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ORIGINAL ARTICLE

Immunoparesis recovery 1 year after ASCT is independently associated with favorable survival in patients with symptomatic multiple myeloma who undergo autologous stem cell transplantation

Wen Gao[1] · Jie Li[1] · Yin Wu[1] · Yanchen Li[1] · Yun Leng[1] · Aijun Liu[1] · Guangzhong Yang[1] · Ying Tian[1] · Huijuan Wang[1] · Guorong Wang[1] · Zhipeng Wu[1] · Zhangyong Ren[1] · Wenming Chen[1]

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Abstract

Immunoparesis is defined as a reduction in the levels of one, two, or three uninvolved immunoglobulins. However, there are very limited data on the incidence and prognostic significance of immunoparesis recovery 1 year after autologous stem cell transplantation (ASCT) in MM. We reviewed medical records of de novo MM patients who received ASCT at Beijing Chao Yang hospital. One hundred eight MM patients were included in the study. Conventional chemotherapy was administered as induction regimen in 16 patients (14.8%), whereas novel agents were used in 92 patients (85.2%). Most patients had immunoparesis at diagnosis (89.1%) and at the moment of ASCT as well (75%). After a median follow-up of 49 months, in the group with immunoglobulin recovery 1 year after ASCT, there was a trend towards longer progression-free survival (PFS) than in the group with immunoparesis ($P = 0.054$). And overall survival (OS) was significantly longer in patients with immunoparesis recovery ($P = 0.004$). In multivariate analysis, immunoparesis recovery 1 year after ASCT was independently associated with improved OS ($P = 0.016$). In conclusion, lack of immunoparesis recovery 1 year after ASCT in MM patients is associated with significantly shorter OS and this group of patients needs new treatment strategy to improve the prognosis.

Keywords Multiple myeloma · Immunoparesis · Autologous stem cell transplantation

Introduction

Multiple myeloma (MM) is a plasma cell malignancy, accounting for 1% of all cancers and 10% of hematologic neoplasms. It is very common for de novo symptomatic multiple myeloma to have immunoparesis, suppression of uninvolved immunoglobulins (Ig) [1–6]. Immunoparesis has been showed to be a risk factor for progression to MM in plasma cell disorders, like smoldering multiple myeloma (SMM) and solitary plasmacytoma of bone (SPB) [7, 8]. In addition, symptomatic multiple myeloma (MM) with suppression of any of the uninvolved immunoglobulins had a reduced progression-free survival (PFS) and overall survival (OS) compared to those with preserved uninvolved immunoglobulins [2]. The suppression of the matched pair uninvolved heavy-light chain at presentation was also shown to correlate with reduced OS in MM patients [9]. However, there are very limited data on the prognostic significance of uninvolved immunoglobulin recovery after autologous stem cell transplantation (ASCT) in symptomatic MM. The studies from Rueff et al. and Hernández et al. showed that B cell reconstitution was a delayed and progressive process, beginning 1 month after ASCT, reaching a normal range at 6 months and ending after 1 year [10, 11]. So, B cell reconstitution is expected to be completed 1 year after transplant. We performed this study to assess the impact of uninvolved immunoglobulin immunoparesis recovery 1 year after ASCT on outcome with symptomatic multiple myeloma.

Patients and methods

Between Feb 2003 and Sep 2014, 108 patients with symptomatic myeloma who received the ASCT in

✉ Wenming Chen
Wenming_chen@yahoo.com

[1] Department of Hematology, Myeloma Research Center of Beijing, Beijing Chao-Yang Hospital, Capital Medical University, Gongtinanlu No8, Chaoyang District, Beijing 100020, China

Table 1 The baseline clinical characteristics of MM patients with preserved uninvolved immunoglobulins and suppression of uninvolved immunoglobulins at 1 year after ASCT

