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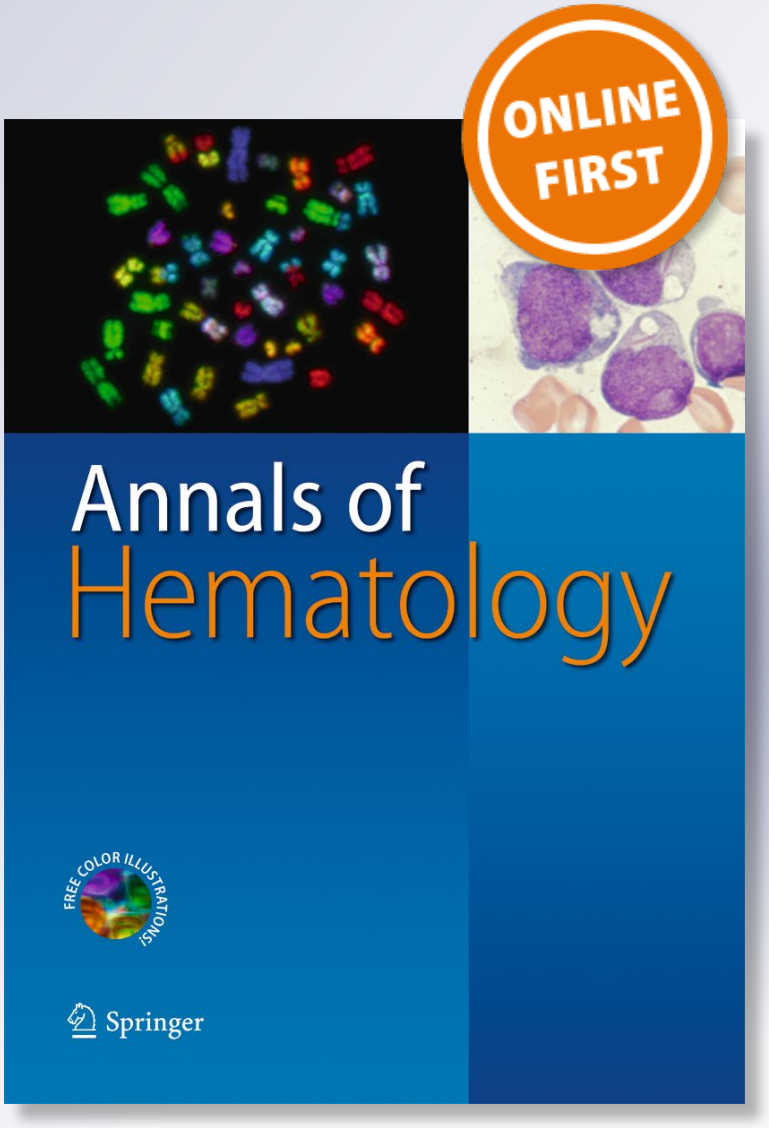

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ORIGINAL ARTICLE

Similar survival outcomes in patients with biclonal versus monoclonal myeloma: a multi-institutional matched case-control study

Artur Jurczyszyn[1] · Alessandro Gozzetti[2] · Joanna Gdula-Argasińska[1] · Jacek Czepiel[1] · Ravi Vij[3] · Mark Fiala[3] · Davila Julio Valls[4] · Krzysztof Mądry[5] · Anna Waszczuk-Gajda[5] · Sebastian Grosicki[6] · Agnieszka Barchnicka[6] · Edvan Crusoe[7] · Vania Hungria[7] · Massimo Gentile[8] · Giuseppe Mele[9] · Marcin Ksieniewicz[10] · David H. Vesole[11] · Jorge J. Castillo[12]

