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ORIGINAL ARTICLE

Clinical characteristics and prognosis of immunoglobulin D myeloma in the novel agent era

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Abstract

Immunoglobulin D (IgD) myeloma is a rare subtype that used to lead to a poor outcome. To investigate the current clinical features, cytogenetic changes and survival of patients with IgD myeloma under novel treatments, we analysed 47 patients with IgD myeloma, 31 men and 16 women, with a median age of 54.5 years. We found that IgD myeloma was associated with higher frequencies of anaemia, renal failure, and hypercalcemia and higher levels of serum LDH compared with non-IgD myeloma. More than 90% of patients with IgD myeloma had at least one cytogenetic abnormality demonstrated by fluorescence in situ hybridisation (FISH). IGH translocations were the most common abnormalities, which were mainly caused by t(11;14). Moreover, 36.2% of patients were at the Revised International Staging System (RISS) stage III when diagnosed. Those patients had significantly shorter PFS and OS compared with patients at RISS stages I and II. In conclusion, IgD myeloma has specific clinical characteristics. The RISS grade was shown to be a simple and effective method to predict the prognosis of patients with IgD myeloma.

Keywords Multiple myeloma · Immunoglobulin D · Revised international staging system · Cytogenetic · Prognosis

Introduction

Multiple myeloma (MM) is a malignancy of plasma cells that produce a complete and/or partial (light chain) monoclonal immunoglobulin protein. The immunoglobulins can have unique idiotypes. Immunoglobulin D (IgD) is a rare subtype, and most IgD myelomas are of the lambda light-chain variety. It has been reported that IgD myeloma is associated with high frequencies of renal failure, hypercalcemia, extramedullary involvement, osteolytic lesions, anaemia and amyloidosis. Moreover, patients with IgD myeloma may have an inferior outcome compared with other patients [1–6]. Over the past 10 years, substantial progress has been made in myeloma treatments, including novel agents and autologous stem cell transplantation. These developments have shown effectiveness against the disease and have benefited most myeloma patients [7–11].

Cytogenetic abnormalities in myeloma affect every aspect of the disease, including the evolution of the disease, response to therapy and prognosis. The deletion of 17p, t(4;14) and t(14;16) is associated with high-risk myeloma. In addition, a high serum level of lactate dehydrogenase (LDH) has been linked to drug resistance and aggressive disease [12–16]. The Revised International Staging System (RISS) has combined these prognostic factors and has been demonstrated to be a simple and powerful prognostic staging system [17, 18].

In this report, we performed an analysis of the clinical features, cytogenetic changes and survival in patients with IgD myeloma in our hospital between 2007 and 2015.

Materials and methods

Patients

We identified 47 patients with IgD myeloma between 2007 and 2015 in our hospital. A variety of clinical factors were analysed and compared with those of non-IgD patients. RISS stage I was defined as ISS stage I with no

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high-risk chromosomal abnormalities [del(17p) and/or t(4;14) and/or t(14;16)] and a normal LDH level; stage III included patients with ISS stage III and either high-risk chromosomal abnormalities or a high LDH level; and stage II included all the patients who had neither stage I nor stage III disease [18].

The response to treatments was evaluated according to the International Myeloma Working Group criteria [19]. Progression-free survival (PFS) was calculated from the date of diagnosis until disease progression or death. Overall survival (OS) was calculated from the date of diagnosis until death.

iFISH

Plasma cells were isolated by CD138 microbeads (Miltenyi Biotec, Bergisch Gladbach, Germany). Plasma cell purity was often over 85%. Interphase FISH (iFISH) was carried out according to the manufacturer's instructions. Probes targeting the following molecules were used to detect cytogenetic aberrations: RB1 (13q14), P53 (17p13), CKS1B (1q21), IGH (14q32), IGH/CCND1, IGH/MAF, IGH/FGFR3 (Abbott molecular, IL, USA), IGH/MAFB and IGH/CCND3 (Cytocell, Cambridge, UK).