	All patients ($n = 108$)	Uninvolved Igs preserved 37	At least one Igs suppressed 71	p value
Male	51.8%	41%	55.2%	0.227
Age, year (median/range)	53 (35–66)			
Age < 50	35.5%	35.9%	34.3%	1
IgG	40.9%	25.6%	47.8%	0.039
IgA	20.9%	30.8%	16.5%	0.094
IgD	10%	10.3%	9%	1
Light chain	28.2%	33.3%	26.9%	0.512
Lytic bone lesions	97.3%	97.4%	97%	1
ISS-I	19.2%	21.1%	19.4%	1
ISS-II	55.8%	50%	58.1%	0.414
ISS-III	25%	28.9%	22.6%	0.812
Hemoglobin < 10 g/dl	47.9%	44.4%	50%	0.672
Platelets < 100×10^9/L	15.2%	5.7%	14.8%	0.304
Creatine ≥ 176umol/L	12.5%	20.6%	6%	0.082
BMPC ≥ 40%	38.1%	38.7%	36%	0.817
LDH > 250 IU/L	9.9%	7.1%	7.3%	1
High risk cytogenetics	52.9%	47.1%	53.1%	0.769
Novel agents	85.2%	89.2%	83.6%	0.565
Response to induction therapy (≥ PR)	91.3%	92.1%	90.3%	1
Maintenance therapy				
Thalidomide	92.6%	89.1%	95.8%	0.364
BD	7.4%	10.9%	4.2%	0.364
CR	43.3%	50%	38.7%	0.676
Uninvolved Igs preserved at diagnosis	10.9%	20.5%	6%	0.029
Uninvolved Igs preserved before ASCT	25%	59.5%	7.5%	<0.001

High-risk cytogenetics, defined as the presence of any of del17p, t(4;14), add1q21 or t(14;16); novel agents, defined as induction with bortezmib, lenalidomide, or thalidomide. Data are expressed as frequencies

ISS International Staging System, *LDH* lactate dehydrogenase, *BMPC* bone marrow progenitor cell, *CR* complete response, *PR* partial response. *BD* bortezomib, and dexamethasone, *Igs* immunoglobulins

Beijing Chao Yang Hospital were included. All patients had available immunoglobulin levels measured by nephelometry, before initiation of any antimyeloma therapy and within 1 month from diagnosis of symptomatic myeloma. Several of these patients had been included in clinical trials, while the majority of patients had been treated outside the context of a clinical trial. Data were extracted from a prospectively maintained database, and all patients had records reviewed to assure data completeness and accuracy. Suppression of immunoglobulins was defined as reduction of an uninvolved immunoglobulin below the lower limit of normal for our laboratory reference range, which for IgG was < 750 mg/dl, for IgA was < 80 mg/dl, and for IgM was < 40 mg/dl. In all cases, immunoglobulins were measured by standard nephelometry. Response to treatment was evaluated according to International Myeloma Working Group (IMWG) [12], and IMWG criteria were retrospectively applied to patients evaluated before 2006. For the purpose of the current analysis, complete response category included complete response (CR) defined as confirmed negative immunofixation of serum and urine, and the category of stringent complete response (sCR), which has been incorporated in the IMWG criteria. Very good partial response (VGPR) included patients with ≥ 90% reduction of the M-spike and urine M-spike < 100 mg/day, as well as patients with no paraprotein in serum or urine electrophoresis but with positive immunofixation. Partial response (PR) was defined as ≥ 50% decrease in serum M-protein concentration and ≥ 90% decrease in

Table 2 The response rate for MM patients with preserved uninvolved immunoglobulins and suppression of uninvolved immunoglobulins at 1 year after ASCT

	Uninvolved Igs preserved ($n = 37$)	At least one Igs suppressed ($n = 71$)	p value
sCR	17.9%	6.3%	0.098
CR	51.3%	32.8%	0.096
VGPR	20.5%	12.5%	0.401
At least VGPR	89.7%	51.6%	< 0.001
PR	5.1%	18.8%	0.076
MR	0	1.6%	1
SD	0	4.7%	0.287
PD	5.1%	23.4%	0.014

sCR stringent complete response, *CR* complete response, *VGPR* very good partial response, *PR* partial response, *MR* minimum response, *SD* stable disease, *PD* progression of disease, *Igs* immunoglobulins

urine M-protein excretion. The database of Beijing Chao Yang hospital is maintained in the department of hematology at Beijing Chao Yang hospital. Approval was obtained from the Institutional Review Board of Beijing Chao Yang Hospital for the analysis and publication of these data.

Fluorescence in situ hybridization (FISH) analysis was performed in selected CD138 plasma cells in the bone marrow samples at diagnosis. All multiple myeloma cell samples were purified using the Miltenyi technology (anti-CD138–coatedmagnetic beads) before FISH, enabling a plasma cell purity higher than 90%. Plasma cells were then analyzed using DNA probes (Abbott Molecular) specific for the following chromosomal aberrations: 17p13 deletion, t(11;14), t(4;14), t(14;16), and 1q21 gains. A total of 200 interphase nuclei were analyzed. The cutoff values were the following: 20% for 17p13 deletion; 10% for t(4;14), t(4;14), and t(14;16); 20% for 1q21 Gains [13].

