Emergence of oligoclonal bands in patients with multiple myeloma in complete remission after induction chemotherapy: association with the use of novel agents

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ABSTRACT

The emergence of oligoclonal bands is associated with a favorable outcome after autologous stem cell transplantation in multiple myeloma. The aim of this study was to determine the prevalence of immunoglobulin oligoclonality in 33 patients with multiple myeloma in complete remission achieved with primary therapy with either cytotoxic agents (n=18, 54.5%) or new induction regimens incorporating novel drugs (n=15, 45.4%). Eleven patients (33.3%) developed oligoclonal bands. In the group treated with novel agents, this oligoclonal immune response was observed in 60% (9 of 15) of the patients *versus* only 11.1% (2 of 18) of those given cytotoxic therapy (P=0.003). This is the first report showing a different frequency of oligoclonal humoral response in patients in complete remission achieved after conventional cytotoxic therapy *versus* induction incorporating novel agents. This difference could be due to a higher antitumor effect associated with the use of novel drugs, a stronger immune reconstitution, or both.

Key words: myeloma, complete remission, oligoclonal band, chemotherapy.

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Introduction

The emergence of an oligoclonal humoral response is a well-recognized event after autologous stem cell transplantation in multiple myeloma (MM), which has been associated with a good prognosis. It is likely due to a more durable immune reconstitution.[1-3] This oligoclonal humoral response can appear as multiple oligoclonal bands in serum and/or urine immunofixation (IFE) resulting in the so-called atypical serum IFE patterns (ASIPs).[4] Though initially described as transient, there is growing evidence to show that this oligoclonal humoral response can last for years.[2-5] Its prevalence is highly variable, ranging from 10% to 73%.[1-3] The appearance of oligoclonal bands has also been reported after treatment with the novel immunomodulatory drug lenalidomide,[4] and less is known concerning its potential relationship with conventional cytotoxic therapy or even with other novel therapeutic approaches. The aim of this study was to determine the prevalence of serum and/or urine IFE oligoclonal bands in two groups of patients with multiple myeloma in complete remission (CR) achieved either after primary therapy with cytotoxic agents or with new induction chemotherapy regimens incorporating novel drugs up-front.

Design and Methods

Thirty-three patients (15 male and 18 female, median age 59 years, range 25-89) with multiple myeloma in complete remission according to EBMT and IURC criteria[6,7] achieved with different induction regimens were enrolled. The diagnosis of multiple myeloma was established according to the criteria of the Chronic Leukemia-Myeloma Task Force.[8] Initial baseline demographics, clinical and laboratory data, and information concerning treatment and follow up were collected. An oligoclonal humoral response was defined as the presence of a serum and/or urine IFE monoclonal spike different from the original myeloma protein either in heavy and/or light chains as well as at IFE migration pattern. Statistical tests were performed with SPSS software 15.0 for Windows®, estimating 95% confidence interval (CI) by Wilson's test. This study was approved by the Hospital Clinic Ethics Board.

Results and Discussion

Eighteen patients (54.5%) received induction with conventional chemotherapy while 15 were initially treated with novel agents (45.5%). The conventional cytotoxic regimens in the first group were: VBCMP/VBAD (55.5%), cyclophos-

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phamide and dexamethasone (11.1%), VAD (11.1%), VCMP/VBAD (11.1%), VBAD (5.6%) and VCAP (5.6%). In the second group, the induction regimen was based on combinations of glucocorticoids with bortezomib (33.3%), lenalidomide (26.7%), thalidomide (26.7%), or bortezomib plus thalidomide (13.3%).

In the overall series, 11 of the 33 patients (33.3%) developed an oligoclonal humoral immune response. These abnormal bands observed in the IFE pattern lasted from 2.2 to 55.7 months (median 11.5 months). This relatively short duration contrasts with that observed after ASCT in our previous report,[5] where it lasted from 8 to 112 months. One explanation for this different duration could be that myeloablative treatment with high-dose melphalan followed by stem cell rescue probably results in higher tumor reduction resulting in a more powerful immune reconstitution than induction chemotherapy not followed by ASCT.

The high frequency of oligoclonal humoral response after only induction therapy was unexpected. In the ASCT context, 10% of the patients from the Arkansas group[1] developed this immunological phenomenon. In a recent report from our group,[5] 41.2% of the patients developed oligoclonal bands after ASCT. Interestingly, in the present series, 5 patients with oligoclonal humoral response have already relapsed (45.5%). In 4 of them, relapse occurred at the same time as the disappearance of the previous oligoclonality, while in the remaining case the oligoclonality disappeared six months before relapse. Our previous experience with oligoclonal bands after ASCT showed that they persisted during follow up in all patients, except in one who relapsed soon after the disappearance of the IFE oligoclonality.[5] These data are also consistent with the benign nature of this oligoclonal immune response as an indirect sign of immune reconstitution, and its disappearance is a hallmark of immediate or early relapse.