Statistical analysis

All statistical analyses were performed with the SPSS program (IBM, version 19.0, NY, USA). Contingency tables using the χ^2 statistic were used for comparisons between groups. PFS and OS were estimated by the Kaplan-Meier method and compared by a log-rank test.

Results

Clinical characteristics

In total, 47 patients with IgD myeloma were confirmed in this study and represented 7.5% of all 623 newly diagnosed MM patients in our hospital between 2007 and 2015. There were 31 men and 16 women, with a median age of 54.5 years (range, 33–78 years). The clinical characteristics of patients are summarised in Table 1. Compared with other myeloma patients, patients with IgD myeloma had higher frequencies of anaemia, renal failure, hypercalcemia and a higher level of serum LDH ($p < 0.05$). Moreover, patients with IgD myeloma showed advanced disease. Among the patients, 76.6% were at ISS stage III at the time of diagnosis ($p = 0.001$), and 36.2% were at stage III according to RISS ($p = 0.155$).

Cytogenetic abnormalities

Our results showed that 91.5% (43/47) of the patients with IgD myeloma had at least one cytogenetic abnormality demonstrated by fluorescence in situ hybridization (FISH). The frequencies of the abnormalities are shown in Table 2. About three fourths of the patients had abnormalities involving IGH, which was much higher than that of patients with non-IgD myeloma (72.3% vs 49.1%, $p = 0.002$). Common translocations in patients with IgD myeloma included t(4;14), t(6;14) and mostly t(11;14), the incidence of which was higher than in patients with non-IgD myeloma (31.9% vs 17.9%, $p = 0.018$). Among IgD myeloma patients, amplification of 1q21 was the second most frequent aberration, followed by 13q deletion, which occurred in 31.9% (15/47) of patients; 17.0% (8/47) of the patients had 17p deletion.

Treatment response and survival

Among the 47 patients with IgD myeloma, 68.1%(32/47) were treated with bortezomib-based chemotherapy, which contained BD (bortezomib and dexamethasone), VTD (bortezomib, thalidomide and dexamethasone), VCD (bortezomib, cyclophosphamide and dexamethasone) and PAD (bortezomib, Adriamycin and dexamethasone), and 31.9%(15/47) were treated with traditional therapies that contained MPT (melphalan, prednisone and thalidomide) and VAD (vincristine, doxorubicin and dexamethasone); and 5 patients received autologous haematopoietic stem cell transplantation (ASCT). Among the IgD patients, 19.1% (9/47) achieved CR, including 12.8% (6/47) with sCR. The overall response rate was 80.9%.

After a median follow-up of 39 months (range, 9–83 months), 4 patients were lost to follow-up, and 19 patients had died. Among the patients with IgD myeloma, the OS of patients who carried the 17p deletion was significantly shorter compared with that of patients without the deletion (median OS 12 months vs 46 months, $p < 0.001$). The PFS of patients with the 17p deletion was also decreased (median PFS 12 months vs 28 months, $p = 0.005$). Moreover, translocation of t(4;14) was strongly associated with shorter OS (median OS 12 months vs 60 months, $p < 0.001$) and PFS (median PFS 12 months vs 28 months, $p = 0.001$). Other genetic aberrations, such as deletion of 13q, amplification of 1q21 and t(11;14), had no significant relationships with prognosis. Meanwhile, patients with a higher LDH level had shorter PFS (median PFS 15 months vs 28 months, $p = 0.046$) and OS (median OS 38 months vs 60 months, $p = 0.055$).

