All-Trans Retinoic Acid for Advanced Multiple Myeloma

To the Editor:

In a recent issue of Blood, Ogata et al\(^1\) described a series of interesting and convincing in vitro studies on fresh human myeloma-tous plasma cells, suggesting that all-trans retinoic acid (ATRA) may have an inhibitory effect on the proliferation of myeloma cells both by the downregulation of interleukin-6 receptor (IL-6R) and/or its signal transducer glycoprotein 130 (gp130) surface expression on neoplastic cells and by inhibition of IL-6 production by myeloma-tous and stromal cells. Previous studies performed on myeloma cells lines had provided similar results but had also shown that ATRA may affect myeloma cell growth via a mechanism distinct from IL-6 modulation.\(^2\)\(^3\) Unfortunately, despite these encouraging experimental in vitro results, none of the so far reported 24 patients with multiple myeloma (MM) treated with ATRA (all described in abstract form, including our preliminary report on 7 patients) has shown significant response to this treatment.\(^4\)\(^5\)

We have now concluded our pilot study on ATRA in MM that enrolled, after informed consent was obtained, 10 patients (5 men and 5 women; mean age, 65 years; range, 54 to 71 years) with advanced (all stage III A), resistant, or relapsing disease after at least three lines of chemotherapy including melphalan, prednisone, intermediate-dose cyclophosphamide, antracyclines or their analogues, vincristine, or high-dose dexamethasone. The M-component was IgG in 7 patients, IgA in 2 patients, and of micromolecular type in 1 patient. ATRA was administered continuatively as the sole antineoplastic treatment at the fixed oral dose of 50 mg twice a day.

In 3 patients administration of the drug was stopped after 12 to 21 days because of relevant side effects (nausea, vomiting, or volumetric increase of skin verrucae). The remaining 7 subjects received ATRA for at least 2 months without significant toxicity. However, none of them showed evidence of response in terms of reduction of M-component, bone marrow plasmocytosis, or bone pain. Disease progression accelerated under ATRA in 4 patients. Serum levels of IL-6 and C-reactive protein increased while on treatment in 5 patients with respect to baseline ones. Hypercalcemia developed in 4 of these patients. Serum levels of soluble IL-6R were also found to be increased after ATRA treatment, with respect to initial values, in 2 of 4 patients in whom such an assay was performed.

Thus, in contrast to the promising results obtained in vitro, our clinical data do not encourage the use of ATRA alone in patients with advanced MM, in whom this drug, at the dose used in the present study, seems instead to induce an unexpected increase of the production of IL-6 and its circulating receptor, which could stimulate the neoplastic growth and the osteoclastic activity of these patients.\(^6\)

The evident contrast between in vitro and in vivo studies on this topic as well as the possible therapeutic role of ATRA in combination with other drugs remain to be elucidated. In this setting, in view of the possible synergistic activity of ATRA with \(\alpha\)-interferon\(^2\) and dexamethasone,\(^7\) we are now evaluating the therapeutic effect of the association of these drugs in patients with advanced MM.
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REFERENCES


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