RESEARCH COMMUNICATION

Significance of Oligoclonal Bands after Stem Cell Transplantation in Multiple Myeloma Cases

Ai-Jun Liu[1], Hong Zong[2], Guang-Zhong Yang[1], Yu-Hua Zhai[2], Li-Hong Li[1]*

Abstract

Objective: To determine the characteristics of oligoclonal bands that are frequently detected by serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) after stem cell transplantation. Methods: We retrospectively analyzed 56 patients with multiple myeloma (MM) undergoing transplantation, and standard immunofixation electrophoresis was used to identify and quantify paraproteins. Results: The median follow-up was 35 months (range, 10-76months) and 21 patients relapsed. Twelve (25.0%) demonstrated oligoclonal bands after a median time 1.4 months (range, 1-3months), with a median duration of 5.8 months (range, 1-15months). The majority patients with oligoclonal bands had normal quantities of immunoglobulins and the one year event free survival (EFS) was 92%, even higher than for patients without OBs (P=0.002). Conclusion: Oligoclonal bands frequent develop post-transplantation in MM cases. In the vast majority of patients, they may not represent relapsed disease, and more likely represent a transient phenomenon representing recovery of impaired immunoglobulin production.

Keywords: Multiple myeloma - stem cell transplantation - oligoclonal band - significance

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Introduction

Multiple myeloma (MM), one of the most frequent hematological malignancies, is characterized by clonal expansion of malignant bone marrow cells engaged in the production of a unique monoclonal immunoglobulin. Switching of the paraprotein isotype or transient presence of oligoclonal bands (OB) detectable by serum immunofixation electrophoresis (IFE) have been reported following not only allogeneic transplantation ,but also after autologous transplantation and even following intensive chemotherapy for leukemia (Gerritsen et al., 1993; Zent et al., 1998).

Switching of the paraprotein isotype can occur during disease relapse in MM, but the appearance of a new single band or OB may disturb the decision about consequent patient management. These OBs are likely to be due to transient dysregulation of the regenerating B cell compartment during recovery post transplant (Zent et al., 1998; Guikema et al., 1999) which has been associated with a good prognosis. It is likely due to a more durable immune reconstitution (Kyle et al., 1981; Vesole et al., 1992; Zent et al., 1998).

In this study, we retrospectively analyzed 56 transplanted multiple myeloma patients' clinical records and results of serial serum IFE, to determine the frequency and clinical significance of oligoclonal band appearance.

Materials and Methods

Between January 2000 and May 2011, 56 patients (29 males and 27 females, median age 51 years, range 29-69) with multiple myeloma undergoing transplantation were enrolled. The diagnosis of multiple myeloma was established according to the criteria of the World Health Organization. 3 patients were excluded because of lack of ISS stage, 2 patients were stage I, 24 were stage II and 27 were stage III. 48 patients received only one autologous transplantation, 8 patients received tandem stem cell transplantation (7 patients received tandem autologous transplantation, and 1 patient received auto-allo tandem transplantation). 24 patients received the FISH examination after 2009. Data recorded included patient and disease characteristics, and outcome data including response to treatment, relapse and survival. Myeloma responses were defined according to the criteria published by the European Group for Bone Marrow Transplantation. (Blade et al., 1998) (patients' characteristics are detailed in Table 1)

Induction therapies were focused on regimen of VAD (16 patients), regimen of BD±T (26 patients), regimen of BAD±T (13 patients), and regimen TD (1 patient). The most commonly utilized regimen of mobilization was high-dose cyclophosphamide or regimen of E-CHOP and cytokine protocols. Peripheral blood progenitor

[1]*Department of Hematology,* [2]*Department of Clinical Laboratory, Chao Yang Hospital, Capital Medical University, Beijing, China*
**For correspondence: llh1996cn@163.com*

Table 1. Patients' Characteristics

N	Age at transplant	male	female	Stage I	Stage II	Stage III	Paraprotein type IgG	IgA	κ	λ	IgD	Non-secretory
56	51(29-69)	29	27	2	24	27	21	9	9	8	7	2

Median monoclonal band size at diagnosis (range) 31g/L (0-97); Median bone marrow plasmacytosis at diagnosis (range) 31.5% (21-89)

Table 2. Comparison Between Patients with or Without OBs

OB present	with OBs	without OBs	P
No. of patients	12	36	
1 year PFS	92%(11/12)	66.7% (24/36)	
2 year PFS	66.7%(4/6)	31.0%(9/29)	
3 year PFS	66.7%(4/6)	16.7%(2/12)	0.002
2 year OS	100%(12/12)	68.2%(15/22)	
3 year OS	100%(6/6)	30.3%(15/22)	
Mean OS to present	45.0months	23.8months	

cells were mobilized with a target minimum CD34+ cell count of 2.0×10^6/kg. Patients all received high-dose therapy consisting of melphalan 200 mg/m^2 i.v. on day–1 ± bortezomib 1.0mg/m^2 day -6, -3, +1, +4. Peripheral blood progenitor cells were infused on day 0. Routine maintenance chemotherapy post-transplant was not utilized in the early study period. After 2005, some patients were managed on a thalidomide ± interferon maintenance therapy (V: vindesine, A: epirubicin, D: dexamethasone, B: bortezomib, T:thalidomide, C: cyclophosphamide, P: Prednisone, and E: Etoposide).