ISS staging system did not work well in predicting patients' survivals of IgD myeloma because most patients were at ISS stage III when diagnosed. We analysed the connection between RISS stage and survivals in patients with IgD myeloma. Our results showed that patients at RISS stage III had

Table 1 Clinical characteristics of patients with IgD and non-IgD myeloma

Characteristics	IgD MM ($N = 47$)		Non-IgD MM ($N = 576$)		p value
	No. of patients	(%)	No. of patients	(%)	
Gender					
Male	31	66.0	343	59.5	0.388
Female	16	34.0	233	40.5	
Median age (years)	54.5 (33–78)		57 (31–85)		
Age (years) < 65	36	76.6	422	73.3	0.619
ISS stage					
I	4	8.5	164	28.5	0.003
II	7	14.9	115	20.0	0.400
III	36	76.6	297	51.6	0.001
RISS stage					
I	3	6.4	144	25.0	0.004
II	27	57.4	279	48.4	0.235
III	17	36.2	153	26.6	0.155
Haemoglobin level < 8.5 g/dL	34	72.3	305	53.0	0.010
Platelet counts < 100G/L	15	31.9	116	20.1	0.057
Serum LDH level ≥ 245 IU/L	15	31.9	78	13.5	0.001
Serum calcium level ≥ 2.65 mmol/L	18	38.3	67	11.6	< 0.001
Serum creatinine ≥ 2 mg/dL	22	46.8	118	20.5	< 0.001
Treatments					
Bortezomib-based therapies	32	68.1	402	69.8	0.807
Traditional chemotherapies	15	31.9	174	30.2	0.807
Autologous stem transplant	5	10.6	57	9.9	0.676

significantly shorter PFS (median PFS 12 months vs 29 months, $p < 0.001$) and OS (median OS 20 months vs 60 months, $p < 0.001$) compared with patients at RISS stages I and II (Fig. 1). Other factors, such as haemoglobin level, platelet counts and serum creatinine, did not show any associations with survival in our study.

To analyse the impact of novel chemotherapies on the outcome of patients with IgD myeloma, we compared the survival of patients receiving bortezomib-based therapies and traditional treatments. Our study indicated that the bortezomib-based therapies may have prolonged patient PFS (median PFS 29 months vs 13 months, $p = 0.061$) and OS (median OS 60 months vs 28 months, $p = 0.039$). Meanwhile, among the patients who got treated with bortezomib, there were 62.5% (10/16) of patients' renal function got improved. And in patients treated with traditional therapies, the rate of improvement of renal function was 33.3% (2/6).

Table 2 Cytogenetic abnormalities of patients with IgD and non-IgD myeloma

Cytogenetic abnormalities	IgD MM ($N = 47$)		Non-IgD MM ($N = 576$)		p value
	No. of patients	(%)	No. of patients	(%)	
Deletion of 13q	15	31.9	247	42.9	0.143
Deletion of 17p13	8	17.0	84	14.6	0.651
Amplification of 1q21	28	59.6	271	47.0	0.098
IGH translocation	34	72.3	283	49.1	0.002
t(11;14)	15	31.9	103	17.9	0.018
t(4;14)	9	19.1	86	14.9	0.439
t(6;14)	4	8.5	9	1.6	0.012
t(14;16)	1	2.4	7	1.2	–
t(14;20)	0	0	3	0.5	–
IGH translocation with unknown partner	5	10.6	52	9.0	–