Statistical analysis

Comparisons for categorical variables among different groups were made with the X^2 test, using Fisher's exact test when appropriate. OS was measured from the date of treatment initiation until the date of death or date of last follow up. PFS was calculated from the date of initiation of therapy until the date of first evidence of disease progression or death. Patients without evidence of progressive disease were censored at the date of last

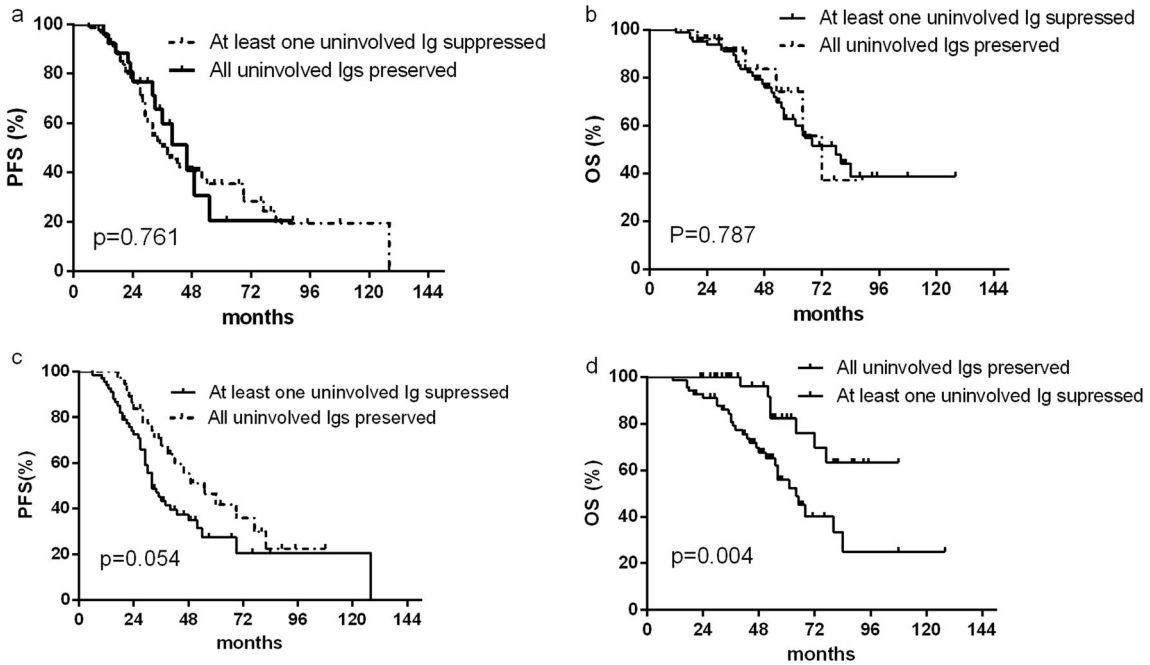

Fig. 1 Impact on PFS and OS of all uninvolved Igs preserved versus at least one uninvolved Igs suppressed before ASCT and one year after ASCT. **a** Impact on PFS before ASCT. **b** Impact on OS before ASCT. **c** Impact on PFS 1 year after ASCT. **d** Impact on OS 1 year after ASCT

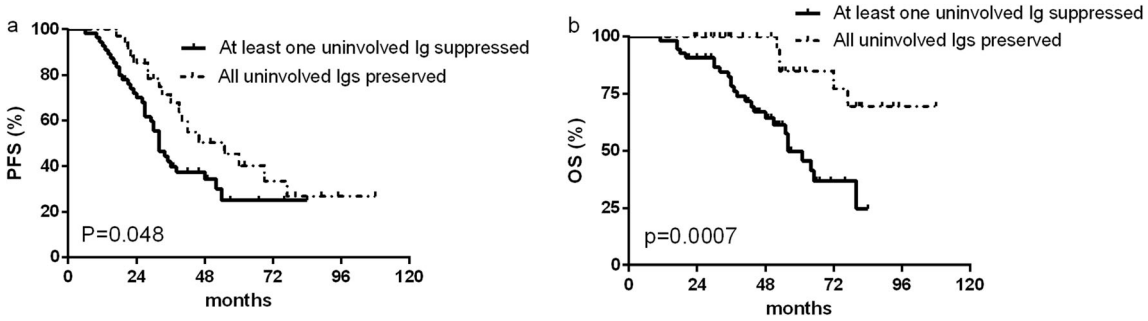

Fig. 2 Impact on PFS and OS of all uninvolved Igs preserved versus at least one uninvolved Igs suppressed 1 year after ASCT in novel agent era. **a** Impact on PFS 1 year after ASCT. **b** Impact on OS 1 year after ASCT

