isotypes. In particular, the outcome after autologous hematopoietic stem cell transplantation (auto-HCT) has not been well defined.

Patients and Methods—Using the Center for International Blood and Marrow Transplant Research (CIBMTR) database, we identified 36 patients with IgD and 11 patients with IgM myeloma among 3578 myeloma patients who received intensive therapy and auto-HCT over a 10-year period.

Results—The progression-free and overall survival probabilities at 3 years were 38% (95% CI, 21%-56%) and 69% (95% CI, 51%-84%) for IgD myeloma, and 47% (95% CI, 17%-78%) and 68% (95% CI, 36%-93%), respectively, for IgM disease. Although formal statistical analysis was limited by the small sample size, these results were comparable to those for IgG and IgA patients autografted during the same time period. Transplantation-related mortality and disease relapse/progression of myeloma were also similar for all isotypes.

Conclusion—This analysis demonstrates comparable outcomes in all immunoglobulin isotypes. Therefore, auto-HCT should be offered to eligible patients with IgD and IgM myeloma.

Keywords

Autotransplantations; IgA; IgG; Immunoglobulin isotype

Introduction

Multiple myeloma represents a malignant proliferation of plasma cells that typically produce a monoclonal immunoglobulin molecule which can be measured in the serum and/or urine. The frequency of the different immunoglobulin isotypes produced by myeloma cells recapitulates that produced normally in that immunoglobulin G (IgG) and IgA subtypes predominate. Immunoglobulin D is an uncommon isotype of this disease and represents only 2% of all myeloma cases.¹ Immunoglobulin D myeloma has been reported to occur in somewhat younger patients than other isotypes. Other features described previously include a predominance of λ light chains, and a higher incidence of light chain proteinuria, extramedullary plasmacytomas, renal dysfunction, and possibly amyloidosis.^{1,2} Clinical outcomes have been described largely in the form of single center case series, but IgD myeloma has been reported to have a more aggressive course than other immunoglobulin isotypes; 2 studies described a median survival of < 2 years in the pre-transplantation era.^{2,3}

The production of monoclonal IgM is typically seen in another B-cell malignancy, Waldenström's macroglobulinemia, which has a different natural history from multiple myeloma. However, IgM myeloma has been described, although it is even rarer than IgD disease, and accounts for approximately 0.5% of cases.⁴⁻⁸ For example, only 3 of 242 cases fulfilling the criteria of multiple myeloma in 1 series had an IgM monoclonal protein.⁴

Published reports have also suggested that IgM myeloma has a poorer prognosis than the more common isotypes.^{5,7} Recently, IgM myeloma has been found to be associated with t(11;14), which represents a translocation between the immunoglobulin heavy chain gene locus on chromosome 14 and cyclin D1 on chromosome 11; 1 case with t(4;14), an unfavorable prognostic factor, has also been reported.^{8,9}

Autologous stem hematopoietic cell transplantation (auto-HCT) has been demonstrated in randomized trials to be superior to conventional therapy alone in newly diagnosed myeloma patients.^{10,11} However, because of their rarity, limited information is available on the affect of auto-HCT on the prognosis of these isotypes. The 2 largest reports of IgD myeloma patients described treatment results in 25 and 26 patients, respectively, and approximately half of them had undergone auto-HCT. One additional single center series from Korea reported the outcome of 8 IgD patients treated with Auto-HCT.^{12–14} Only sporadic reports of auto-HCT in IgM myeloma have been published.¹⁴ A retrospective analysis of 1180 myeloma patients aggressively treated with tandem transplantations on the Total Therapy 1, 2, and 3 programs at the University of Arkansas included only 8 cases of IgD and no cases of IgM disease.¹⁵ The current study uses the database of the Center for International Blood and Marrow Transplant Research (CIBMTR) to describe the results of auto-HCT in patients with these uncommon immunologic isotypes.