Serum and urine protein electrophoresis and immunofixation were performed by Hydrasys 2 System (Sebia, France), Serum and urine protein were quantified by Beckman image (America).

Statistical tests were performed with SPSS software 16.0 for Windows®, estimating 95% confidence interval (CI) by Wilson's test.

Results

Fifty-six patients with plasma cell malignancies underwent high dose chemo- therapy and stem cell transplantation during the study period. Before transplantation, 28 patients achieved complete remission (CR), and 28 achieved partial remission (PR). After transplantation, 33 patients achieved CR, and 23 achieved PR. With a median follow-up of 35 months (range, 10-76), 21 patients relapsed at a median of 9 months (range, 1-20). 10 patients relapsed within 3 months following transplantation, and they were most achieving PR patients (PR 9, CR 1). 1 year progression free survival (PFS) was 78.2% (43/55), 39 patient's estimated 2 year PFS, was 43% (17/39), and 24 patient's estimated 3 year PFS, was 25% (6/24). 44patient's estimated 2 year survival was 84.9% (37/44). 33 patient's estimated 3 year survival was 63.6% (21/33). 16 patient's estimated 5 year survival, was 31.3% (5/16). Among the patients who received one autologous transplantation, 39.6% (19/48) relapsed, and the median PFS was 6 months (range, 1-20). 25% (2/8) relapsed in the tandem stem cell transplantation group.

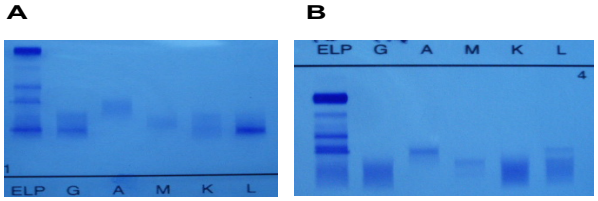

Figure 1. A. The OB was Ig Gλ; B. The OBs were Ig Aλ and Ig Mλ

Eight were excluded from analysis due to lack of first year follow-up data after transplantation. Other patients received SPEP and IFE every one or two months during the first year after stem cell transplantation. Twelve (25.0%, 12/48) patients developed small OBs on serum protein electrophoresis in the post-transplant period, but clonal plasmas were not seen in bone marrow flow cytometry analysis at the same time. The median time to development of an episode of OBs was 1.4 months post-transplant (range, 1-3), and they persisted for a median duration of 5.8 months (range, 1-15). Eleven patients achieved CR after OBs disappeared, and 1 patient was still PR. 2 patients of the patients with OBs relapsed, and one of them died, OS was 56months A comparison between the patients with or without OBs is shown in Table 2 .Of the 12 patients with OBs, one patients relapsed, and the PFS was 11 months. One patient had two episodes of OBs, and three patients had three episodes. The quantities of OBs were normal or slightly elevated (Table 3, Figure 1).

Table 3 Clinical Characteristic of OBs

OB group	OB quantity	Before transplantion	After OBdisappeared	PFS
Ig Aκ→ IgGκ→ Ig Gκ, Ig G λ→ Ig G λ	Ig G 18.7-19.4g/L	PR	CR	no progression
IgGκ→ Ig Gκ	Ig G 10.6-13.3g/L	CR	CR	no progression
Ig G λ→ Ig G λ	Ig G 0.7-11.5g/L	CR	CR	no progression
Ig D λ→ Ig Gκ, Ig G λ	Ig G 12.3-15.4g/L	PR	CR	no progression
IgGκ→ Ig Gκ, Ig G λ	Ig G 11.7-12.4g/L	PR	CR	no progression
κ→ λ	urineλ0.02g/24h	CR	CR	no progression
Ig Aλ→ IgMλ, Ig Aλ	IgM0.05-0.06g/L, Ig A0.2-0.4g/L	PR	PR	no progression
Ig Aκ→ Ig G λ	Ig G 11.2-14.6g/L	PR	CR	no progression
κ→Ig Gκ→ Ig G λ→ Ig Gκ	Ig G 10.4-13.2g/L	CR	CR	no progression
Ig Gλ→ Ig Aκ, Ig Gλ	Ig G 0.6-20.4g/L	CR	CR	no progression
Ig D λ→ Ig Gλ, Ig Gκ	Ig G 11.5-14.7g/L	PR	CR	no progression
IgGκ→ Ig Gκ, Ig G λ	Ig G 10.7-19.7g/L	PR	CR	no progression

