Isotype class switching after transplantation in multiple myeloma

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Switching of the paraprotein isotype or transient presence of oligoclonal bands detectable by serum immunofixation electrophoresis has been reported following not only transplantations, but also after intensive chemotherapy for leukemia.

Retrospective analysis of 72 transplanted myeloma patients was carried out to determine the frequency and clinical significance of the appearance of abnormal proteins bands (APB) distinct from the original paraprotein.

APB presence was observed in 31 patients (43%) already after the first autotransplant, the median interval from transplant was 2 months (range, 1 to 6 months). The most frequent occurrence of APB was observed after allogeneic transplantation. In the group of patients with APB presence more patients achieved complete remission (32.2% versus 17.1%), statistically significant differences were also established when we compared the percentage of surviving patients and overall survival, to the present date, among both groups of patients (p=0.03). All relapsed patients with previous isotype class switching had disease characterized by the same type of paraprotein as that detected at diagnosis.

The development of APB is likely related to the recovery of impaired immunoglobulin production after transplantation. We confirmed favourable prognostic significance of this finding in transplanted myeloma patients.

Key words: paraprotein switching, transplantation, multiple myeloma, prognosis, immunofixation

Multiple myeloma (MM) is the second most frequent hematological malignancy usually characterized by production of a single serum monoclonal protein of constant isotype (paraprotein) and light-chain restriction. Switching of the paraprotein isotype or transient presence of oligoclonal bands (OB) detectable by serum immunofixation electrophoresis (IFE) has been reported following not only allogeneic transplantation, but also after autologous transplantation and even following intensive chemotherapy for leukaemia [1–4]. Because the analysis of monoclonal proteins by IFE is most important method in monitoring response to therapy in MM, the appearance of a new single band or OB may pose problems in decision about consequential patient management.

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Abbreviations: APB – abnormal proteins bands; GVHD – graft versus host disease; CR – complete remission; IFE – immunofixation electrophoresis; Ig – immunoglobulin; IgH – immunoglobulin heavy chain; IS – isotype switch; MM – multiple myeloma; OB – oligoclonal bands; OS – overall survival; PBSC – peripheral blood stem cells; Tx – transplantation

The reconstitution of the immune system after transplantation has been the subject of a large number of studies [1, 5–8]. Restricted electrophoretic heterogeneity of serum immunoglobulin (Ig) and the appearance of homogeneous Ig components, first reported by Radl in 1972 [9], could be detected in up to 100% patients after transplantation depending on the sensitivity of the detection technique applied [1–3]. Some of these immunological abnormalities may reflect a recapitulation of early immunocyte ontogeny, whereas others appear to relate to development of graft versus host disease (GVHD), use of posttransplantation immunosuppressive drugs, and or other pathologic complications connected with blood stem cells transplantation [1, 3, 7, 8].

In this study, we conducted a retrospective analysis of the clinical records and results of serial serum IFE in transplanted multiple myeloma patients to determine the frequency and clinical significance of abnormal proteins bands appearance.

Patients and methods

Patients. We carried out a retrospective analysis of 72 myeloma patients who had undergone 138 transplantation

procedures at the Charles University Teaching Hospital Hradec Králové in the period from 1996 to 2002 to determine the frequency and clinical significance of the appearance of abnormal proteins bands (APB) distinct from the original paraprotein. All patients had multiple myeloma staged by standard criteria [10]. There were 38 (53%) males and 34 females aged 38 to 69 years, the mean age was 56 years. 71 patients underwent the first autologous transplantation of peripheral blood stem cells (PBSC), in one patient only a classic-type allogeneic transplantation from a related donor was performed. In 43 patients (61%) the second autologous transplantation of PBSC and in 9 (13%) patients even the third autologous transplantation was done and in 15 patients (21%) a non-myeloablative transplantation of PBSC from a related donor was performed as the second transplantation procedure.

Biochemical techniques. The nature of serum monoclonal proteins was determined in the Institute of Clinical Biochemistry and Diagnostics at the Charles University Teaching Hospital Hradec Králové. Each serum protein analysis included a serum protein electrophoresis and immunofixation electrophoresis for IgG, IgM, IgA and κ and λ light chains (SEBIA, France). An apparent isotype switch (IS) was defined as a single distinct protein band with a different heavy chain class or light-chain type from the original paraprotein, oligoclonal bands presence was reported when two or more discrete Ig bands were detected. Patients with OB and a single protein band of a different isotype (distinct from the original paraprotein) were considered to have both OB and IS.