Patients and Methods

Patient Population

We conducted a retrospective analysis of 3578 multiple myeloma patients who underwent auto-HCT between 1995–2005 reported to the CIBMTR, and identified 36 with IgD and 11 with IgM immunoglobulin isotypes. Plasmacytosis on bone marrow aspirates and/or biopsies was required for the diagnosis of myeloma, although independent pathology review was not required, and all patients were staged using the Durie-Salmon system. Patient characteristics are summarized in Table 1. The median follow-up of survivors was 41 months (range, 2–130 months) for IgD and 58 months (range, 5–101 months) for IgM myeloma transplant recipients.

Definitions

For this analysis, patients were considered to be responsive to pre-transplant chemotherapy if 50% reduction in serum monoclonal protein level was achieved; patients were deemed to be resistant if these criteria were not met. The European Group for Blood and Marrow Transplantation (EBMT) criteria were used to define post–auto-HCT responses and disease progression/relapse.¹⁶

Statistical Analysis

The probabilities of progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier estimator, with the variance estimated by Greenwood's formula. The probabilities of non-relapse mortality (NRM) and relapse/progression were calculated using cumulative incidence estimates to accommodate competing risks.¹⁷ Progression-free survival was defined from the date of auto-HCT until disease relapse or progression, or death from causes other than myeloma; patients were censored at the date of last follow-up without relapse or progression. The OS was calculated from the date of auto-HCT until the date of death from any cause; surviving patients were censored at the time of last follow-up. Because of the small sample size, assessments of potential prognostic factors for outcomes were not evaluated in multivariate analysis.

Results

Table 1 summarizes the characteristics of IgD and IgM patients who underwent auto-HCT. The median age of patients with IgD subtype was 52 years and 67% were male. IgM patients had a median age of 58 years and 36% were male. Compared with the IgM patients, a higher proportion of IgD patients had a creatinine over 2 mg/dL (36% vs. 9%) and produced λ light chains (59% vs. 36%). In both isotypes, the majority of patients had Durie Salmon stage III disease. Before auto-HCT, 78% of IgD patients were chemosensitive and 25% had received more than 2 lines of chemotherapy; and all IgM patients were chemosensitive and had received 2 lines of previous therapy. Bone marrow cytogenetics were not routinely available in these patients. Median time from diagnosis to transplantation was 9 months in both isotypes. The most common conditioning regimen was single-agent melphalan, and all but 1 individual with IgD disease were grafted with peripheral blood stem cells.

Table 2 outlines the outcomes of the patients with IgD and IgM isotypes. For IgD myeloma, no early deaths were reported, and the 1-year and 3-year NRM was 0% and 3% (95% CI, 0%-13%), respectively. The probability of relapse/progression was 21% at 1 year and 59% at 3 years after auto-HCT. The 1-year and 3-year PFS was 79% (95% CI, 63%-91%) and 38% (95% CI, 21%-56%), respectively, and the 1-year and 3-year OS was 87% (95% CI, 74%-97%) and 69% (95% CI, 51%-84%), respectively.

In the small group of patients with IgM myeloma, there was 1 early death, for a 100-day NRM of 9% (95% CI, 0%-32%). The 1- and 3-year NRM was 9% (95% CI, 0%-32%) and 21% (95% CI, 2%-51%); the single late death was due to a stroke. The probability of relapse/progression at 1 year was 20% (95% CI, 2%-49%) and at 3 years was 32% (95% CI, 8%-64%). For PFS, the probability at 1 year was 71% (95% CI, 41%-93%) and at 3 years was 47% (95% CI, 17%-78%), while the 1-year and 3-year OS was 91% (95% CI, 68%-100%) and 68% (95% CI, 36%-93%), respectively.