follow up [12]. Time-to-event curves were plotted with the method of Kaplan and Meier, and comparisons among groups were made using log rank test. For multivariate analysis, factors associated with time-to-event were introduced into Cox proportional hazards model. IBM SPSS v21 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Patients and baseline characteristics

The baseline characteristics of the patients are outlined in Table 1. The median age was 53 years (range 35–66 years). Of the patients, 51.8% were male. IgG is the most common M protein. Of the patients, 12.5% have kidney damage (creatine ≥ 176 μmol/L). Conventional chemotherapy was administered as an induction regimen in 16 patients (14.8%) who received VAD (vincristine, adriamycin, and dexamethasone). The remaining 92 ((85.2%)) patients received IMIDs or proteasome inhibitor-based therapies: 1 patient (0.9%) had received RD (lenalidomide and dexamethasone); 14 patients (12.9%) received TAD (thalidomide, adriamycin and dexamethasone); 16 patients (14.8%) received PD (bortezomib and dexamethasone); 17 patients (15.7%) received PTD (bortezomib, thalidomide and dexamethasone); and 44 patients (40.7%) received PAD (bortezomib, adriamycin, and dexamethasone). Cytogenetics data using fluorescence in situ hybridization (FISH) was available for 47.2% of patients. Among them, 52.9% of patients had high risk cytogenetics (defined as presence of any of del17p, t (4;14), add1q21, or t (14;16)). Among patients with high-risk cytogenetics, 1q21 gains were observed in 43.5% (20 of 46), del17p were observed in 19.6% (10 of 51), and t (4;14) were observed in 15.7% (8 of 51). No patients with (14;16) were observed (0 of 51). There are no differences in incidence of suppression of at least one uninvolved immunoglobulin 1 year after ASCT between patients with and without high-risk cytogenetics (68 vs 62.5%, $P = 0.769$). Of the patients, 10.9% have preserved uninvolved immunoglobulins at diagnosis. After induction therapy, 25% of patients achieved uninvolved immunoglobulin recovery. Both uninvolved immunoglobulin preservation at diagnosis and immunoglobulin recovery before ASCT was more common in patients with immunoparesis recovery 1 year after ASCT ($p = 0.029$ and $p < 0.001$) (Table 1). Suppression of at least one uninvolved immunoglobulin 1 year after ASCT was slightly more common in patients with IgG myeloma ($P = 0.039$).

There were no differences in sCR, CR, VGPR, and PR respectively between patients with uninvolved immunoglobulin recovery, and those with suppression of at least one uninvolved immunoglobulin 1 year after ASCT. However, at least VGPR 1 year after ASCT was higher in patients with uninvolved immunoglobulin recovery compared to those with suppression of at least one uninvolved immunoglobulin 1 year after ASCT (89.7 versus 51.6%, $P < 0.001$) (Table 2).

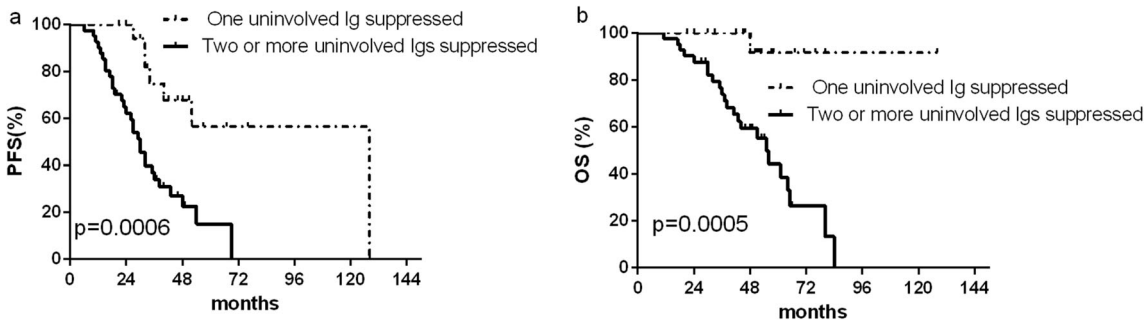

Fig. 3 Impact on PFS and OS of one uninvolved Igs suppressed versus two or more uninvolved Igs suppressed 1 year after ASCT. **a** Impact on PFS 1 year after ASCT. **b** Impact on OS 1 year after ASCT