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Abstract Multiple myeloma is a plasma cell malignancy characterized by clonal proliferation of plasma cells in the bone marrow and associated organ damage. Usually, patients with myeloma present with a single monoclonal protein in serum and/or urine constituted by one heavy chain and one light chain. In less than 5% of the patients, more than one monoclonal protein can be identified. The aim of our retrospective multicenter matched case-control study was to describe the characteristics of cases with biclonal myeloma and compare them against a control group of monoclonal myeloma patients matched by age, sex, and year of diagnosis. A total of 50 previously untreated cases with biclonal myeloma and 50 matched controls with monoclonal myeloma were included in this study. The controls were matched (1:1) for age, sex, year of diagnosis, and participating center. There were no differences in the rates of anemia (52 vs. 59%; $p = 0.52$), renal dysfunction (36 vs. 34%; $p = 0.83$), hypercalcemia (9 vs. 16%; $p = 0.28$), or presence of lytic lesions (23 vs. 16%; $p = 0.38$) between groups. Similarly, there was no difference in the rates of overall response to therapy (85 vs. 90%; $p = 0.88$) or survival rates of cases with biclonal myeloma and controls with monoclonal myeloma (4-year survival 72 vs. 76%; $p = 0.23$). Results of our study suggest that patients with biclonal myeloma have similar response and survival rates than patients with monoclonal myeloma.

Keywords Biclonal multiple myeloma · Survival · Treatment · Clinical outcomes

✉ Artur Jurczyszyn
mmjurczy@cyf-kr.edu.pl

[1] Jagiellonian University Medical College, Kraków, Poland

[2] Azienda Ospedaliera Universitaria Senese, Siena, Italy

[3] Washington University School of Medicine, St. Louis, MO, USA

[4] Department of Hematology Hospital Universitario de Salamanca, Salamanca, Spain

[5] Medical University, Warsaw, Poland

[6] Department of Cancer Prevention, School of Public Health, Medical University of Silesia, Katowice, Poland

[7] Santa Casa Medical School, Sao Paolo, Brazil

[8] Hematology Unit, Department of Onco-Hematology, Cosenza, Italy

[9] Hematology, Ospedale A. Perino, Brindisi, Italy

[10] Department of Hematology, Bydgoszcz, Poland

[11] John Theurer Cancer Center, Hackensack UMC, Hackensack, NJ, USA

[12] Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by the clonal proliferation and accumulation of plasma cells in the bone marrow microenvironment and associated organ damage [1]. In the last decade, a great improvement in myeloma survival in both young and old patients has been seen, likely due to the introduction of agents with novel mechanisms of action [2].

Usually, patients with myeloma have a single clone that secretes a single monoclonal protein. An IgG monoclonal

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protein is produced in more than 50% of cases and IgA in 20% of cases. Another 20% of cases produce only monoclonal light chains [3]. In less than 5% of the patients, however, more than one monoclonal protein can be identified in serum and/or urine protein electrophoresis and immunofixation [4]. Given its rarity, data on response to treatment and survival of patients with biclonal myeloma are limited to case reports and small case series [5–10].

The aim of our retrospective multicenter matched case-control study was to describe the characteristics of cases with biclonal myeloma and compare them against a control group of monoclonal myeloma patients matched by age, sex, year of diagnosis, and participating center to further investigate the actual effect of biclonality on the outcomes of patients with myeloma.

Methods

Case selection

Between 2001 and 2015, cases were defined as previously untreated patients with a diagnosis of biclonal myeloma identified from the medical records at participating institutions. Biclonal myeloma was defined by the presence of two clones identified by serum or urine protein electrophoresis (SPEP/UPEP) and immunofixation (IFX).The clones could be of different heavy chain isotype (e.g., IgG, IgA or IgM), discordant FLC in the same heavy chain isotype (e.g., IgG kappa and IgG lambda), or discordant free light chain (FLC) in addition to a heavy chain isotype (e.g., IgG kappa and free lambda). Controls were defined as patients diagnosed with monoclonal myeloma based on SPEP, UPEP, and/or IFX, and were matched 1:1 for age (± 2 years), sex, year of diagnosis (± 2 years), and participating center. Pathological reports and/or samples were reviewed by expert hematopathologists at the participating institutions. The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