Because of the small number of patients, formal statistical comparison was not performed to compare the outcomes of patients with IgD and IgM myeloma to patients with IgG and IgA isotypes. However, outcome data for patients with IgG and IgA myeloma reported to the CIMBTR during the same accrual period were available for reference. It was of interest that the early NRM was similar (4% for IgG and 3% for IgA). The probability of relapse/progression was 16% (95% CI, 14%-19%) for IgG and 22% (95% CI, 17%-27%) for IgA myeloma at 1 year, and 34% (95% CI, 30%-37%) for IgG and 44% (95% CI, 38%-50%) for IgA disease at 3 years after transplantation. For PFS, the 1- and 3-year probabilities were 78% (95% CI, 75%-80%) and 49% (95% CI, 46%-53%) for IgG disease and 74% (95% CI, 69%-78%) and 42% (95% CI, 36%-48%) for IgA myeloma. Finally, for OS, the 1 and 3 year probabilities were 86% (95% CI, 84%-88%) and 63% (95% CI, 59%-66%) in the IgG patients and 87% (95% CI, 83%-90%) and 57% (95% CI, 53%-63%), respectively, in the IgA group.

Figure 1 shows the probability of PFS for IgD and IgM myeloma, as well as for the 1100 patients with IgG myeloma and the 375 patients with IgA myeloma who underwent auto-HCT during the same time period. Figure 2 shows the OS for these 4 patient groups. Figure 3 illustrates the cumulative incidence of NRM after auto-HCT and Figure 4 shows the cumulative incidence of relapse/progression by myeloma isotype.

The causes of death for patients with IgD and IgM myeloma are listed in Table 3. Underlying multiple myeloma was the most common cause of death in all patients, accounting for 84% of the deaths in the IgD and 20% in the IgM patients. No fatal secondary cancers were reported. Similarly, recurrent myeloma accounted for the majority of deaths among patients with IgG (63%) and IgA (67%) myeloma.

Discussion

IgD myeloma is a rare disease, and over a 10-year period, represented only 1% of all myeloma autologous transplants reported to the CIBMTR. Because of the small numbers, formal statistical comparisons with other isotypes were not feasible. However, IgD patients tended to be younger (median age 52 years compared with 58 years with all other subtypes) and frequently had a creatinine over 2 mg/dL at diagnosis (36% of patients vs. 13% for all other groups), λ light chains and the presence of urinary light chain features that are similar to those described in earlier studies. In this series, the outcome of IgD myeloma patients was comparable to other myeloma isotypes, with a low NRM and OS of 69% at 3 years. Two other small series have described the outcome of auto-HCT in IgD myeloma patients. In 1 single center report of 25 patients, the 11 who had undergone auto-HCT had a median PFS of over 4 years, compared with 1.23 years in those treated with conventional chemotherapy; the median OS was 5 years versus 2 years, respectively.¹² More recently, the outcome of 26 patients treated in different centers by the Czech Myeloma Group has been reported. Ten of these received auto-HCT as part of first-line therapy; of note, 4 of these received a second auto-HCT after relapse. The median PFS in this study was 18 months, compared with 20 months for the conventionally treated group. However, the median OS exceeded 36 months, compared with 34 months for those who received conventional therapy.¹³ Our results in a larger series of IgD patients demonstrate an efficacy of auto-HCT comparable to that seen in other myeloma isotypes. We cannot exclude in a registry analysis the possibility, however, that the results in IgD patients were favorably biased, as patients with amyloidosis, extramedullary disease such as plasma cell leukemia and severe renal dysfunction may have been excluded from auto-HCT.