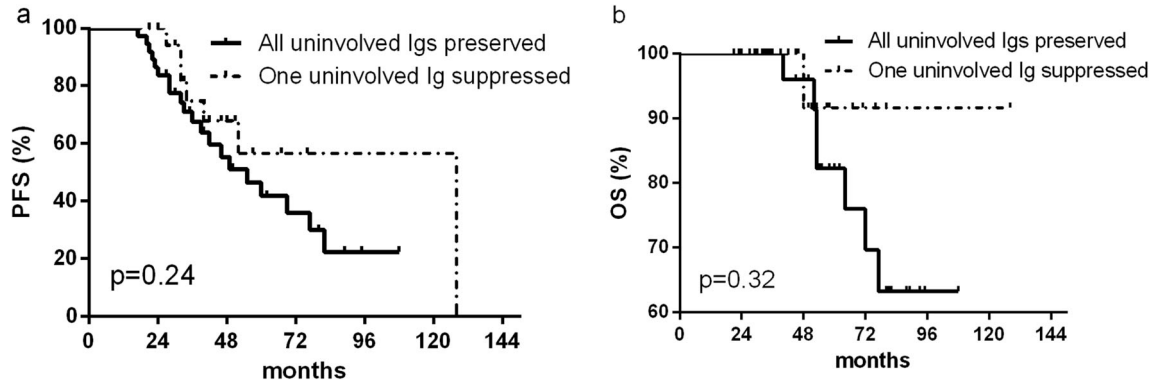

Fig. 4 Impact on PFS and OS of one uninvolved Igs suppressed versus all uninvolved Igs preserved 1 year after ASCT. **a** Impact on PFS 1 year after ASCT. **b** Impact on OS 1 year after ASCT

Effect of uninvolved immunoglobulin suppression on survival

There was no difference in the estimated PFS (46 vs 38 months, $P = 0.761$) and OS (72 vs 78 months, $P = 0.787$) between patients with uninvolved immunoglobulins recovery ($n = 26$) and patients with suppression of at least one uninvolved immunoglobulin before ASCT($n = 82$) (Fig. 1a, b). Patients with recovered immunoglobulins 1 year after ASCT ($n = 37$) had the tendency to have a longer PFS than patients with suppression of at least one of the uninvolved immunoglobulins ($n = 71$) (estimated PFS of 55 vs 32 months, $P = 0.054$) (Fig. 1c). Overall survival was significantly longer in patients with recovered immunoglobulins 1 year after ASCT ($n = 37$) compared to patients with suppression of at least one of the uninvolved immunoglobulins ($n = 71$) (estimated overall survival of not reach vs 64 months, $P = 0.004$) (Fig. 1d). For patients who received the novel agent containing regime (Ig recovered $n = 34$ versus Ig suppressed $n = 58$) as induction therapy, the similar tendency was observed for PFS (estimated PFS of 55 vs 32 months, $P = 0.048$) (Fig. 2a) and OS (estimated overall survival of not reach vs 61 months, $P = 0.0007$) (Fig. 2b) respectively. The survival for patients with one ($n = 19$) or with more than one ($n = 41$) uninvolved immunoglobulin suppression 1 year after ASCT was investigated further. The results showed that the former had both longer PFS (estimated PFS of 128 vs 30 months, $P = 0.0006$) and OS (estimated OS of not reach vs 55 months, $P = 0.0005$) than the latter (Fig. 3a, b). Compared with patients with one uninvolved immunoglobulins suppression ($n = 19$), patients with recovered immunoglobulins (n-37) 1 year after ASCT have the similar PFS (estimated PFS of 55 vs 128 months, $P = 0.24$) and OS (both estimated OS not reach, $P = 0.32$) (Fig. 4a, b). In addition, the survival comparison between patients with one suppressed or recovered immunoglobulins ($n = 56$) and those with two or three suppressed uninvolved immunoglobulins ($n = 41$) 1 year after ASCT were made. There was very significant difference in the PFS (estimated PFS of 55 vs 30 months, $P < 0.0001$) and OS (estimated OS of not reach vs 55 months, $P < 0.0001$) (Fig. 5a, b). Finally, for patients with at least VGPR 1 year after ASCT ($n = 73$), impact on PFS and OS of all uninvolved Igs preserved ($n = 40$) versus at least one uninvolved Igs suppressed ($n = 33$) 1 year after ASCT was analyzed. There was no difference in the estimated PFS (55 vs 43 months, $P = 0.36$) and (Fig. 6a). Overall survival was significantly longer in patients with recovered immunoglobulins 1 year after ASCT compared to patients with suppression of at least one of