Statistical analysis. The basic assessment was calculated by summary statistics based on binary and ordinary variables. Comparisons between groups of patients with and without APB presence after transplantation were carried out using the Mann-Whitney U-test. The method of Kaplan and Meier was used to compute the survival curves [11]. Results were considered statistically significant when the p value was less than 0.05.

Results

We observed an apparent abnormal protein band distinct from the paraprotein present at diagnosis in 31 patients (43%). An apparent isotype switch was found in 5 (7%) patients, 12 (17%) patients had oligoclonal bands and 14 (19%) patients had both isotype switch and oligoclonal bands after

Table 1. Patients with apparent isotype switch

Patient No.	Gender	Time	Isotype change	Maximum IS [g/l]	Duration [months]
1	M	post-Tx1, Tx2, Tx3 (auto)	IgA-ρ to IgG-ρ, to IgG-ρ + oligo	3.25	3 6
2	F	post-Tx1 + Tx2 (auto)	IgA-ρ to IgG-ρ + IgM-lll	2.14 + 1.72	24
3	F	post-Tx3 (alo)	IgG-ρ to IgM-lll + oligo	< 1.0	3
4	M	post-Tx3 (auto)	IgG-ρ to IgG-ρ + IgM-lll + oligo	3.16	2
5	F	post-Tx1 + Tx2 (auto) (alo)	IgG-ρ to IgG-ρ + oligo	1.52	11
6	M	post-Tx1 + Tx2 (auto)	IgG-ρ to IgG-ρ + IgG-lll + oligo to IgG-lll	1.4 2.3	10 15
7	F	post-Tx1 + Tx2 + Tx3 (auto)	IgG-lll to IgG-ρ + oligo	2.09	5
8	F	post-Tx3 (auto)	IgG-lll to IgG-lll + IgG-ρ	< 1.0	3
9	M	post-Tx1 + Tx2 (auto)	free-lll to IgG-ρ + IgG-lll	0.84 + 0.95	29
10	F	post-Tx2 (auto)	IgA-ρ to IgG-ρ	1.28	5
11	M	post-Tx3 (auto)	IgG-lll to IgG-lll + IgG-ρ + IgA-ρ	1.22 < 1.0	2
12	F	post-Tx2 (auto)	IgG-lll to IgG-lll + IgG-ρ + oligo to IgG-lll + IgM-ρ	0.72 1.1	3
13	M	post-Tx2 (alo)	IgG-ρ to IgG-ρ + IgG-lll + oligo to IgG-ρ + IgM-lll + oligo	< 1.0 < 1.0	4 2
14	M	post-Tx1 + Tx2 (auto)	free-ρ to IgG-ρ + IgM-ρ + oligo	1.9 + < 1.0	1
15	F	post-Tx1 + Tx2 (auto) (alo)	free-lll to IgG-ρ + IgM-lll + oligo	2.44 + < 1.0	9
16	M	post-Tx1 + Tx2 (auto) (alo)	IgG-lll to IgG-lll + IgG-ρ + oligo	6.53	2
17	M	post-Tx1 (auto)	IgA-ρ to IgA-ρ + IgG-ρ	1.67	10
18	F	post-Tx3 (alo)	IgG-lll to IgG-lll + IgG-ρ + oligo	1.68	1
19	F	post-Tx1 + Tx2 (auto)	IgG-lll to IgG-lll + IgG-ρ + oligo	1.05	7

The single band Ig isotype and light chain are specified for each observation.
Tx = transplantation

transplantation identified by IFE (Table 1). 17 patients (24%) developed APB already after the first autotransplant, the median interval of APB identification from transplant was 2 months (range, 1 to 6 months), 5 patients developed APB after a second and 3 patients even after a third autologous transplantation. Immunofixation analysis revealed 71% of the APB to be of the IgG type, 23% IgM and 6% IgA; 58% were kappa and 42% were lambda. The most frequent occurrence of APB was observed after allogeneic transplantation, 6 patients (38%) developed APB in a median interval of 5 months from transplant (range, 3 to 36 months). The appearance of APB in the group of patients after allogeneic transplantation correlated statistically significantly with development of GVHD (4 patients in APB+ resp. only 2 patients in APB- group). APB persisted an average of 7 months (range, 1 to 29 months) in the whole group of patients.