Four patients (36.4%) had a fluctuating oligoclonal pattern during their follow up on the basis of the different heavy and/or light chains combinations of IFE bands, while the remaining showed a single oligoclonal immunoglobulin. As in previous reports, a preponderance of IgG-κ oligoclonal immunoglobulin was observed.[4,5] This isotype predominance is likely due to a selective advantage of a B-cell population related to the recovery of impaired immunoglobulin production after a robust response to therapy.[4,5] In the group of patients treated with cytotoxic agents, the presence of oligoclonal bands was observed in 2 of them (11.1%, 95% CI 3.1-32.8). These 2 patients had been treated with cyclophosphamide and dexamethasone. In contrast, in the group of patients treated with novel drugs, 9 of 15 (60%, 95% CI 35.75-80.18) developed oligoclonal bands in serum and/or urine (two-sided χ^2 test, P=0.003). Main characteristics of patients who developed oligoclonal bands as well as the treatment given are shown in Table 1.

With treatment with melphalan and prednisone the complete remission rate was less than 5%. The new regimens, MPT (melphalan, prednisone and thalidomide),[9,10] MPV (melphalan, prednisone and bortezomib),[11] MPR (melphalan, prednisone and lenalidomide)[12] or lenalidomide/dexamethasone[13] are showing unprecedented complete remission rates of 15%, 30%, 24% and 24%, respectively. With the progressive use of novel drugs the complete remission rate and consequently the proportion of patients who develop an oligoclonal immune response with oligoclonal bands will likely increase. In fact, in the BiRD study, Mark *et al.*[5] reported that 33% of patients treated with clarithromycin, lenalidomide and dexamethasone developed ASIPs (atypical serum IFE patterns) consisting in the emergence of monoclonal and oligoclonal immunoglobulins unrelated to the original monoclonal protein. In our series, including patients treated with novel therapies such as thalidomide, lenalidomide and bortezomib, this phenomenon was observed in up to 60% of patients.

The mechanism associated with the emergence of oligoclonal bands and the prognostic significance of this phenomenon are still unknown. Molecular studies by semi-nested ASO-RT-PCR and DNA sequencing immunoglobulin variable genes have demonstrated a non-clonal related origin of plasma cells in multiple myeloma patients in complete remission with oligoclonal bands.[14] In spite of the value of an oligoclonal immune response after ASCT,[1] in terms of prolonged event free survival and overall survival, the prognostic impact of the emergence of IFE oligoclonality after induction has not been established. A signif-

Table 1. Characteristics of patients with oligoclonal bands.

Patient Number	Age (years)	Sex	Primary CT	ASCT	Original M-spike	Primary oligoclonal band	Other oligoclonal band	Oligoclonal band duration (months)
1	79	M	TD	No	IgA-κ	IgG-λ	-	2.34
2	54	F	BD	Yes	IgA-λ	IgG-κ	-	4.41
3	72	F	CD	No	IgD-λ	IgG-κ	IgG-λ	9.8+
4	59	M	CD	No	IgA-λ	IgG-κ	IgM-κ	2.2
5	64	F	TD	No	IgG-λ	IgG-κ	-	11.5+
6	67	M	B	No	κ	IgG-κ	-	8.1+
7	47	M	M2/B	No	κ	IgM-λ	-	14.9+
8	54	F	BTD	Yes	IgM-λ	IgG-κ	-	17.6+
9	61	F	TD	No	IgG-λ	IgG-κ	IgM-λ	55.3
10	51	F	BD	No	IgD-λ	IgG-κ	-	12.7+
11	76	M	LD	No	IgA-λ	IgG-λ	λ	13.9

CT: chemotherapy; ASCT: autologous stem cell transplantation; T: thalidomide; D: dexamethasone; B: bortezomib; C: cyclophosphamide; M2: vincristine, BCNU, cyclophosphamide, melphalan and prednisone alternating with vincristine, BCNU, doxorubicin and dexamethasone; L: lenalidomide.

icant impact on the short-term outcome in the BiRD study with the new drug lenalidomide in patients who developed ASIPS (71% *vs.* 23%) is of interest, but long-term benefits have not yet been reported.

In summary, this is the first report showing a higher frequency of oligoclonal humoral immune response in patients with multiple myeloma in complete remission after induction therapy incorporating novel agents *versus* those who were treated with conventional cytotoxic therapy. The observed difference in patients receiving novel drugs could be likely due to a higher tumor reduction, a stronger immune reconstitution, or both. The mechanisms facilitating the emergence of immunoglobulin oligoclonality as well as its prognostic significance after induction therapy, particularly when using new drugs, deserve further investigation.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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