Data analysis

Clinical data were gathered from the medical records of patients fulfilling the inclusion criteria. Clinical parameters included age (in years), sex, heavy chain and light chain isotypes, hemoglobin level, serum calcium and lactate dehydrogenase (LDH) levels, estimated glomerular filtration rate (GFR), presence vs. absence of lytic bone lesions (as assessed by skeletal surveys or magnetic resonance imaging), international scoring system (ISS stage 1, 2, and 3), cytogenetic abnormalities (high risk vs. other), and overall survival (OS) time. Data on frontline treatment and response to treatment were also obtained. OS was defined as the time in months from diagnosis to last follow-up or death. Response to therapy was categorized into complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR) [11]. For this analysis, CR includes stringent and near CR, and NR includes stable and progressive disease. The distribution of missing data appeared random, and was as follows (biclonal vs. monoclonal): hemoglobin (4 vs. 8%), calcium level (10 vs. 2%), LDH level (6 vs. 10%), presence of bone lytic lesions (6 vs. 2%), and ISS stage (2 vs. 6%). All other data were complete.

Statistical analysis

The chi-square and the rank-sum tests were used to compare categorical and continuous variables, respectively. For the survival analysis, the Kaplan-Meier method was used to generate survival curves, which were then compared using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate survival models reported as hazard ratio (HR) with 95% confidence intervals (CI). Due to high rates of missing data, cytogenetic abnormalities were not included in the survival analyses. All reported p values are two-sided, and were considered significant if less than 0.05. Calculations and graphics were obtained using the statistical software STATA version 13.1 (College Station, Texas, USA).

Results

A total of 50 cases with biclonal myeloma and 50 matched controls with monoclonal myeloma were included in this study. Of the 50 biclonal myeloma cases, 20 (40%) were IgG (major clone) and IgA (minor clone), 10 (20%) were IgA and IgG, 8 (16%) were IgG and discordant FLC, 6 (12%) were IgG and IgM, 3 (6%) were IgG and IgG, 2 (4%) were IgA and discordant FLC, and 1 (2%) was IgA and IgM. Of the 50 monoclonal myeloma controls, 34 (68%) were restricted for IgG, 12 (24%) for IgA, and 4 (8%) for FLC. The clinical characteristics of cases and matched controls are shown in Table 1. There were no differences between biclonal myeloma cases and monoclonal myeloma controls with regards to age, sex, hemoglobin levels, estimated GFR, calcium levels, LDH levels, presence of lytic lesions, ISS stage, epoch of diagnosis, and region of participating center. Also, there were no statistical differences between cases and controls with regards to laboratory values, presence of lytic lesions, as well as frontline treatment modalities used. Regarding response, there were no differences in overall response (83 vs. 91%, respectively) as well as major response rates (50 vs. 58%, respectively) between biclonal and monoclonal myeloma patients.

Table 1 Patients' characteristics of biclonal myeloma cases versus matched monoclonal myeloma controls

	Biclonal myeloma cases (n = 50)	Monoclonal myeloma controls (n = 50)	p value
Age			
Median (IQR)	65 (58–72)	64 (58–71)	0.94
Sex			
Female	24 (48%)	24 (48%)	1.00
Male	26 (52%)	26 (52%)	
Hemoglobin			
≥ 10 g/dl	23 (48%)	19 (41%)	0.52
< 10 g/dl	25 (52%)	27 (59%)	
Estimated GFR			
> 60 ml/min/1.73 m^2	32 (64%)	33 (66%)	0.83
≤ 60 ml/min/1.73 m^2	18 (36%)	17 (34%)	
Calcium level			
Normal	41 (91%)	41 (84%)	0.28
Elevated	4 (9%)	8 (16%)	
LDH level			
Normal	40 (85%)	36 (82%)	0.67
Elevated	7 (15%)	8 (18%)	
Lytic lesions			
Absent	11 (23%)	8 (16%)	0.38
Present	36 (77%)	41 (84%)	
Stage			
ISS stage 1	12 (24%)	19 (40%)	0.25
ISS stage 2	17 (35%)	13 (27%)	
ISS stage 3	20 (41%)	15 (32%)	
Cytogenetic abnormalities			
High risk	5 (17%)	8 (28%)	0.35
Other abnormalities	24 (83%)	21 (72%)	
Epoch of diagnosis			
2001–2005	5 (10%)	3 (6%)	0.71
2006–2010	16 (32%)	15 (30%)	
2011–2015	29 (58%)	32 (64%)	
Region			
Europe	29 (58%)	29 (58%)	1.00
USA	16 (32%)	16 (32%)	
Latin America	5 (10%)	5 (10%)	

GFR glomerular filtration rate, *LDH* lactate dehydrogenase, *ISS* international scoring system

Similarly, there were no difference between cases and controls with regards to frontline therapy, as similar rates of chemotherapeutic agents, immunomodulating drugs, and/or proteasome inhibitors were used in both groups, with similar rates of complete, very good partial, partial, and no response between groups. There were no differences between the rates of patients who underwent autologous transplant or maintenance therapy. Detailed information on treatment and response rates are shown in Table 2.

