Moving forward in myeloma research

During the last two decades there has been impressive steps forward in myeloma research. This has been due to several facts: (i) an increasing number of investigators and specialized institutions devoted to clinical and laboratory research in this disease, (ii) the role of two Myeloma Foundations, the International Myeloma Foundation (IMF) and the Multiple Myeloma Research Foundation (MMRF) supporting both research and patient care, (iii) the introduction of high-dose therapy/stem cell support leading to complete remission in a significant proportion of patients offering the hope of long-lasting disease control, (iv) better supportive measures (bisphosphonates, erythropoietin) and (v) the availability of effective anti-myeloma drugs (thalidomide, IMiDs, bortezomib) with new mechanisms of action. As demonstration of this increased interest, nine International Myeloma Workshops, plus a number of specific Symposia, have been organized in recent years. In fact, the number of attendees has increased from about 30 at the first Workshop in 1987 to more than one thousand at the last one in 2003 and the whole myeloma community is eagerly awaiting the 10th Workshop to be held in Sidney in April 2005. In this context, it is not surprising that the clinical and laboratory research is resulting in a large number of high-quality publications. We will briefly discuss the main messages from four papers published in the present issue of Haematologica.

High-dose therapy/stem cell transplant (HDT/SCT) is currently considered an important part of the front-line therapy of patients with multiple myeloma.[1] A number of prognostic features have been identified as indicators of poor outcome after autologous transplantation (e.g., 13q deletion, high β2-microglobulin serum levels).[2] In this issue of Haematologica, Moreau *et al.*[3] report that patients with the CD45 negative phenotype, which accounts for about 30% of all myelomas, form a subset with a poor outcome after HDT/SCT. Of interest, the presenting features and the response after HDT were similar in both subgroups (CD45 positive and CD45 negative), the poorer overall survival in patients lacking CD45 at diagnosis being the consequence of a short survival after relapse. The mechanism by which CD45 negative patients have a shorter survival after relapse is unclear. It has been suggested that CD45 negative myeloma cells have a higher peripheral blood circulating potential and a lower bone marrow homing potential.[4] This could result in greater extramedullary spread at the time of relapse. Thus, given the higher circulating potential of CD45 negative myeloma cells, it would be of interest to look carefully at the relapse pattern as well as at the response to salvage therapy after relapse, particularly the response to new agents targeting not only the myeloma cell but also the bone marrow microenvironment.

Thalidomide produces a response in approximately 40% of patients with relapsed/refractory MM[5] and in about one-third of patients with smoldering multiple myeloma.[6,7] This drug has antiangiogenic and immunomodulatory effects, likely mediated by several cytokines such as vascular endothelial growth factor, fibroblastic growth factor, hepatocyte growth factor, interleukin-6 and tumor necrosis factor α (TNF-α). It has been suggested that TNF-α has an important role in the pathogenesis of MM[8] and also that this cytokine has modulating properties on thalidomide.[9] Brenne *et al.*[10] report in the current issue of Haematologica that low serum levels of TNF-α soluble receptor (TNFR p55) were associated with a significantly higher response rate and to a longer survival in patients with advanced myeloma treated with thalidomide. Controversial results have been reported concerning the impact of TNF-α serum levels in myeloma patients treated with thalidomide. Thus, Neben *et al.*[11] found that high levels of TNF-α were associated with a better outcome while Thompson *et al.*[12] reported that high levels of TNF-α adversely influenced progression-free survival. In agreement with the results from Thompson *et al.*,[12] we found that baseline TNF-α serum levels were significantly lower in responding patients.[13] In addition, in our experience patients with extramedullary plasmacytomas, who are unlikely to respond to thalidomide,[14] have significantly higher serum levels of TNF-α than do patients without extramedullary involvement.[13] These types of studies are important to understand the mechanisms of action of thalidomide in multiple myeloma better and might be helpful in delineating the profile of potential responders. In our experience, patients with high plasma cell tumor burden, measured by serum and/or urine M-protein size as well as by the proportion of bone marrow plasma cells, with no extensive skeletal involvement and with no extramedullary plasmacytomas are those likely to respond to thalidomide (Rosiñol *et al.*, *submitted*). It seems that plasma cell bone marrow homing is crucial in the response to thalidomide.

Further research to understand the mechanisms of action of thalidomide, as well as those of other new anti-myeloma drugs with anti-angiogenic/pro-apoptotic activity is obviously needed. There is growing

evidence that the achievement of complete remission, particularly after HDT/SCT, is the crucial step for long-lasting response and durable survival in patients with MM.[15,16] In this regard, Fenk *et al.*[17] found that quantitative molecular monitoring by immunoglobulin heavy chain polymerase chain reaction (PCR) using patient-specific probes provides information highly predictive of relapse after HDT/SCT in patients with MM. Of note, greater tumor burden immediately before autotransplantation predicted faster disease progression. Considering that the degree of tumor reduction after HDT is associated with the tumor burden before transplant,[16,18] the findings of the Fenk's study suggest that greater efficacy of pretransplant induction therapy is a crucial step in the up-front therapy of patients with MM. As recently highlighted,[19,20] PCR, flow cytometry studies and measurements of free light chains are more sensitive techniques that immunofixation and may be more helpful in predicting the long-term outcome of patients with MM who achieve complete remission defined by immunofixation.

Symptomatic skeletal involvement (bone pain, lytic bone lesions and or/severe osteoporosis with pathological fractures) is a major feature in patients with MM. Increased serum levels of C-terminal telopeptide of collagen type I (ICTP) as well as elevated urinary levels of N-terminal telopeptide of collagen type I (NTx) are predictive of early bone disease progression in patients with MM treated with standard chemotherapy.[21] On the other hand, the Mayo Clinic group reported that ICTP was the most significant marker of myeloma bone disease.[22] In this issue of Haematologica, Abildgaard *et al.*[23] report the results of their sequential studies of the abovementioned markers and bone densitometry (DEXA-scans) in patients with MM treated with conventional chemotherapy. Increased ICTP and NTx were predictive of progressive bone disease while pretreatment low lumbar bone mineral density predicted early vertebral fractures. However, sequential DEXA-scans were not found to be useful. We found it interesting that patients with *non-responding, non-progressive disease* had better preserved bone mineral density, one year after the initiation of therapy than did responding patients. The authors' hypothesis that these patients with *primary stable disease* may have less bone remodeling activity along with a lower proliferative activity seems very likely. It is also our experience that these patients have a relatively indolent disease course and better prognosis than the general myeloma population.[24] The incorporation of these markers in clinical trials might be most useful in defining the indications for initiation of bisphosphonate therapy in patients with smoldering myeloma or with symptomatic myeloma but no bone lytic lesions as well as in the assessment of the effectiveness of these drugs.

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Myeloma research in Haematologica

This issue of Haematologica reports four papers and an accompanying editorial on multiple myeloma. The reader might be interested in original papers on the same topic that appeared in the journal in the last two years[1-14] and that are accessible for free online onto our website (*www.haematologica.org*).

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