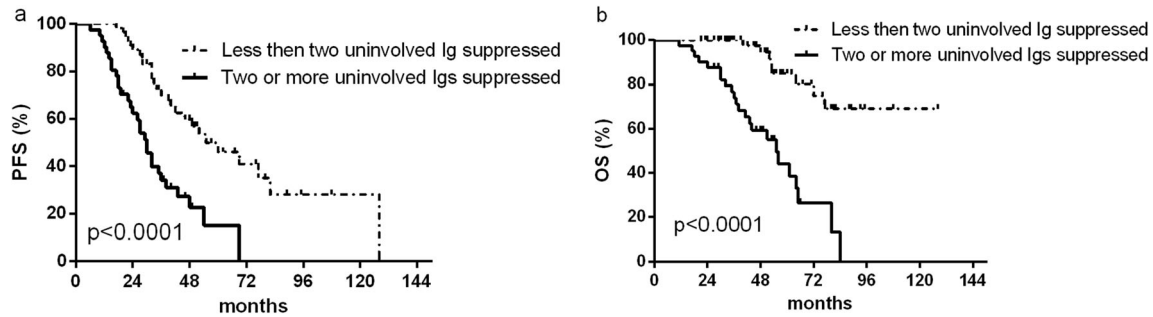

Fig. 5 Impact on PFS and OS of two or three uninvolved Igs suppressed versus less than two uninvolved Igs suppressed (one uninvolved Igs suppressed or all uninvolved Igs preserved) 1 year after ASCT. **a** Impact on PFS 1 year after ASCT. **b** Impact on OS 1 year after ASCT

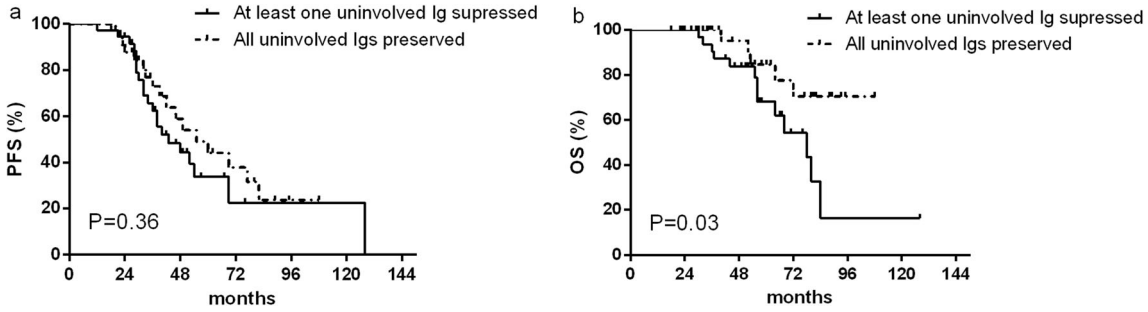

Fig. 6 Impact on PFS and OS of all uninvolved Igs preserved versus at least one uninvolved Igs suppressed 1 year after ASCT for patients with at least VGPR 1 year after ASCT. **a** Impact on PFS for patients 1 year after ASCT. **b** Impact on OS for patients 1 year after ASCT

the uninvolved immunoglobulins (estimated overall survival of not reach vs 78 months, $P = 0.03$) (Fig. 6b). Because of limited number, for patients with less than VGPR 1 year after ASCT, impact on PFS and OS of all uninvolved Igs preserved ($n = 4$) versus at least one uninvolved Igs suppressed ($n = 31$) 1 year after ASCT could not be analyzed.