With a median follow-up time of 43 months (95% CI 32–59 months), 42 patients (33%) had died, 20 (40%) in biclonal myeloma cases, and 15 (30%) in monoclonal controls. The median OS for the entire cohort was 63 months (95% CI 55–123 months). The median OS for biclonal myeloma cases was 58 months (95% CI 55–127 months), and for monoclonal controls was 77 months (95% CI 52–123 months). The 4-year OS for biclonal cases was 72% (95% CI 55–84%), and for monoclonal controls was 76% (95% CI 55–88%). There was no difference in the survival distribution of biclonal cases and monoclonal controls (p = 0.23; Fig. 1). Older age, estimated GFR ≤ 60 ml/min, elevated LDH levels and ISS stage 3 were factors also associated with worse survival outcomes in the univariate analysis. Detailed information on the univariate survival models is shown in Table 3.

Table 2 Frontline treatment and response in biclonal myeloma cases versus matched monoclonal myeloma controls

	Biclonal myeloma cases (n = 50)	Monoclonal myeloma controls (n = 50)	p value
Frontline treatment			
Chemotherapy + IMIDs	15 (30%)	17 (34%)	0.15
Chemotherapy + PIs	13 (26%)	11 (22%)	
IMIDs + PIs	7 (14%)	13 (26%)	
Chemotherapy + IMIDs + PIs	1 (2%)	1 (2%)	
Chemotherapy only	3 (6%)	0 (0%)	
IMIDs only	8 (16%)	2 (4%)	
PIs only	3 (6%)	6 (12%)	
ASCT	19 (38%)	21 (42%)	0.68
Maintenance	4 (8%)	5 (10%)	0.73
Response to treatment			
Complete response	12 (26%)	14 (28%)	0.88
Very good partial response	12 (26%)	12 (24%)	
Partial response	16 (34%)	19 (38%)	
No response	7 (15%)	5 (10%)	

IMIDs immunomodulatory drugs, *PIs* proteasome inhibitors, *ASCT* autologous stem cell transplantation

Discussion

To the best of our knowledge, this is the largest study to date retrospectively describing the characteristics and outcomes of 50 biclonal myeloma cases and comparing them to 50 monoclonal myeloma controls matched for age, sex, year of diagnosis, and participating center. Other clinical features such as anemia, renal dysfunction, hypercalcemia, and presence of lytic lesions were relatively well balanced between groups. Our study shows that when receiving similar treatment approaches (including ASCT), biclonal myeloma does not portend a worse or better prognosis than monoclonal myeloma.

In a previous study, biclonality was not associated with a faster progression rate towards active myeloma in patients with monoclonal gammopathy of undetermined significance [12]. Additionally, both clones appear to respond well to therapy. Although the dominant clone in almost all cases was responsible for relapse. However, no comparative analyses were performed against patients with monoclonal myeloma. Our study, argues against a difference in response and/or survival outcomes between patients with biclonal and monoclonal myeloma. Although not specifically balanced for treatment, our study did not show differences on how biclonal myeloma is being treated when compared to monoclonal controls, as similar rates of chemotherapy, immunomodulatory drugs, proteasome inhibitors, and/or autologous stem cell