The University of Arkansas group has evaluated potential prognostic factors in different myeloma isotypes in over 1000 patients treated on sequential trials of tandem transplants. The more recently treated patients had gene expression profiling (GEP) performed on CD138⁺ purified plasma cells, and were assigned risk scores and molecular subgroup designations as previously described. The 8 patients with IgD myeloma had a significantly higher incidence of cytogenetic abnormalities, and increased levels of LDH, β_2 -microglobulin, and C-reactive protein. Although the frequency of GEP-defined high-risk myeloma was comparable to that in other myeloma isotypes, significantly more IgD patients had a proliferation signature, indicating a more aggressive proliferative potential. However, the IgD isotype itself did not independently confer a shorter event-free survival (EFS) and OS.¹⁵ The association of IgD MM with more aggressive biologic features may explain the poorer results reported in some reports in the era before auto-HCT, as well as in some small transplant series.¹⁴

Even less information is available on the prognosis of patients with IgM myeloma, which accounted for 0.3% of the cases reported to the CIBMTR in the current series. In our report, the 3-year OS was virtually identical to IgD myeloma at 69%. A single early death in our series (because of hemorrhage) and late non-relapse death (as a result of stroke) occurred, which increased the overall NRM from 9% to 21% at 3 years—a cumulative incidence that is somewhat higher than reported for other isotypes. However, these findings likely reflect the small numbers of patients with IgM disease rather than an intrinsically higher risk of auto-HCT in this isotype. The OS, PFS and probability of relapse/progression in IgM myeloma patients were similar to the other myeloma isotypes.

The CIBMTR offers an opportunity for evaluating outcomes in rare disorders, and our data illustrate that the results of Auto-HCT in the IgD and IgM isotypes are comparable to those for the more common entities. These patients should be routinely considered for this therapy if otherwise eligible.

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Figure 1. Progression-Free Survival of Patients Undergoing Auto-HCT According to Immunoglobulin Isotype

Abbreviations: auto-HCT = autologous hematopoietic stem cell transplantation; Ig = immunoglobulin; PFS = progression-free survival

Figure 2. Overall Survival of Patients Undergoing Auto-HCT According to Immunoglobulin Isotype

Abbreviations: Auto-HCT = autologous hematopoietic stem cell transplantation; Ig = immunoglobulin; OS = overall survival

Figure 3. Non-Relapse Mortality After Auto-HCT According to Immunoglobulin Isotype
 Abbreviations: Auto-HCT = autologous hematopoietic stem cell transplantation; IgA = immunoglobulin; NRM = non-relapse mortality

Figure 4. Relapse/Progression After Auto-HCT According to Immunoglobulin Isotype
 Abbreviations: auto-HCT = autologous hematopoietic stem cell transplantation; IgA = immunoglobulin; NRM = non-relapse mortality

Table 1A

Characteristics of Patients Who Underwent Autologous Transplantations for IgD or IgM Multiple Myeloma, Reported to the CIBMTR Between 1995 and 2005

Characteristic	IgD	IgM
	n (%)	n (%)
Patient Related		
Number of patients	36	11
Number of centers	27	10
Median age, years (range)	52 (31–68)	58 (29–64)
Male sex	24 (67)	4 (36)
Karnofsky Score Pre-Transplant		
< 90	10 (28)	4 (36)
90	20 (55)	5 (46)
Missing	6 (17)	2 (18)
Race		
White	29 (81)	9 (82)
Non-White	7 (19)	2 (18)
Disease Related		
Durie-Salmon stage at diagnosis		
I	1 (3)	0
II	12 (33)	2 (18)
III	23 (64)	9 (82)
Hemoglobin at diagnosis		
< 10 g/dL	12 (33)	3 (27)
Albumin at diagnosis		
< 3.5 g/dL	6 (17)	2 (18)
β_2 -microglobulin level at diagnosis		
5.5 mg/L	9 (25)	0
Creatinine at diagnosis		
> 2 mg/dL	13 (36)	1 (9)
2 mg/dL	14 (39)	9 (82)
Missing	9 (25)	1 (9)
Lytic bone lesions any time before transplantation		
Yes	27 (75)	9 (82)
No	6 (17)	0
Missing	3 (8)	2 (18)
Serum light chain		
κ	12 (33)	6 (55)
Λ	21 (59)	4 (36)
Missing	3 (8)	1 (9)

Characteristic	IgD	IgM
	n (%)	n (%)
Light chain in urine at diagnosis		
Present	22 (61)	5 (45)

^aOther conditioning regimens were: etoposide (n = 1) and thiotepa (n = 1).