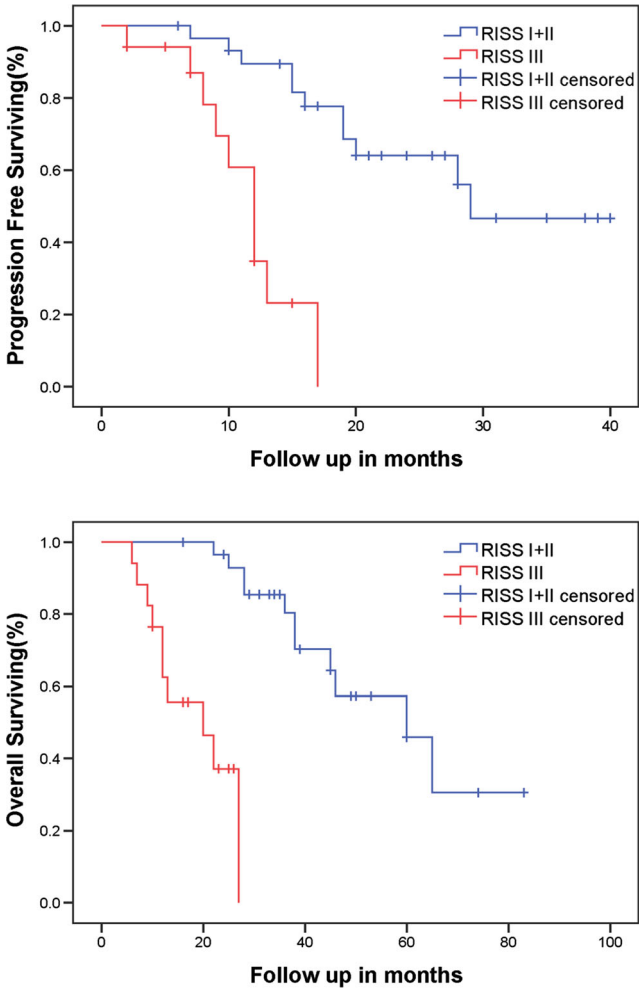

Fig. 1 Survival analysis of RISS in patients with IgD myeloma: Patients at RISS stage III had significant shorter PFS (median PFS 12 months vs 29 months, $p < 0.001$) and OS (median OS 20 months vs 60 months, $p < 0.001$) compared with patients at RISS stages I and II

In non-IgD myeloma patients, 69.8% (402/576) were treated with bortezomib-based therapies, and 30.2% (174/576) were treated with traditional chemotherapies. The percentage which received bortezomib-based therapy was similar with patients with IgD myeloma. Among those patients, 30.7% (177/576) achieved CR, with 11.3% (65/576) of them achieving sCR. The overall response rate was 89.4%. We compared survivals in patients with IgD myeloma and non-IgD myeloma. The median PFS of patients with IgD myeloma was 28 months and for patients with non-IgD myeloma was 27 months. There were no differences between the two groups ($p = 0.598$). In addition, the median OS of patients with IgD and non-IgD myeloma was 46 months and 57 months, respectively ($p = 0.755$). Besides that, in those who carried adverse factors, patients with IgD myeloma and non-IgD myeloma had similar PFS and OS (Fig. 2). The results were summarised in Table 3.

Discussion

IgD myeloma is a rare subtype of myeloma in the Caucasian population, accounting for only 2% of myeloma patients [1, 3, 6, 20, 21]. In China, there are many more patients with IgD myeloma, but it is still relatively uncommon, accounting for approximately 6~10% of all myeloma patients [22, 23]. At present, there are still many hospitals in China that cannot diagnose IgD myeloma because IgD monoclonal proteins are too rare to confirm. Therefore, those patients with IgD myeloma are probably been considered as light-chain subtypes when diagnosed. As a result, clinical data of patients with IgD myeloma is rarely seen.

In our study, we confirmed the diagnosis of 47 patients with IgD myeloma during 2007–2015 in our hospital. The incidence was 7.5% of all newly diagnosed myeloma patients. Male patients with IgD myeloma were much more common than females. We analysed clinical factors and compared them with those of patients with other myeloma subtypes. Patients with IgD myeloma showed advanced disease when diagnosed, with 76.6% of the patients at ISS stage III, and 46.8% of the patients had varying degrees of renal failure. In addition, 72.3% of the patients had obvious anaemia, and 38.3% had hypercalcemia. Notably, more IgD myeloma patients exhibited a high LDH level than non-IgD myeloma patients. The clinical and biological characteristics of our patients were similar to those of patients in previously reported studies [1–4].