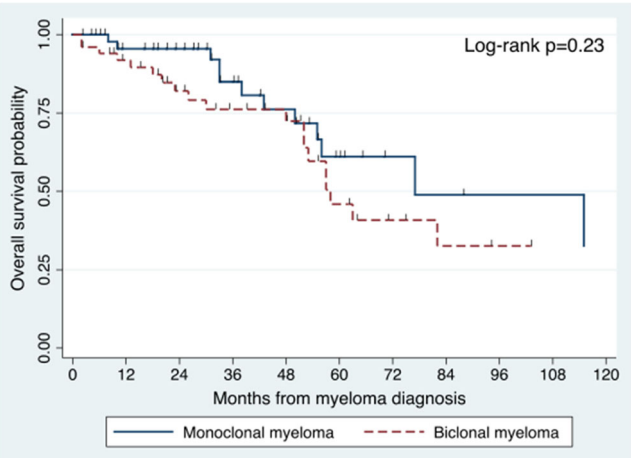

Fig. 1 Overall survival curves in biclonal myeloma cases versus matched monoclonal myeloma controls

Table 3 Univariate models for overall survival in patients with biclonal myeloma cases versus matched monoclonal myeloma controls

	Univariate analysis	
	HR (95% CI)	p value
Age	1.04 (1.00–1.09)	0.04
Male sex	1.88 (0.90–3.89)	0.09
Hemoglobin ≥ 10 g/dl	1.42 (0.64–3.13)	0.38
Estimated GFR ≤ 60 ml/min	2.43 (1.20–4.93)	0.01
Elevated calcium	1.31 (0.53–3.23)	0.56
Presence of lytic lesions	1.23 (0.47–3.20)	0.67
Elevated LDH	3.74 (1.41–9.90)	0.008
ISS stage 2 vs. stage 1	1.01 (0.43–2.42)	0.98
ISS stage 3 vs. stage 1	2.32 (1.05–5.11)	0.04
Biclonal myeloma	1.54 (0.76–3.10)	0.23

HR hazard ratio, *CI* confidence interval, *GFR* glomerular filtration rate, *ISS* international scoring system, *LDH* lactate dehydrogenase

transplant (ASCT) were observed. Therefore, it is our recommendation that patients with biclonal myeloma should be treated identical to patients with monoclonal myeloma.

Recent studies have shown that myeloma is not composed of a single neoplastic clone but rather a collection of multiple subclones, which can develop by either natural progression of the disease or by the stress derived by continual exposure to therapy [13, 14]. The progression of myeloma was historically thought to follow a multistep linear process in which genomic hits are acquired sequentially, increasing genetic complexity. Next-generation sequencing (NGS) techniques, however, have shown that mutations in myeloma are present at different frequencies within a tumor sample. This finding has been defined as intraclonal heterogeneity and appears to be a relevant feature of myeloma. With these NGS techniques, an average five different major subclones can be detected at diagnosis in myeloma, and serial genomic analyses of samples collected at different points during disease progression have found that myeloma can progress following both linear and branching patterns [15, 16]. A potential interesting research endeavor could focus on studying the patterns of genetic heterogeneity in cases of biclonal myeloma.

Our study, however, is not without limitations. The median follow-up time for the entire cohort was 3.5 years, which can be considered short. The short clinical follow-up could be a consequence of the heterogeneity of the patient cohorts that overlap almost two decades of treatment algorithms in five different countries. Nevertheless, a median follow-up time of 3.5 years could be clinically relevant, specifically to identify a group of patients who will succumb early in the course of the disease. Given the retrospective nature of our study, it is possible that selection bias could have been introduced. To mitigate this limitation, the cases and controls were adequately matched for age, sex, year of diagnosis, and participating center. With a sample size of 50 biclonal cases and 50 monoclonal controls, our study could have been underpowered to show a difference in survival between groups. However, with our sample size, we had 80% power of identifying a statistically significant difference in survival at 4 years, assuming 75% survival rate in one group and 50% survival rate in the other group. In our study, biclonal and monoclonal cases has a 4-year OS of 74 and 72%, respectively. Finally, studies like ours usually suffer from missing data. In our study, specifically, the rate of missing data was 10% or lower with exception of cytogenetic abnormalities in which missing data was over 30%. For this reason, we excluded this factor from study analysis.

In conclusion, the presence of a second clone in myeloma patients does not seem to affect response rates to frontline treatment or survival rates. Open questions remain with regard to intrinsic biological and/or genetic characteristics of the two clones present and how they may affect aggressiveness of subsequent relapses.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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