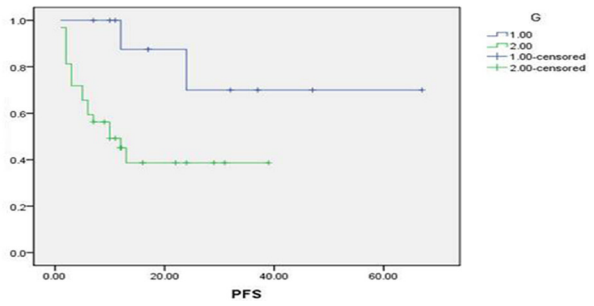

Figure 2. Progression Free Survival Post-transplant According to the Presence or Absence of an Oligoclonal Band on Serum Protein Electrophoresis (The blue curve was the presence of an oligoclonal band, its PFS was better than the absence of an oligoclonal band)

The relationship between post-transplant response and OS could not be analyzed because of the short follow-up. Compared to those who had a normal SPEP, the 12 patients who developed OBs had superior progression-free survival (1 year PFS 92% vs 66.7%, p=0.002), for comparison of PFS see Figure 2. Overall survival was not analyzed.

Discussion

We have reported a single institute's experience of oligoclonal band detection in 12 patients with multiple myeloma, after receiving autologous or allogeneic hematopoietic stem cell transplantation. The prevalence, etiology, and clinical significance of this event is still unknown. In 25.0% (12/48) of patients, OBs occurred at a median of 1.4 months post-transplant. This incidence was reported to be 73% by Sala et al. (2009) and Hovenga et al. (2000), 10% by Zent et al.(1998), and 43% by Maisnar et al. (2007). The differences in incidence of these small bands may be related to assay sensitivity (Tormey, 1989).

Previous studies have shown that antibody production is impaired after allogeneic and autologous stem cell transplantation and that transient OBs detectable in serum IFE are common during the recovery of Ig production (Mitus et al., 1989; Gerritsen et al., 1993; 1994). So the presence of OBs after transplantation could be related to the recovery of impaired Ig production rather than to a change in the paraprotein production by the malignant plasma cell clone. This B cell reconstitution recapitulates normal ontogeny but in a clonally dysregulated fashion, which may last more than 5 years after transplantation, probably as a result of impaired T-cell regulation (Velardi et al., 1988; Small et al., 1990; Bergsagel et al., 1996).

In assessing OBs, isoelectric focusing (IEF) proved to be a useful tool. It can immediately demonstrate which discrete bands are oligoclonal and thus are not clinically concerned with disease relapse. Isoelectric focusing also documented the presence of discrete bands of up to 5g/L which appeared monoclonal, but had different immunoglobulin or electrophoretic properties to the original myeloma paraprotein. But we have not been able do this examination in our center till now.

The appearance of OBs should be considered as an additional serum marker for the evaluation of prognosis in allogeneic and autologous stem cell transplantation patients due to the mean OS times obtained for these patients (Mariel et al., 2010). Hari reported the same conclusions, indicating the need for newer schemes incorporating other prognosis markers. This is because neither of the systems currently used are strongly predictive of outcomes for all stages (Hari et al., 2009).

The serum free light chain (FLC) ratio appears to be an independent risk factor for progression, and a sensitive technique for monitoring disease response and relapse. However, a previous report showed that the incidence of abnormal serum FLC κ/λ ratios in patients with MM and long lasting CR indeed correlated with the presence of OBs (De Larrea et al., 2009). But we did not have the data of serum FLc measurements in our study.

In our data, there was only one patient with OBs that really relapsed, much lower than the patients without OBs. This patient relapsed 6 months after the OBs disappeared. Some PR patients with OBs reached CR after OBs disappeared, one year PFS of the patients with OBs was superior to the patients without OBs. So OBs may not be a bad clinical event, but the appearance of OBs in the post-transplant setting may cause clinician confusion, and disturb the decision making of the treatment. Although its clinical significance is uncertain, it needs carefully monitoring by the laboratory.

In summary, the development of small OBs and immunoglobulin isotype switch post-transplant in patients with myeloma is common, appears to have no adverse clinical significance and can not be considered a sign of disease relapse. Nonetheless, the appearance of such small OBs and immunoglobulin isotype switch requires careful reporting and monitoring as these bands may occasionally represent true isotype switching leading to disease relapse.

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