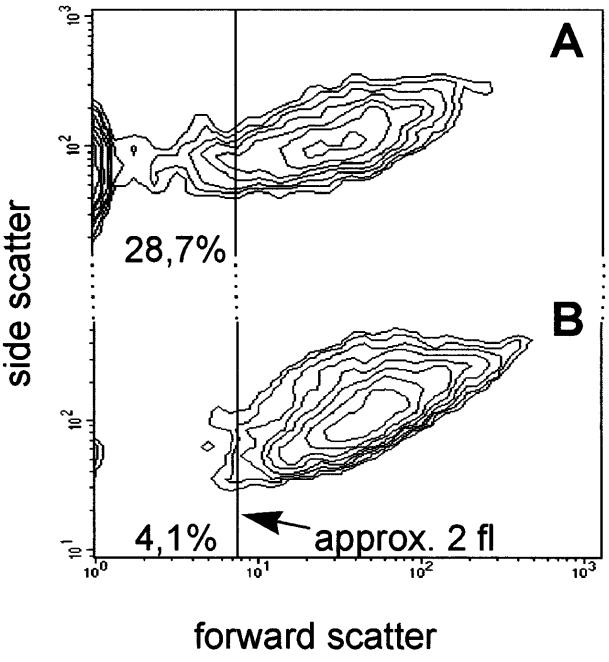


**Fig 1. Flow cytometric analysis (contour plot) of platelets and platelet-derived microparticles in a patient with acute myelogenous leukemia (A) and a normal individual (B) using anti-CD61 and anti-CD42b antibodies. Whole blood was treated with platelet-specific fluorescent antibodies as described previously.[5] $CD61^+/CD42b^+$ events (n = 50,000), representing platelets and platelet-derived microparticles, were gated and are shown in forward and side scatter mode. Normal-size platelets (>2 fL) and platelet-derived microparticles (<2 fL) were defined as shown in the graph by a size-threshold of 2 fL, established with the help of fluorescent calibration beads.**

above the normal mean. Bleeding episodes were not observed during chemotherapy when counts of normal-size (>2 fL) platelets were between 5,000 and 10,000/µl and microparticle levels were similar or higher than those of normal-size platelets. Bleeding episodes (gastrointestinal bleeding and hematuria) seen in 4 patients during chemotherapy were associated with reduced platelet microparticle levels (<2%) and total platelet events of 2,300, 2,700, 3,400, and 4,900/µL, respectively.

These observations indicate that a platelet transfusion threshold of 5,000/µL formerly suggested by Gmür et al[2] (who used a time-consuming microscopic platelet counting method) is more appropriate than the 10,000/µL platelet threshold suggested recently by Rebulla et al[1] provided that automated technology based on immunodetection is used for platelet counting. This may lead to a further considerable reduction in platelet transfusions and costs (despite the possible investment needed to update laboratory equipment). Furthermore, our results suggest that the favorable role of platelet-derived microparticles in hemostasis needs to be given more consideration in platelet transfusions.

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## The Italian Experience on Interferon as Maintenance Treatment in Multiple Myeloma: Ten Years After

*To the Editor:*

The role of interferon maintenance treatment in patients with multiple myeloma (MM) is still debated. In 1990, the Italian Multiple Myeloma Study Group published the results of the first randomized study on the role of interferon a2-b (IFN) as maintenance treatment in patients responding to induction therapy.[1] One hundred one MM patients responding to traditional first-line induction chemotherapy were randomized to receive (n = 50) or not receive (n = 51) IFN maintenance. Patients were recruited from a group of 202 symptomatic MM patients observed in the three university institutions of Rome, Bari, and Turin, Italy. The results originally demonstrated that a maintenance treatment with IFN prolonged response and survival duration in patients with MM who have responded to conventional induction therapy.

After this experience, five large randomized studies were published comparing IFN maintenance versus untreated control: two of them did not demonstrate any advantage as for response and survival duration[2,3]; one showed a clear advantage in response duration but not in survival duration[4]; and two demonstrated a significant improvement both in response duration and in survival duration.[5,6]

The updated results of the Italian study 9 years after the randomization of the last patient confirm a significant prolongation of response duration in IFN maintained patients: the median response duration (from time of randomization to maintenance treatment) is 24 months in patients receiving IFN and 13 months in untreated patients ($P = .0016$). The results in terms of prolongation of survival are less significant: the median overall survival is of 50 and 39 months, respectively ($P = .21$); among patients who had an objective response to induction chemotherapy (>50% reduction in M protein), the median survival was 50 and 35 months, respectively ($P = .07$; Fig 1). However, 9 patients are still alive and in response in the IFN-maintained group versus 2 in the unmaintained group.

