



splenectomy thrombosis history. Post-splenectomy thrombosis occurred in none (0%) of the 17 patients receiving preemptive full systemic heparinization; by contrast, the particular complication occurred in 15 (26%) of 58 patients receiving low systemic heparinization and 17 (40%) of 43 patients receiving no systemic anticoagulation ($P = .002$). Of note, there was no difference, among the different treatment groups, in age ($P = .35$) and sex ($P = .12$) distribution, presence or absence of pre-splenectomy thrombosis history ($P = .52$), platelet ($P = .26$) or leukocyte ($P = .8$) counts or major hemorrhagic events prior or after the institution of anticoagulant therapy (Table 1). At the time of this writing, 95 (79%) deaths and 30 (25%) leukemic transformations were documented; postsplenectomy overall and leukemia-free survivals were not affected by either thrombosis history before splenectomy or the occurrence of early thrombotic event following splenectomy ($P > .2$ in all instances).

This study provides evidence that suggests the antithrombotic superiority of full therapeutic dose heparin therapy, compared to treatment with lower dose heparin or no systemic anticoagulation, in preventing early thrombotic complications, following splenectomy in MF. The fact that >90% of these incidents constituted venous thrombosis is in line with consistent with the observation regarding the most optimal treatment strategy; furthermore, it is possible that the procoagulant nature of the underlying disease (ie, myeloproliferative neoplasm often associated with JAK2 mutation) might have contributed to the need for higher heparin dose. A similar argument can be made to explain the difference in the incidence of postsplenectomy thrombosis between patients receiving low-dose heparin and those not receiving systemic anticoagulation. The retrospective nature of our study dictates that our observations should be considered preliminary but worthy of further perusal in a controlled setting.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

ORCID

Mythri Mudireddy <http://orcid.org/0000-0002-0550-8933>

Naseema Gangat <http://orcid.org/0000-0002-9104-6172>

Ayalew Tefferi <http://orcid.org/0000-0003-4605-3821>

Mythri Mudireddy¹

Naseema Gangat¹

Terra L. Lasho¹

Christy Finke¹

Curtis A. Hanson²

Rhett P. Ketterling²

Aneel A. Ashrani¹

Animesh Pardanani¹

David M. Nagorney³

Ayalew Tefferi¹

¹Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota

²Department of Laboratory Medicine, Mayo Clinic, Rochester, Minnesota

³Department of Surgery, Mayo Clinic, Rochester, Minnesota

Correspondence

Ayalew Tefferi, Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905.

Email: tefferi.ayalew@mayo.edu

REFERENCES

1. Tefferi A, Mesa RA, Nagorney DM, Schroeder G, Silverstein MN. Splenectomy in myelofibrosis with myeloid metaplasia: a single-institution experience with 223 patients. *Blood*. 2000;95:2226-2233.
2. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114:937-951.
3. Passamonti F, Cervantes F, Vannucchi AM, et al. Dynamic international prognostic scoring system (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. *Blood*. 2010;116:2857-2858.

Received: 13 June 2018

Accepted: 18 June 2018

DOI: 10.1002/ajh.25209

Clinical characteristics and treatment outcomes in IgE multiple myeloma: A case-control study

To the Editor:

Although the clinical features of IgE multiple myeloma (MM) are generally believed to be similar to other MM isotypes, this assumption is based primarily on single case reports and a few small case series, usually published before the novel agent era.¹ The characteristics of IgE MM patients have not been formally compared with other MM isotypes.

We analyzed the clinical features and outcomes of patients with IgE MM and age-, sex-, and center-matched controls with IgG MM. The retrospective chart review included data from 9 clinical centers in Hungary, Italy, Israel, Poland and the United States. In total 18 patients diagnosed with IgE MM in 1982-2016 were compared with 54 age-, sex- and center-matched IgG MM controls diagnosed during the same period.

