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Recombinant Interferon-γ in a Patient With Multiple Myeloma

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Interferon-γ (IFN-γ) HAS a potent anti-proliferative activity in some systems superior to that of IFN-α and -β. *In vitro*, IFN-γ showed anti-tumoral effect against myeloma cells and inhibited bone resorption [2]. In one study, IFN-γ was administered to 15 multiple myeloma (MM) patients, but no response was observed [3], in another IFN-γ induced a 12% response rate [4].

We report on an MM patient who showed response to IFN-γ treatment. A 52-year-old woman was diagnosed with IgG/λ MM (stage 1A): M-component was 12 g/l, bone marrow plasma cell infiltration 15%, bone X-ray disclosed a typical "punched out" osteolytic lesion at the right clavicle. The patient was first treated with radiotherapy (30 Gy). Serum M-protein rapidly rose to 18 g/l, bone marrow plasma cell infiltration and bone lesion were unchanged. The patient was then started on IFN-γ (Imukin, Bohering, Germany), 120 μg/m² subcutaneously (s.c.) three times a week for 3 months. During treatment, clinical toxicity included only myalgia and fatigue. No fever, chills, nausea, vomiting or anorexia were observed. The only laboratory abnormality was moderate neutropenia (neutrophils 1.2×10^9/l), occurring after 1 month of treatment. Treatment was safely performed on an out-patient basis.

Throughout treatment, serum M-component remained stable and, after IFN-γ discontinuation, gradually decreased from 20 l/g to 9 g/l after 6 months, and is stable after 16 months of follow-up (Figure 1). Bone marrow plasma cell infiltration was reduced from 15 to 5% at the end of therapy and then to 1% after 16 months of follow-up. The percentage of marrow myeloma cells in the S-phase, labelling index, determined by examining 5-bromo-2-deoxyuridine incorporation, decreased from 0.7 to 0.2%. CT scans of the osteolytic lesion, performed at the beginning of the therapy and 2.5 months later, revealed an important improvement with a partial reconstruction of the cortical bone.

Neopterin (from 9.9 to 30 nmol/l) and β-2-microglobulin (from 2.5 to 4.6 mg/l) increased to the same extent as observed in previous studies with higher IFN-γ doses (200–500 μg/m²), but with higher toxicity rate. In fact, our data indicate that the biological effectiveness of IFN-γ can be reached at the doses we employed.

In vitro studies show that IFN-γ greatly inhibits proliferation without effect on Ig secretion [5] indicating that inhibition of proliferation may be combined with increased Ig secretion in terminally differentiated plasma cells. We did not detect any decrease in serum M-component, but a substantial reduction was noticed after 6 months of follow-up. Plasma cell infiltration and proliferation were also reduced. These data suggest a strong IFN-γ anti-myeloma effect *in vivo* and a possible plasma cell differentiation activity that may prevent an immediate M-component reduction.

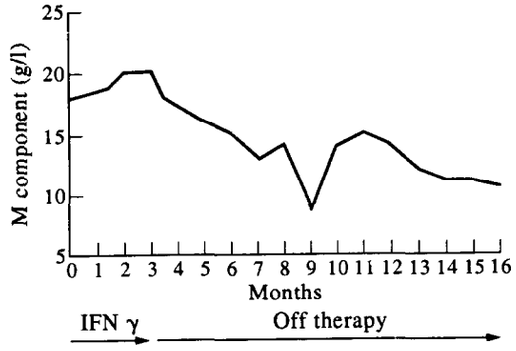

Figure 1. M-Component at diagnosis, during and after treatment with IFN-γ (IFN-G).

A synergistic effect between radiotherapy and IFN-γ may have played a role in the bone repair of the osteolytic lesion, since partial bone repair after radiotherapy is usually seen after at least 3–4 months of follow-up. Furthermore, IFN-γ was shown to induce the down-regulation of the IL-6 receptor expression in experimental models [6], that may explain the IFN-γ inhibition of bone resorption, a process completely dependent on the endogenous IL-6 produced by bone tissue [7]. Our report may represent evidence that IFN-γ could contribute to bone resorption inhibition *in vivo*.

In conclusion, further clinical trials are warranted to determine whether IFN-γ is a potent *in vivo* inhibitor of myeloma cell proliferation and plays a role in the inhibition of bone resorption.

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