Most studies on IgD myeloma have reported that patients with IgD myeloma have shorter survival times than patients with other subtypes of active myeloma [1–4]. However, recently, some studies have shown that patients with the IgD subtype have outcomes similar to patients with other subtypes. Novel treatments have played an important role in this change. Reese et al. found that among myeloma patients who underwent autologous haematopoietic stem cell transplantation, the 3-year PFS and OS of IgD patients were 38% (95% CI, 21–56%) and 69% (95% CI, 51–84%), respectively, which are comparable to the 3-year PFS and OS of IgG and IgA patients. In addition, transplantation-related mortality and disease relapse/progression of myeloma were also similar for all subtypes [21]. Another study showed that the IgD subtype was not associated with a different prognosis (HR, 0.965; 95% CI 0.56–1.45; $p = 0.887$). Because of novel treatments, the OS of patients with IgD myeloma who started therapy after 2000 was 51.5 months, which is a significant improvement compared with that of those who started therapy before 2000 (44 months, $p = 0.018$) [24]. In our hospital, although patients with IgD myeloma had severe symptoms and advanced disease at the time of diagnosis, they still had response rates and survival times that were

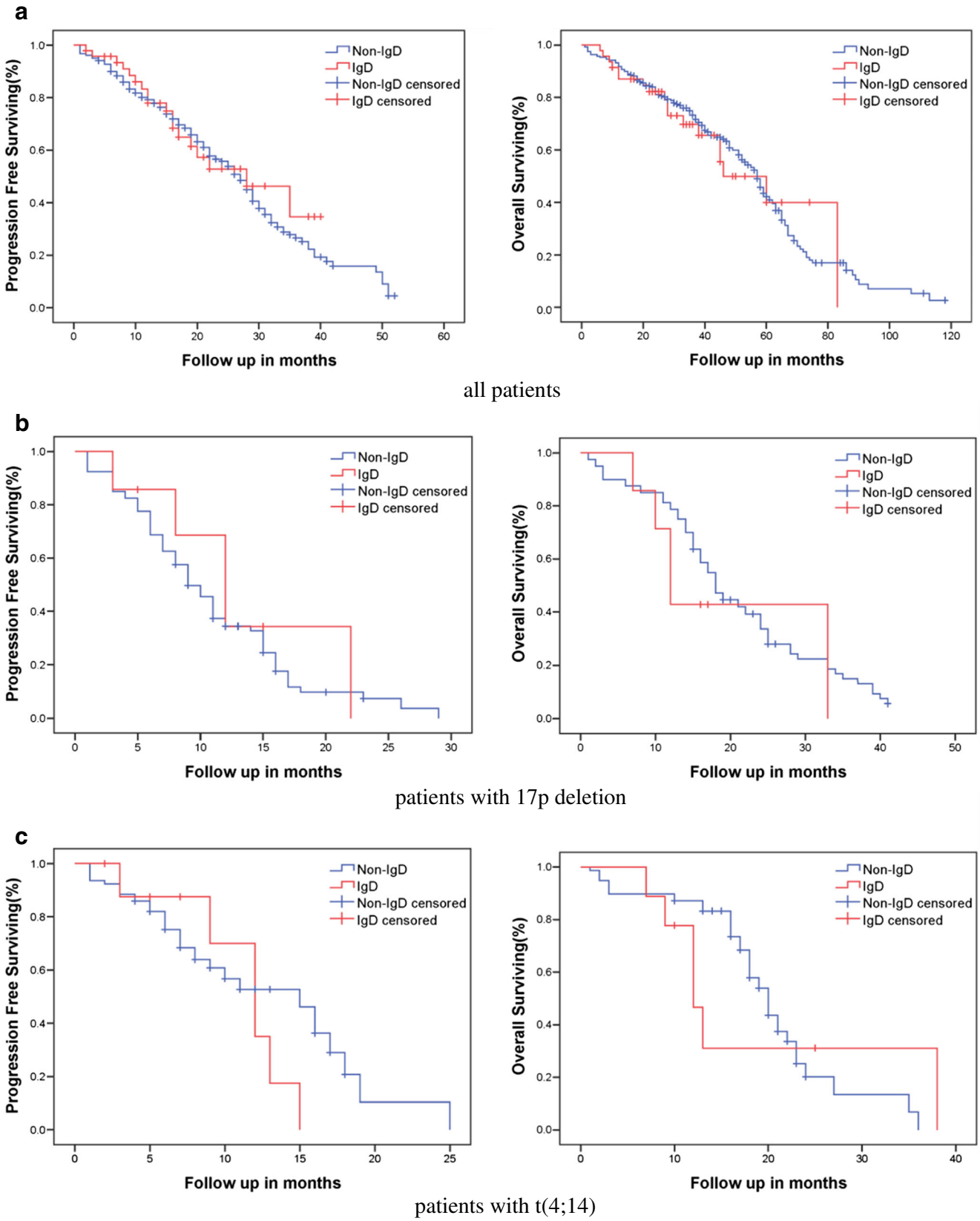

Fig. 2 The Kaplan-Meier analysis of survivals between IgD and non-IgD myeloma in all patients (**a**), patients with 17p deletion (**b**) and patients with t(4;14) (**c**). The PFS and OS showed no differences between each groups

Table 3 Median survivals of patients with IgD and non-IgD myeloma

Survivals (month)	PFS			OS		
	IgD MM	Non-IgD MM	*p* value	IgD MM	Non-IgD MM	*p* value
All patients	28	27	0.598	46	57	0.755
RISS stage						
I	Not-reached	Not-reached	–	Not-reached	Not-reached	–
II	29	25	0.194	60	58	0.414
III	12	11	0.762	20	19	0.431
del(17p13)	12	9	0.537	12	18	0.445
t(4;14)	12	15	0.323	12	20	0.949

similar to those of patients with non-IgD myeloma. The possible reason is that a majority of patients with IgD myeloma in our hospital received treatment with novel drugs, which prolonged their survival time.