The clinical and laboratory features are presented using descriptive statistics. Response was assessed using the International Myeloma Working Group consensus criteria, either current,² or older versions depending on the date the patients were diagnosed. Between-group comparisons were performed using chi-square, Fisher exact and Mann-Whitney U-tests, when appropriate. Overall survival (OS) was estimated using the Kaplan-Maier method and compared with log-rank test. All reported *P*-values are 2-sided and were

considered significant if $< .05$. Calculations and graphics were obtained using the STATA (StataCorp, College Station, TX, USA).

Median age of patients with IgE MM was 60 years, and male to female ratio for this group was 1.25:1. No statistically significant differences were detected in laboratory and clinical characteristics of patients with IgE MM and IgG MM at the time of the diagnosis (Table 1). The study groups were also similar in terms of the cytogenetic abnormality profiles; however, these parameters were not subjected to statistical analysis because of a low proportion of patients with available data.

The indication for treatment in the IgE MM group included MM-related bone disease (12/14, 86%), constitutional symptoms (5/14, 36%), anemia (3/14, 21%), renal failure (1/12, 7%), and/or paresthesia (1/12, 7%). Patients with IgG MM were qualified to treatment due to bone disease (21/26, 81%), anemia (8/26, 38%), and/or constitutional symptoms (7/26, 27%).

16/18 (89%) patients with IgE MM and 51 (94%) with IgG MM received a first line treatment. Immunomodulatory drugs (IMiDs) were administered to 37.5% vs 61%, proteasome inhibitors (PIs) to 62.5%

vs 45%, and conventional chemotherapy to 69% vs 47% of individuals with IgE MM and IgG MM, respectively. In 7/16 (44%) patients with IgE MM and in 36/51 (47%) with IgG MM, the first line treatment was followed by autologous stem cell transplantation (ASCT).

Responses to the first line treatment were evaluable in 10/16 (62.5%) patients with IgE MM and in 34/51 (67%) with IgG MM. These included complete response (CR) in 40% vs 26%, very good partial response in 30% vs 35%, and partial response (PR) in 30% vs 26%, for IgE and IgG MM, respectively. The overall response rate (ORR) in the evaluable IgE MM and IgG MM patients were 100% (10/10) and 88% (30/34), respectively.

The median follow-up for IgE MM and IgG MM groups was 8.1 years (95% CI 3.7-9.9) and 7 years (95% CI 5.2-11.7), respectively. A total of 7/18 (39%) patients with IgE MM and 20/54 (37%) with IgG MM died during the follow-up period. Cause of death was reported in 3/7 (43%) patients with IgE MM (disease progression, amyloidosis and secondary plasma cell leukemia—PCL), and unknown in the remaining 4 cases. Median OS was not reached in either IgE MM or IgG MM group. 5-year OS rates for patients with IgE MM

TABLE 1 Clinical and laboratory characteristics of 18 patients with IgE MM and 54 controls with IgG MM

Parameter	IgE MM (n = 18)		IgG MM (n = 54)		P-value
	Valid (n)	Result	Valid (n)	Result	
Age (years)	18	60 (35-77)	54	60 (38-86)	.780
Men (n)	18	10 (56%)	54	30 (56%)	1.000
ISS stage (n)					
ISS I	11	8 (73%)	36	13 (36%)	.090
ISS II	11	2 (18%)	36	11 (31%)	
ISS III	11	1 (9%)	36	12 (33%)	
R-ISS stage (n)					
I	8	5 (63%)	14	5 (36%)	.550
II	8	3 (38%)	14	7 (50%)	
III	8	0 (0%)	14	2 (14%)	
Light chain MM (N)	18	11 (61%)	45	28 (62%)	.940
Hemoglobin (g/dL)	16	11.0 (8.4-14.0)	43	10.5 (7.1-13.9)	.430
GFR (mL/min)	9	45 (9-99)	39	69 (25-99)	.050
Serum ca (g/dL)	15	10.0 (9.0-12.7)	39	9.5 (8.1-18.4)	.080
Serum albumin (g/dL)	11	3.6 (2.6-4.9)	42	3.7 (2.5-5.0)	.890
Serum B2M (g/dL)	12	3.2 (1.7-17.8)	46	3.7 (0.7-18.6)	.600
Lytic lesions (N)	12	10 (83%)	31	26 (84%)	.970
Flow cytometry (N)					
CD38	6	6 (100%)	9	9 (100%)	N/A
CD138	6	6 (100%)	9	9 (100%)	
CD20	6	0 (0%)	9	1 (11%)	
CD56	6	3 (50%)	3	3 (100%)	
Cytogenetic data (N)					
t(11;14)	11	2 (18%)	20	3 (15%)	N/A
del13q	11	2 (18%)	20	4 (20%)	
del17p	11	2 (18%)	20	3 (15%)	
t(14;4)	11	1 (9%)	20	3 (15%)	
t(14;16)	11	0 (0%)	20	1 (5%)	

