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Exciting times for myeloma research

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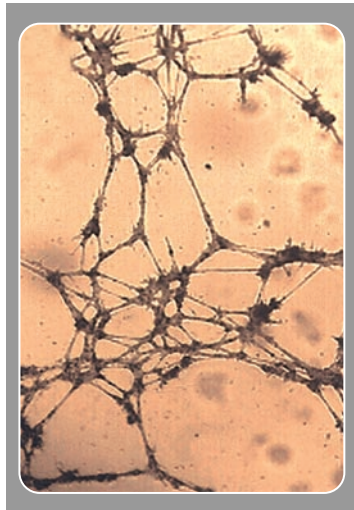


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Exciting times for myeloma research

The importance of the interaction of myeloma cells with bone marrow microenvironment has recently been recognized. Myeloma cells were found to interact with bone marrow stromal cells, osteoblasts, osteoclast precursors, and osteoclasts to trigger disease progression, and



this knowledge is likely to be transferred into novel and, one hopes, more effective treatment strategies. Another important interaction of myeloma cells concerns bone marrow endothelial cells.

Folkman introduced the concept of angiogenesis in solid tumors 3 decades ago.¹ Vacca et al were the first to show that bone marrow angiogenesis is increased in active compared with nonactive multiple myeloma.² Recently, angiogenesis has been shown to be increased in a large variety of hematologic malignancies. Among them, myeloma was the first malignancy in which increased bone marrow angiogenesis was shown to be an independent prognostic factor for survival by Rajkumar et al³ and our group.⁴ This research field was also in-

spired by the work of Barlogie's group showing that thalidomide induces remissions in refractory myeloma patients, which was an important milestone in the treatment of multiple myeloma, even though this drug also has other properties besides its antiangiogenic action.⁵

In this issue of *Blood*, Vacca and colleagues (page 3340) provide new insights into the role of endothelial cells in multiple myeloma. The authors studied a variety of biologic features of endothelial cells extracted from bone marrow of patients with active multiple myeloma (MMECs) and compared these results with biologic features of human umbilical vein endothelial cells (HUVECs) as a model of normal quiescent endothelial cells. Genetic, phenotypic, functional, and ultrastructural features of endothelial cells are described. Vacca et al show that MMECs exist in subsets, secrete growth and invasive factors for myeloma cells, and can be inhibited by thalidomide. These results expand our understanding of the biology of MMECs and of the possible paracrine and cell-to-cell interactions of endothelial and myeloma cells.

Where do we go from here? Myeloma cells secrete a variety of angiogenic cytokines and activate multiple pathways to induce angiogenesis. Furthermore, different subsets of MMECs were found in the present study by Vacca et al. These results are consistent with the suggestion that the inhibition of a single signaling pathway in this complex system may be overcome by the activation of alternative pathways, and an appropriate combination of inhibitors may be necessary to achieve the desired goals in the treatment of multiple myeloma.

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“Full length, midi, or mini”: a fashion statement for transplants in myeloma

High-dose therapy (HDT) with autologous hematopoietic stem cell transplantation (AH SCT) is the standard of care for patients with newly diagnosed multiple myeloma.¹ This results in an event-free survival and overall survival (OS) of approximately 30 and 60 months, respectively. Unfortunately, there is no plateau in survival curves. It is highly controversial whether the outcomes of single HDT with planned tandem AH SCT improves survival.² The final analysis of the Intergroupe Francais Du Myélome 94 (IFM94) trial is the only one of 5 randomized trials (none yet published) to show a survival benefit (although one could argue that the other trials do not have long enough follow-up). Even with tandem AH SCT, plateaus in survival curves are not observed.

The etiology of disease relapse has been hypothesized as due to (1) infusion of contaminating tumor cells in the autograft, and/or (2) inability to eradicate minimal residual disease. Allogeneic transplantation (AlloTx) may overcome both of these obstacles by infusing tumor-free grafts and eradication of minimal residual disease through a graft-versus-myeloma (GVM) effect. There are indications that a plateau may be present following AlloTx. In patients who relapse following AlloTx, a GVM effect has been demonstrated by donor lymphocyte infusions.

Conventional (“full length”) AlloTx's have excessively high mortality rates: the transplant-related mortality (TRM) has ranged from 20% to 57% within the first year. Thus, in the setting of 5-year median survivals with AH SCT, conventional AlloTx's have been terminated by the “fashion police” as too toxic. Is there a “kinder and gentler” approach for patients with myeloma that may lead to a cure? Trials using reduced dose-intensity regimens have been explored in myeloma. The initial trials included