In conclusion, the majority of randomized studies on IFN maintenance in MM as well as our results demonstrate that IFN maintenance significantly prolongs the response duration phase in MM patients responsive to previous induction therapy, whereas the efficacy on survival

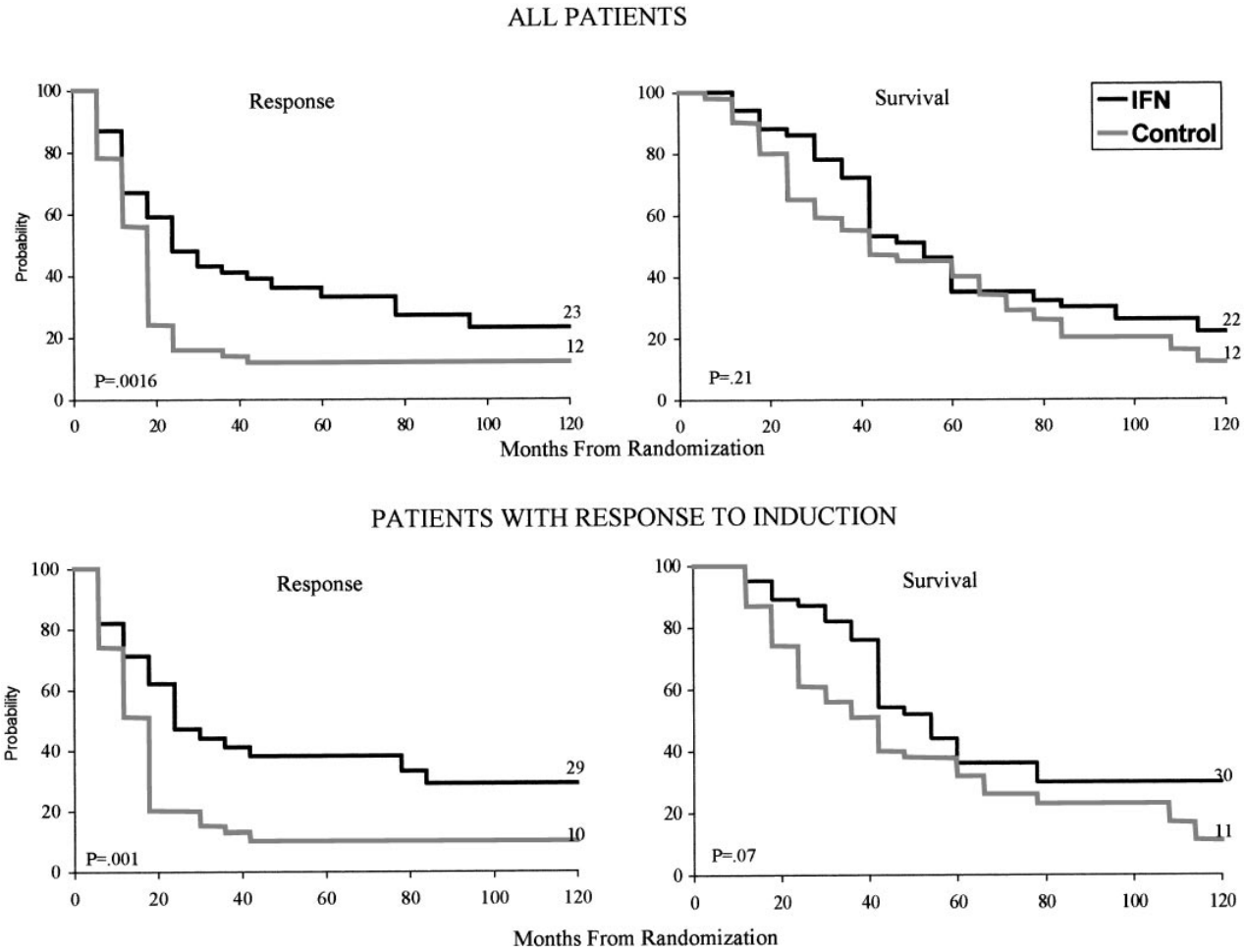


**Fig 1. Kaplan-Meier curves for response and survival after randomization of patients to the interferon maintenance group or control group.**

prolongation is less clear. Despite the uncertain effect on survival duration, IFN maintenance is still appropriate in responding myeloma patients, because delaying relapse appearance allows a higher quality of life in patients with MM. Nevertheless, accurate quality of life evaluation is required in these patients to confirm this assumption.

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## Kaposi's Sarcoma-Associated Herpesvirus Is Not Detected With Immunosuppression in Multiple Myeloma

*To the Editor:*

Kaposi's sarcoma-associated herpesvirus (KSHV) is involved in the pathogenesis of all forms of Kaposi's sarcoma (KS).[1] In acquired immunodeficiency syndrome (AIDS)-associated KS, KSHV detection in peripheral blood mononuclear cells increases with immunosuppression.[2] Posttransplant KS are generally due to KSHV reactivation,[3] and complete KS remission is often achieved after reduction or cessation of immunosuppressive therapy.[4] Serologic studies have shown that 80% to 90% of KS patients have detectable antibodies against KSHV.[5] These data clearly demonstrate that KSHV is under immunological control in KS patients.