Abbreviations: ISS, International Staging System; R-ISS, Revised International Staging System; GFR, glomerular filtration rate; B2M, beta-2-microglobulin; N/A, not applicable. Results presented as medians (ranges) or numbers (percentages).

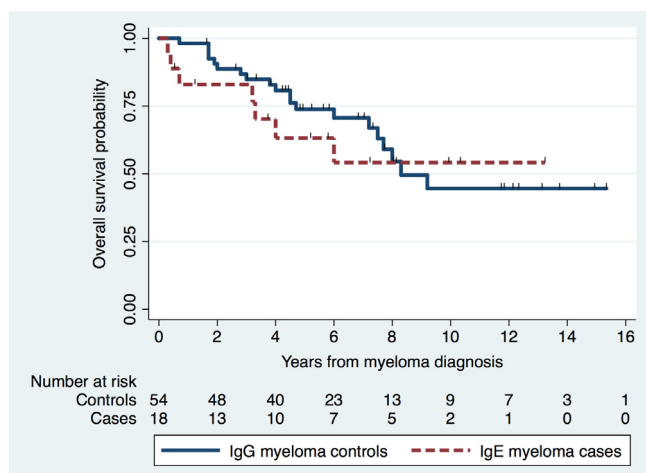


FIGURE 1 OS estimates in 18 patients with IgE MM and 54 controls with IgG MM

and IgG MM were 63% (95% CI 35%-82%) and 74% (95% CI 59%-84%), respectively, and 10-year OS rates were 54% (95% CI 26%-76%) and 45% (95% CI 26%-62%), respectively (Log-rank $P = .630$; Figure 1).

Our findings suggest that the clinical characteristics and outcomes in IgE MM were similar as in the more common IgG MM. This observation is consistent with the data from previously published individual case reports and small case series. According to Macro et al.,³ who reviewed data from 29 case reports on IgE MM published between 1967 and 1992, this condition was diagnosed at a mean age of 62 years, and there was a slight preponderance of male patients (male to female ratio 1.23:1); both these values were similar as documented in our series. Although anemia, osteolytic lesions, hepatomegaly and/or splenomegaly, and PCL were frequently reported in IgE MM, none of those manifestations seem to constitute a characteristic feature of this condition.^{1,3,4}

Prognosis for IgE MM was postulated to be worse than for other MM types, with a median survival of 12.5 months,³ even after ASCT.⁵ However, those data originate from the preIMiD and prePI era. The evidence from more recently published case reports suggests that the outcomes in IgE MM patients treated with novel agents, such as bortezomib, lenalidomide, or thalidomide, are markedly better.⁶ Our findings are consistent with those data, implying that prognosis in patients with IgE MM treated with IMiDs (38%) and/or PIs (63%) and ASCT (44%) may be no worse than in IgG MM.

This study was not free from potential limitations, such as the presence of missing data on clinical and laboratory findings, especially immunophenotypic and cytogenetic characteristics of IgE MM. Moreover, it should be remembered that IgE status is not routinely examined in many centers and hence, some patients with IgE MM may be misdiagnosed with light chain MM. Consequently, our series might not be fully representative for the whole population of patients with IgE MM. Nevertheless, our results suggest that the clinical and laboratory characteristics of IgE MM are similar to IgG MM, and in the era of novel therapeutic agents, the prognosis in this rare condition may be better than previously reported.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the article.