Abbreviations: BM = bone marrow; MR = minimal response; NR = non-response; PBSC = peripheral blood stem cell; SD = stable disease; TBI = total-body irradiation

Table 1B

Characteristics of Patients Who Underwent Autologous Transplantations for IgD or IgM Multiple Myeloma, Reported to the CIBMTR Between 1995 and 2005

Characteristic	IgD	IgM
	N (%)	N (%)
Disease Related		
Number of lines of chemotherapy		
1	16 (44)	8 (73)
2	11 (31)	3 (27)
> 2	9 (25)	0
Sensitivity to chemotherapy before transplantation		
Sensitive	28 (78)	11 (100)
Resistant	7 (22)	0
Disease status before transplantation		
Complete/partial remission	25 (71)	10 (91)
MR/NR/SD	8 (20)	1 (9)
Relapse/progression	2 (6)	0
Transplant related		
Median time from diagnosis to transplantation, months (range)	9 (3–59)	9 (7–20)
Conditioning regimen		
Melphalan alone	27 (75)	7 (64)
Melphalan + TBI	1 (3)	0
Melphalan + other	6 (16)	4 (36)
Other ^a	2 (6)	0
Graft type		
BM	1 (3)	0
PBSC ± BM	35 (97)	11 (100)
Transplantation group		
1 transplant, second not planned	25 (69)	8 (73)
2 transplants, second not planned	2 (6)	0
2 transplants, second planned (tandem)	3 (8)	2 (18)
1 transplant, second planned	6 (17)	1 (9)
Year of transplantation		
1995–1996	5 (14)	0
1997–1998	4 (11)	1 (9)
1999–2000	6 (17)	4 (37)
2001–2002	7 (19)	2 (18)
2003–2004	8 (22)	2 (18)
2005	6 (17)	2 (28)

^aOther conditioning regimens were: etoposide (n = 1) and thiotepa (n = 1).

Abbreviations: BM = bone marrow; MR = minimal response; NR = non-response; PBSC = peripheral blood stem cell; SD = stable disease; TBI = total body irradiation

Table 2

Univariate Analyses Among Patients who Underwent Autologous Transplantations for IgD, or IgM Multiple Myeloma, Reported to the CIBMTR Between 1995 and 2005

Outcomes	IgD		IgM	
	Number of Patients Evaluated	Probability, % (95% CI)	Number of Patients Evaluated	Probability, % (95% CI)
100-Day Mortality	36	0	11	9 (0–32)
NRM				
At 1 year	36	0	11	9 (0–32)
At 3 years		3 (0–13)		21 (2–51)
Relapse/Progression				
At 1 year	36	21 (9–37)	11	20 (2–49)
At 3 years		59 (41–76)		32 (8–64)
PFS				
At 1 year	36	79 (63–91)	11	71 (41–93)
At 3 years		38 (21–56)		47 (17–78)
OS				
At 1 year	36	87 (74–97)	11	91 (68–100)
At 3 years		69 (51–84)		68 (36–93)

Abbreviations: NRM = non-relapse mortality; OS = overall survival; PFS = progression free survival

Table 3

Causes of Death Among Patients who Underwent Autologous Transplantations for IgD or IgM Multiple Myeloma, Reported to the CIBMTR Between 1995 and 2005

Characteristic	IgD	IgM
	Number of Patients	Number of Patients
Number of Patients	36	11
Number of Deaths	14	5
Causes of Death		
Primary disease	12	1
Infection	1	0
GVHD ^a	1	0
Stroke	0	1
Hemorrhagic pericarditis/hemodynamic collapse	0	1
Unknown	0	2

^aPatient had a subsequent allogeneic transplantation after autologous transplantation.

Abbreviation: GVHD = graft-versus-host disease