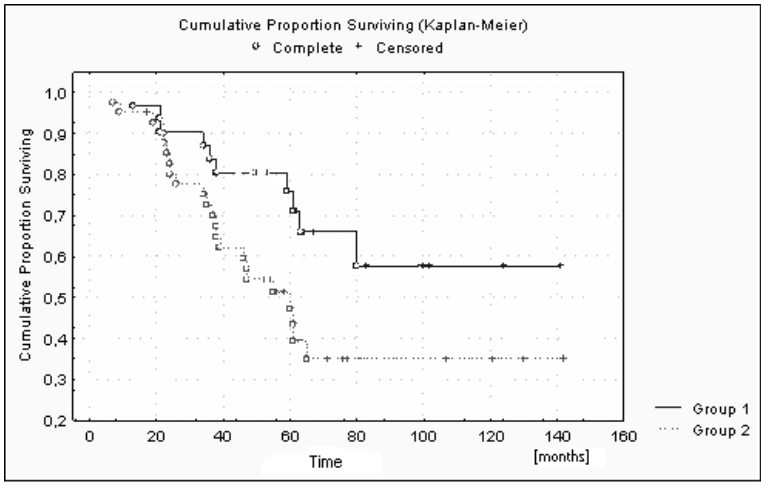

Figure 1. Kaplan – Meier survival curves of both groups of patients. Group 1: patiens with APB presence; Group 2: patients without APB presence after transplantation

We compared the clinical outcome of patients with APB occurrence with that of patients without APB to determine if APB had prognostic significance (Table 2). In the group of patients with APB presence more patients achieved complete remission (CR), 32.2% versus 17.1%. Statistically significant differences were also established when we compared the percentage of surviving patients and overall survival (OS), to the present date, among both groups of patients (p=0.03). Kaplan-Meier survival curves for both groups of patiens are shown in Figure 1.

All patients with isotype class switching who failed to achieve CR or relapsed after transplantation had disease characterized by a paraprotein with the same immunofixation characteristics as that detected at diagnosis.

Discussion

We have reported a single institution's experience of abnormal protein band detection in 72 adult patients with multiple myeloma after receiving autologous or allogeneic hematopoietic stem cell transplantation. The prevalence, etiology, and clinical significance of this finding is not yet known. In the studies involving larger numbers of patients, the incidence of APB was reported to be between 42% and 90% depending on the sensitivity of the detection technique applied [1–4]. By means of retrospective analysis we noticed APB presence totally in 31 (43%) patients.

It is clear that the process of illegitimate isotype switching is heavily implicated in the pathogenic development of neoplastic B cells in multiple myeloma. Rearrangements of the immunoglobulin heavy chain (IgH) locus at 14q32 can occur in up to 74% of cases [12]. It has been hypothesized that translocation to the IgH loci provide one of the initial immortalizing events in the molecular pathogenesis of myeloma [13]. Previous studies have shown that antibody production is impaired after both allogeneic and autologous stem cells transplantation and that transient OB detectable in serum IFE are common during the recovery of Ig production [1, 3, 5]. So the presence of APB 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 an impaired T-cell regulation [7, 8, 13]. Recapitulation of Ig levels according to normal ontogeny is compatible also with the observation that a high proportion of peripheral B cells in the first months after transplantation show the phenotype and functional characteristics of cord blood B cells [7, 8, 14, 15].

However we must not overlook the possibility that new paraprotein bands may also be caused by lymphoproliferative disorder complicating immunosupression after transplantation procedure [1, 3] or may represent a rare case of true clonal isotype switching [16]. In our observation we did not notice

Table 2. Comparison of treatment results in both groups of patients

APB presence	No. of Pts	No. of CR	Alive to present	OS to present
Patients with APB presence	31	10 (32%)	21 (64.5%)	62.5 months
Patients without APB	41	7 (17%)	18 (43.9%)	51.1 months

APB = abnormal proteins bands; CR = complete remission; OS = overall survival

any posttransplantation lymphoproliferative disease, all patients with APB presence who failed to achieve CR or repeatedly relapsed had disease characterized by a paraprotein with the same IFE characteristics as that detected at diagnosis. However several published cases suggest that even the possibility that the original type of paraprotein in multiple myeloma might change should be regarded [17, 18]. Walker suggested that the reason could be a neoplastic clone mosaic of 1) cells capable of synthesizing both light and heavy chains with 2) cells producing light chains only in some patients with myelomatosis [19].

It has been published only one study demonstrating prognostic significance of APB appearance after transplantation in MM patients yet [4]. We confirmed the results of this study showing that patients with an apparent APB after transplantation had a significantly better survival. In the group of patients with APB presence we observed higher percentage of achieved CR and surviving patients and also longer overall survival. The appearance of APB after transplantation seems to be a helpful marker of normal immune reconstitution which is necessary for the immunosuppressive effect on the residual MM clone.

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