Recently, KSHV was detected in long-term cultures of bone marrow stromal cells (BMSC) with a phenotype of dendritic cells (DC)[6] and in bone marrow (BM) core biopsies from patients with multiple myeloma (MM).[7,8] The physiopathological relevance of KSHV in this interleukin-6 (IL-6)–related disease could be that it encodes for a viral IL-6 (vIL-6) able to stimulate the growth of human MM cell lines.[9] However, these results contradict what is known about KSHV infection and MM. Epidemiological studies show that KSHV and non-AIDS KS are found at higher incidence in Italy[5] and that this is clearly not the case for MM.[10] In addition, five groups reported a lack of antibodies against KSHV antigens in MM patients despite a normal humoral response to other herpesvirus.[11-15] Finally, we and others were recently unable to found KSHV in DC samples obtained from apheresis cells of MM patients,[16,17] and Masood et al[14] failed to detect KSHV DNA in long-term BMSC cultures from MM patients. This discrepancy led us to explore the possibility that an extremely low level of KSHV infection in MM patients, leading to variable detection, may be reactivated during severe immunosuppression.

Ten patients with MM were treated with a double high-dose chemotherapy (HDC; 140 mg/m$^2$ melphalan plus 8 Gy total body irradiation) supported by autograft with purified CD34$^+$ cells (reinjection of 4.02 $\pm$ 1.03 $\times$ 10$^6$ CD34$^+$/kg; range, 2.88 to 5.73 $\times$ 10$^6$/kg). CD34$^+$ progenitors were purified by the clinical-grade method from Cellpro (Bothell, WA), leading to a 35.6-fold enrichment in hematopoietic progenitors from a mean value of 2.4% $\pm$ 1.08% CD34$^+$ cells (range, 0.99% to 3.47%) before purification to 85.4% $\pm$ 7.1% CD34$^+$ cells (range, 72.4% to 92.8%) after purification. The resulting graft was 1,407-fold depleted of T cells (reinjection of 0.11 $\pm$ 0.08 $\times$ 10$^6$ CD3$^+$ cells/kg; range, 0.05 to 0.25 $\times$ 10$^6$/kg). Four of 10 patients relapsed within 1 year. The peripheral blood CD4$^+$ T-cell count was monitored at 3, 6, and 12 months after the second purified autograft. Eight of 10 patients had less than 200 CD4$^+$ cells/μL for at least 3 months, with a mean duration of 7 months for the 6 evaluable over 1 year (Table 1). Many infectious events arose during this first year after second HDC (median of 3 episodes per patient). In particular, 7 of 10 patients suffered from herpesvirus reactivation (Table 1). Because KS has rarely

**Table 1. CD4$^+$ T-Cell Counts and Infectious Events in Autografted MM Patients**

| Patient No. | No. of CD4$^+$ T Cells/μL: Before First HDC | Day 90 After Second HDC | Day 180 After Second HDC | Day 360 After Second HDC | Cumulative No. of Months With CD4$^+$ T Cells <200/μL | Infectious Events After Second HDC* |
|---|---|---|---|---|---|---|
| 1 | 892 | 170 | 291 | 266 | 4 | VZV, CMV |
| 2 | 361 | 91 | 11 | 351 | 6 | VZV, CMV |
| 3 | 350 | 95 | 150 | 146 | 8 | HZV, CMV |
| 4 | 315 | 327 | 307 | 234 | 0 | HSV |
| 5 | 259 | 77 | 75 | 88 | 12 | Other |
| 6 | 369 | 168 | 148 | 160 | 12 | CMV,Other |
| 7 | 430 | 140 | 149 | † | 11/11‡ | Other |
| 8 | 593 | 310 | ND | † | 0 | CMV |
| 9 | 124 | 64 | 199 | § | 6/6‡ | |
| 10 | 412 | 128 | † | † | 4/4‡ | CMV |
| Mean $\pm$ SD | 410.5 $\pm$ 207.5 | 157 $\pm$ 92.5 | 166.2 $\pm$ 99.8 | 207.5 $\pm$ 94.9 | | |

CD4$^+$ T-cell count was monitored by flow cytometry.

Abbreviation: ND, not done.

*Viral manifestation of varicella (VZV), zooster (HZV), herpes (HSV), other virus (Other), or cytomegalovirus antigen detection (CMV).

†Patient died before evaluation.

‡CD4 count could be evaluated only during the indicated time.

§Patient has not reached day 360 after HDC.