Designed the study and drafted the initial article: Jurczyszyn, Castillo, Vesole

ORCID

Artur Jurczyszyn <http://orcid.org/0000-0001-9796-8365>

Jorge J. Castillo <http://orcid.org/0000-0001-9490-7532>

Anna Waszczuk-Gajda <http://orcid.org/0000-0001-5626-1750>

Morie A. Gertz <http://orcid.org/0000-0002-3853-5196>

Artur Jurczyszyn¹

Jorge J. Castillo²

David H. Vesole³

Jieqi Liu⁴

Irit Avivi⁵

Anna Waszczuk-Gajda⁶

Ewa Lech-Maranda^{7,8}

Massimo Gentile⁹

Gabor Mikala¹⁰

Thomas Guerrero-Garcia¹¹

Anna Suska¹

Morie A. Gertz¹²

¹Department of Hematology, Jagiellonian University Medical College, Cracow, Poland

²Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

³John Theurer Cancer Center, Hackensack University Medical Center, Jersey

⁴Rutgers New Jersey Medical School, Newark, New Jersey

⁵Tel Aviv Medical Center, Israel

⁶Department of Hematology, Oncology and Internal Diseases, Warsaw Medical University, Warsaw, Poland

⁷Institute of Hematology and Transfusion Medicine, Warsaw, Poland

⁸Centre of Postgraduate Medical Education, Warsaw, Poland

⁹Hematology Unit, Department of Onco-Hematology, A.O. of Cosenza, Cosenza, Italy

¹⁰Department of Hematology and Stem Cell Transplantation, South-Pest Central Hospital, National Institute of Hematology and Infectology, Budapest, Hungary

¹¹Dana-Farber Cancer Institute at St Elisabeth's, Boston, Massachusetts

¹²Division of Hematology, Mayo Clinic, Rochester, Minnesota

Correspondence

Artur Jurczyszyn, Jagiellonian University Medical College, Department of Hematology, 17 Kopernika Str  e, 31-501 Cracow, Poland.

Email: mmjurczy@cyf-kr.edu.pl

Additional Supporting Information may be found online in the supporting information tab for this article.

REFERENCES

1. Pandey S, Kyle RA. Unusual myelomas: a review of IgD and IgE variants. *Oncology*. 2013;27(8):798-803.
2. Kumar S, Paiva B, Anderson KC, et al. International myeloma working group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346.
3. Macro M, André I, Comby E, et al. IgE multiple myeloma. *Leuk Lymphoma*. 1999;32(5-6):597-603.
4. Kairemo KJ, Lindberg M, Prytz M. IgE myeloma: a case presentation and a review of the literature. *Scand J Clin Lab Invest*. 1999;59(6):451-456.
5. Morris C, Drake M, Apperley J, et al. Efficacy and outcome of autologous transplantation in rare myelomas. *Haematologica*. 2010;95(12):2126-2133.
6. Sato H, Komiya Y, Hoshino S. Bortezomib plus melphalan and prednisone (VMP regimen) as the initial treatment for IgE multiple myeloma: a case study. *Int J Hematol*. 2014;99(6):786-789.

Received: 13 June 2018

Accepted: 18 June 2018

DOI: 10.1002/ajh.25208

Drug-induced thrombotic microangiopathy: An updated systematic review, 2014-2018

To the Editor:

In 2015, we reported our systematic review of publications, 1946-March 2014, describing patients with drug-induced thrombotic microangiopathy (DITMA) and defining criteria for levels of evidence supporting a causal association of the drug with TMA. We identified 78 drugs that were reported to cause TMA; 22 of the 78 drugs had definite evidence for a causal association with TMA.¹ We also reported the DITMA experience of the Oklahoma Registry and the BloodCenter of Wisconsin.²

In March 2018, we updated our systematic review (Table S1, Supporting Information). Fifty-nine articles reported evaluable data for 111 individual patients with TMA attributed to 24 drugs; 2 articles reported group data on 3 drugs (Table S2). Twenty of the 59 articles presented data on 8 drugs (41 patients) that provided definite evidence supporting a causal association with TMA. Table 1 summarizes the data for these 8 drugs.