Most myeloma patients have genetic aberrations, and cytogenetic changes detected by FISH are associated with prognosis. In our study, 91.5% (43/47) of patients with IgD myeloma had at least one abnormality. The frequency of IGH translocation was higher in IgD patients than in other myeloma patients. The most common translocation in patients with IgD myeloma was t(11;14), which occurred much more than in patients with non-IgD myeloma. However, the underlying mechanism is still unclear. Another study from China showed that 58.3% (7/12) of IgD myeloma patients carried t(11;14), which is much higher than the percentage of IgG and IgA myeloma patients with this translocation ($p < 0.05$) [25]. We analysed the survival of patients with different genetic changes and found that patients with deletion of 17p and/or the t(4;14) translocation had significantly shorter PFS and OS. Other genetic aberrations, such as deletion of 13q, amplification of 1q21 or t(11;14), had no relationship with prognosis. We could not confirm whether t(14;16) or t(6;14) affected patient outcomes because of their low incidences.

ISS is a simple and classical risk-stratification system, and it plays an important role in predicting outcomes in patients with non-IgD myeloma. However, in our study, the ISS stage had no relationship with the survival of patients with IgD myeloma. One possible reason is that the number of IgD patients in our study was insufficient, and most patients (76.6%) were at ISS stage III. Moreover, there were too few patients at ISS stage I and stage II. Therefore, ISS did not seem to be helpful in forecasting the prognosis of IgD myeloma patients. RISS combines the prognostic power of high-risk cytogenetic aberrations and LDH assessment with ISS stage and better sorts patients with IgD myeloma into three survival subgroups. Patients with IgD myeloma at RISS stage III had significantly shorter PFS and OS than patients at RISS stage I and stage II in our study. Thus, RISS was found to be a powerful prognostic tool for IgD myeloma.

Conclusion

Our study suggests that, first, patients with IgD myeloma are much more common in the Chinese population than in the Caucasian population, and a majority of them are male. Second, the IgD subtype has special characteristics: it is associated with higher frequencies of anaemia, renal failure, and hypercalcemia and a higher level of serum LDH; it has a high frequency of IGH translocation, mostly t(11;14). However, the prognosis of IgD myeloma patients is not worse than that of patients with non-IgD myeloma, especially in the novel agent therapy era. Finally, RISS is a simple and effective method to predict the outcomes of patients with IgD myeloma.

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Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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