Multivariate analysis for survival

Given the association of immunoglobulin suppression with other features of advanced disease, we performed a multivariate analysis to adjust for the impact of other well-defined prognostic factors. A multivariate analysis for OS was performed in one model (Table 3). The model incorporated ISS III, less than VGPR 1 year after ASCT, and recovered immunoglobulin 1 year after ASCT. The recovery of uninvolved immunoglobulins 1 year after ASCT in the multivariate analysis was independently associated with improved survival (hazard ratio (HR): 3.091, 95% confidence interval (CI) 1.238–7.721, $P = 0.016$). Other factor that was independently associated with inferior survival in the multivariate analysis included less than VGPR 1 year after ASCT (hazard ratio (HR) 0.338, 95% confidence interval (CI) 0.158–0.720, $P = 0.005$).

Discussion

This study has assessed the impact of uninvolved immunoglobulins immunoparesis at 1 year after ASCT in symptomatic multiple myeloma. We observed the association of immunoparesis with shorter OS. The negative impact on the OS of immunoparesis was confirmed in a multivariate analysis. It demonstrates the uninvolved immunoglobulin immunoparesis at 1 year after ASCT in patients with symptomatic myeloma is an independent prognostic factor. However, the impact of immunoparesis at 1 year after ASCT may be most relevant for those patients who have reached at least VGPR at this time, since for all other patients, a poorer prognosis can be simply concluded from their inferior remission state. Our study further conformed OS benefit of immunoparesis recovery for patients with at least VGPR 1 year after ASCT.

The prognostic importance of the preservation of the uninvolved immunoglobulins has been studied in some studies [1, 2, 6]. In 2009, Bradwell et al. [14] developed immunoglobulin heavy/light chain immunoassays—"Hevylite"(HLC). Ludwig H et al. [9]. used this immunoassay in 203 MM patients with intact-immunoglobulin myeloma. Severe (> 50%) HLC-matched pair suppression was identified in 54.5% of the 156 newly diagnosed patients and was associated with significantly shorter survival (45.4 vs. 71.9 months, $P = 0.019$).

Table 3 Univariate and multivariate analysis of factors associated with overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p* value	HR	95%CI	*p* value
ISS III	1.777	0.850–3.715	0.127	0.480	0.223–1.034	0.061
Age < 50 years	1.102	0.559–2.172	0.78			
Cr ≥ 176umol/L	2.102	0.692–5.855	0.199			
Hb < 10 g/dL	1.768	0.865–3.616	0.118			
Platelets < 100×10^9/L	2.029	0.869–4.739	0.102			
Less than VGPR 1 year after ASCT	3.645	1.869–7.110	0.000	0.338	0.158–0.720	0.005
preserved Igs	0.315	0.137–0.725	0.007	3.091	1.238–7.721	0.016

ISS International Staging System, *Cr* creatine, *Hb* hemoglobin, *VGPR* very good partial response, *preserved Igs* preservation of uninvolved immunoglobulins at 1 year after ASCT, *HR* hazard ratio

Table 4 The baseline clinical characteristics of our cohort and Spanish cohort with different immunoglobulins recovery 1 year after ASCT

	Our cohort 108	Spanish cohort 169	*p* value
Age at diagnosis			
≥ 65 years, no. (%)	3 (3)	33 (20)	< 0.001
< 65 years, no. (%)	105 (97)	136 (80)	< 0.001
High-risk cytogenetics, no. (%)	10 (20)	25 (22)	0.798
Treatment induction, no. (%)			
Conventional chemotherapy	16 (15)	86 (51)	< 0.001
Novel agents	92 (85)	83 (49)	< 0.001
ISS-I, no. (%)	21 (19)	79 (50)	< 0.001
ISS-II, no. (%)	60 (56)	53 (33)	< 0.001
ISS-III, no. (%)	27 (25)	27 (17)	0.109
NA, no. (%)	0	10 (6)	

High-risk cytogenetics, defined as the presence of any of del17p, t(4;14), or t(14;16); novel agents, defined as induction with bortezmib, lenalidomide, or thalidomide. Data are expressed as frequencies

ISS International Staging System, *NA* not available

This correlation was statistically significant in IgG patients (46.4 vs. 105.1 months, $P = 0.017$), but not in patients with IgA myelomas (32.9 vs. 54.1 months, $P = 0.498$). Bradwell et al. [15] used the same method in 339 MM patients with intact-immunoglobulin myeloma and found that abnormal IgGk/IgGλ and IgAk/IgAλ ratios in the respective tumor isotypes at diagnosis were predictive of shorter PFS, predominantly owing to the suppression of the uninvolved immunoglobulin of the same isotype as the tumor. However, there are very limited data on the prognostic significance of uninvolved-immunoglobulin immunoparesis recovery 1 year after ASCT in symptomatic MM.