Opioids: oxymorphone-extended release (Opana-ER) and oxycodone-extended release (oxycontin). Nine reports described 28 patients with Opana-ER-induced TMA, all from the United States. Our previous review¹ identified only one report of Opana-ER-induced TMA. That report was the initial epidemiologic description by the Centers for Disease Control, however their data only supported a probable causal association with TMA. One of the 9 reports identified by our current

literature search described 18 episodes of TMA in 15 patients from one hospital for 14 months.³ Another report⁴ described 3 patients and definitively documented the etiology of Opana-ER-induced TMA. In 2012, extended-release oxymorphone tablets were reformulated to contain a crush resistant, insoluble inert ingredient containing high molecular weight (~7 000 000 Da) polyethylene oxide (PEO). The goal of this reformulation was to deter the intravenous abuse that involved crushing the tablets and solubilizing the oxymorphone. Hunt et al.⁴ determined that the cause of TMA was the PEO, not the oxymorphone. Their initial clue was the presence of gelatinous material that occluded the apheresis tubing during therapeutic plasma exchange. Using the same process that the patients used to solubilize Opana-ER tablets, they estimated that the patients' plasma concentration of PEO would be ~5 µg/mL. This concentration of PEO in guinea pigs recapitulated the pathologic features of TMA. PEO altered blood flow causing vessel wall shear stress and mechanical red cell damage; the intense hemolysis caused kidney injury.⁴

Oxycodone tablets were similarly reformulated with PEO to produce long-acting, tamper-resistant oxycontin, which was approved in Australia in 2014. Three reports, from Australia, 2015-2017, provided definite evidence for a causal association of oxycontin with TMA, presumably also caused by the PEO.

These data illustrate a new aspect of the global opioid epidemic. Clinicians evaluating patients with clinical features of TMA must be alert for IV opioids as a potential etiology.

Proteasome inhibitors. Recognition of proteasome inhibitors as a cause of TMA was also increased in our current review. Our previous review identified 3 reports of describing bortezomib-induced TMA, but the evidence only supported a possible or unlikely causal association.¹ In this review, there were 5 reports with definite evidence supporting a causal association for bortezomib (1 patient), carfilzomib (4 patients), and ixazomib (1 patient). The authors suggested that proteasome inhibitors as a class may have a risk for acute kidney injury with the hematologic abnormalities of TMA.⁵ Clinicians must be alert for the clinical features of TMA with the use of these 3 drugs and also the new proteasome inhibitors, marizomib, and oprozomib, currently in clinical trials.

Palbociclib, a selective inhibitor of cyclin-dependent kinases, CDK4 and CDK6, received FDA approval in 2015 for advanced ER+, HER-2-negative breast cancer. The principal previously reported adverse effects were neutropenic infections and thrombocytopenia. Our review identified the report of one patient who developed hemiparesis and fluctuating aphasia with microangiopathic hemolysis, thrombocytopenia, and acute kidney injury after 2 weeks of daily oral palbociclib. Two weeks after palbociclib was stopped, her hematocrit and platelet count recovered but her neurologic and kidney abnormalities persisted.

Intravenous immunoglobulin (IVIg). Although IVIg has been previously associated with venous thrombosis and kidney injury, these adverse effects are uncommon and may be related to specific IVIg products. The 2 patients, reported from Australia, had a failure of their kidney allografts and were treated with IVIg for BK virus infection. The patients became febrile and oliguric following the infusion; increased serum creatinine, thrombocytopenia, and anemia occurred during the next several days. Both patients had kidney biopsies