Therapeutic management of hematological malignancies in elderly patients. Biological and clinical considerations

Part IV: Multiple myeloma and Waldenström’s macroglobulinemia

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ABSTRACT. Following recent data on multiple myeloma (MM) in the literature, a possible model of myeloma development, involving different cytokine signals, is advanced, and the prognostic significance of two principle staging systems is evaluated. Different therapeutic approaches to MM have been employed, consisting of either treatment with only melphalan and prednisone, or combination chemotherapy, especially in patients with a poor prognosis. However, for the initial therapy, melphalan plus prednisone in doses that compensate for individual variation in drug absorption still appears the best choice in the vast majority of MM patients. The main clinical and hematological features which distinguish Waldenström’s macroglobulinemia from MM are described, as are the criteria which should be used in choosing the most appropriate treatment based, when necessary, on chemotherapy with standard alkylating agents, as well as on the new nucleoside analogues, and repeated courses of plasmapheresis.

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MULTIPLE MYELOMA

The incidence and mortality rates for Multiple Myeloma (MM) vary greatly in different parts of the world and in different racial groups. Indeed, the overall figures for population incidence in terms of number of cases seen annually per 100 000 may be meaningless without accompanying data on factors such as the age range of the study population, because MM is very much a disease of the elderly, and is rare below the age of 30. MM is more common in men than women at all ages, with a ratio of 1.6 : 1. On an international level, where age standardized rates are available, Asian populations appear to have a low incidence, perhaps half that of Caucasians, whereas the incidence in Black populations is twice as high as the Caucasian rates. As these striking differences are present in widely separated parts of the world, and are maintained among immigrant populations living in altered environments, they may imply the existence of a genetically determined racial predisposition (1).

There is convincing evidence that myeloma may develop after exposure to various forms of ionizing radiation. A 5-fold increase in MM incidence was observed in survivors at Hiroshima and Nagasaki, albeit with a latent period greater than that for leukemias and exceeding 15 years.

As far as chemical agents are concerned, there is little to suggest that cytotoxic drugs may induce myeloma; indeed, their tumorigenic effect is directed overwhelmingly against the myeloid, rather than the lymphoid cell series. Their use, however, may influence later malignant progression or transformation to myeloma, and thus some drugs may exercise a pathogenetic role. MM patients receiving standard chemotherapy that involves alkylating agents, such as melphalan or cyclophosphamide, have an increased risk of subsequently developing acute mye-
Multiple myeloma (MM), which is frequently preceded by a myelodysplastic state. While the risk is 100 to 200-fold greater than that normally expected, it may in part be due to an intrinsic relationship between myeloma and AML, independent of chemotherapy, as the two diseases occasionally may present together, and AML has been reported to occur in well-documented cases of myeloma before any chemotherapy or radiation has been administered. Nevertheless, there is little doubt that any such natural association is greatly enhanced by cytotoxic therapy, in a manner similar to that seen in other hematological malignancies, notably lymphomas (2).

Even without a genetically determined defective immune response, the proliferation of antibody-forming cells in plasmacladoid neoplasia might well occur as a consequence of a mutational change in a cell that is still capable of renewal but is committed to plasmaclad formation and antibody-production. The initial event might be due to a thymic involution and the loss of normal thymus-mediated control of early B-cell development (3), and could involve abnormal cytokine production. An abnormal proliferation of multiple clones may follow, and one of these expanded clones could be subjected to a random genetic alteration, resulting in malignant transformation. Some degree of response to normal cytokine signals might still be maintained, thus limiting the growth of the clone; this situation would correspond to those cases diagnosed as “monoclonal gammopathy of undetermined significance (MGUS)”. Further oncogenic alterations might result in the full malignant phenotype of MM (3).

In accordance with this model, multiple cytokines appear to be active on MM cells. Interleukin-6 (IL-6) appears to be the major growth factor for myeloma cells (4). Tumor necrosis factor (TNF) and Interleukin-1 (IL-1) increase IL-6 production by marrow stromal cells (5). Furthermore, all three cytokines (IL-6, IL-1, TNF) act as osteoclast activating factors (OAF), and thereby contribute to the bone reabsorption in myeloma. In vitro studies have shown that interleukin-3 (IL-3), granulocyte-macrophage growth factor (GM-CSF) and IL-5, all synerize with IL-6 to stimulate myeloma cell proliferation (6).

The possibility that GM-CSF and G-GSF might influence myeloma cell proliferation might have important clinical implications, as these growth factors are currently employed in clinical practice and may have the theoretical potential to cause disease progression in some cases of myeloma.

The above model of myeloma development postulates the presence of genetic alterations. Numerous chromosome abnormalities, both numerical and structural, have been reported, despite the generally low rates of mitosis; oncogenic activation is frequently observed. The myeloma cells of about 25% of the patients have increased levels of c-myc mRNA, and up to 30% have mutations of N-ras (7, 8).

Unlike follicular lymphomas, there have been no reports of translocation of the Bcl-2 gene, an oncogene that acts by prolonging cell survival, and its involvement in myeloma seems quite remote (9). Fairly recent studies found that up to 20% of MM patients have p53 mutations (10).

As myeloma is a very slow growing tumor, its clinical onset is commonly very subtle, with the gradual development of scattered bone pain and minor symptoms of anemia; however, there often is an episode of an acutely exacerbated bone pain due to vertebral compression or other pathological fracture, sometimes following minor trauma. Indeed, pain is the major presenting symptom in 60-70% of patients with anemic or uremic symptoms; in another 20% pain is marked, while the remaining patients present a variety of less common features, ranging from the intercurrent infections often affecting myelomatous patients to hyperviscosity syndromes, acute hypercalcemia, localized manifestations of amyloidosis, and secondary consequences of bone destruction, such as paraplegia due to spinal cord compression. A mixture of presenting symptoms is commonly observed in myeloma, namely bone marrow infiltration with >20% plasma cells, radiologically detectable osteolytic lesions, and the presence of a serum paraprotein and/or a urinary monoclonal light chain, associated in either case with immunosuppression.

For a diagnosis of myeloma to be accepted, at least two of these criteria are generally required (1). Multiple myeloma is subclassified histologically as low, intermediate and high grade malignancy on the basis of the predominating cell type. Cases with small, mostly mononuclear cells with dense clockface chromatin blocks in non-nucleolated nuclei have the longest survival; cases with more nuclear irregularities, including cleavage, fragmentation and multinuclearity, and the presence of nucleoli in abundant weakly eosinophilic cytoplasm are associated with intermediate survivals. The most rapidly progressive cases show chiefly plasmoblastic characteristics, including nucleolated nuclei with less prominent chromatin markings, a high nuclear-cytoplasmic ratio, and more marked basophilia; aggressive osteoclastic bone destruction is more common in these more aggressive and malignant cases (Figs. 1-3).

The extent of myelomatous infiltration of the bone