Another important finding in our study is that it seemed to have similar PFS and OS for the patients with suppression of one of the uninvolved immunoglobulins compared to patients with preserved uninvolved immunoglobulins at 1 year after ASCT. And patients with suppression of one of the uninvolved immunoglobulins had longer PFS and OS than the patients with two or more at 1 year after ASCT. However, there was no difference between the survival of patients with one vs two or more suppressed immunoglobulins at diagnosis [2]. It is possible that induction therapy plus ASCT can overcome the negative impact on the outcome for the suppression of one of the uninvolved immunoglobulins 1 year after ASCT.

In novel agent era, the preservation of uninvolved immunoglobulins for de novo MM before treatment can predict the better PFS and OS [2]. It is important issue whether immunoparesis recovery at 1 year after ASCT still retain the prognostic significance. Our results showed that after induction therapy with the novel agent containing regime, patients with immunoparesis recovery have longer OS than patients without immunoparesis recovery 1 year after ASCT. It means, in novel agent era, immunoparesis recovery at 1 year after ASCT still has the prognostic significance.

The possible associations of specific cytogenetic abnormalities with immunoparesis are also very important issue. In our study, cytogenetic studies were available for just less than one half patients, and patients with and without high-risk cytogenetics had similar incidence of suppression of at least one uninvolved immunoglobulin 1 year after ASCT. It seemed that there were no associations of specific cytogenetic abnormalities with immunoparesis 1 year after ASCT.

In the literature, for de novo multiple myeloma, uninvolved-immunoglobulin suppression was in 85–90% of patients before treatment. [1, 2, 4, 6]. The uninvolved immunoglobulins were reduced in 97% of patients with IgA and 88% of IgG MM [2, 4]. In our study, uninvolved-immunoglobulin suppression was in 89.1% of patients before treatment. The uninvolved immunoglobulins were reduced in 91.3% of patients with IgA vs 93.3% of IgG MM. At 1 year after ASCT, uninvolved-immunoglobulin suppression occurred in 65.4% of patients. The uninvolved immunoglobulins were reduced in 47.8% of patients with IgA vs 76.2% of IgG MM. The mechanism for the uninvolved-immunoglobulin suppression is not clear. The possible explanations comprise of competition for the occupation of bone marrow niches by normal and malignant plasma cells[13], cellular[14], and humoral factors.[15].

Recently, a study from Spain showed the similar results as ours [16]. They found that 1 year after transplant, among 169 patients progression-free, 88 patients (52%) had recovered immunoglobulins and 81 (48%) had not. The group with immunoglobulin recovery had a significantly longer median progression-free survival than the group with persistent immunoparesis (median 60.4 vs. 27.9 months, respectively; hazard ratio = 0.45, 95% CI 0.31–0.66; $P < 0.001$) and improved overall survival (11.3 vs.7.3 years; hazard ratio = 0.45, 95% CI = 0.27–0.74, $P = 0.002$). Compared to Spanish cohort, our patients are younger since in our cohort, only 3% were ≥ 65 years ($P < 0.001$). In addition, in our cohort, there are similar patients with high-risk cytogenetics, but more patients with novel agents and less patient with ISS-1 disease (Table 4). Although there are significant differences between the Spanish cohort and our series of patients, patients with immunoglobulin recovery retains its prognostic significance, especially under the treatment of novel agent or not. It is important that the performance of a risk assessment tool is not restricted to a specific patient population so that it can be used more extensively.

There are some limitations that should be considered when interpreting our results. Firstly, this is a retrospective study. Secondly, it should be acknowledged that the follow-up of patients is not enough and further larger population studies are still needed to verify the results.

In conclusion, our study confirms that lack of immunoparesis recovery 1 year after ASCT in MM

patients is associated with significantly shorter OS and this group of patients needs new treatment strategy to improve the prognosis.

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Authorship statement W.G. collected and analyzed data and wrote the manuscript. J.L., G.Z.Y., Y.W., Y.C.L., Y.L., A.J.L., Y.T., H.J.W., G.R.W., T.H.H., Z.P.W., and Z.Y.R. contributed with treatment of patients and reviewed and approved the manuscript. W.M.C contributed with study design, data collection and interpretation, and manuscript writing.

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Compliance with ethical standards Approval was obtained from the Institutional Review Board of Beijing Chao Yang Hospital for the analysis and publication of these data.

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

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