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

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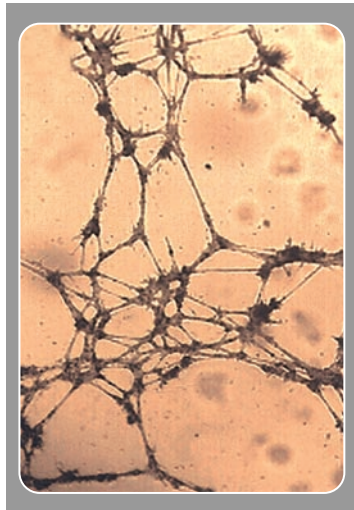


Martin MA, Dickie P. Infection of human immunodeficiency virus 1 transgenic mice with *Toxoplasma gondii* stimulates proviral transcription in macrophages in vivo. *J Exp Med*. 1996;183:1645-1655.

5. Murphy PM. Viral exploitation and subversion of the immune system through chemokine mimicry. *Nat Immunol*. 2001;2:116-122.

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.

—Orhan Sezer

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1. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285:1182-1186.
2. Vacca A, Ribatti D, Roncali L, et al. Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol*. 1994;87:503-508.
3. Rajkumar SV, Leong T, Roche PC, et al. Prognostic value of bone marrow angiogenesis in multiple myeloma. *Clin Cancer Res*. 2000;6:3111-3116.
4. Sezer O, Niemöller K, Eucker J, et al. Bone marrow microvessel density is a prognostic factor for survival in patients with multiple myeloma. *Ann Hematol*. 2000;79:574-577.

5. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med*. 1999;341:1565-1571.

“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

intermediate dose (“midi”) regimens (melphalan 100 mg/m² [Badros et al³]; melphalan 180 mg/m², and fludarabine 125 mg/m² [Giralt et al⁴]) in predominantly heavily pretreated patients with chemoresistant disease. Although high response rates were observed, the majority were not durable and the TRM was only modestly less than conventional AlloTx (one-year TRM, 33% and 40%, respectively).

Maloney and colleagues (page 3447) have combined the 2 transplantation modalities: AHSCT (melphalan 200 mg/m²) to affect maximal tumor cytoablation followed by a nonmyeloablative (“mini”) AlloTx using only 2 Gy total body irradiation to allow donor alloreactive T lymphocytes to eradicate minimal residual disease via a GVM mechanism. They observed a 52% complete remission (CR) rate, far higher than that observed with either AHSCT (even tandem) or conventional AlloTx. At a median follow-up of 18 months, only 3 of 31 patients with CR have relapsed. The projected 2-year progression-free survival (PFS) for all patients was 55%. However, when scrutinizing the data further, it is apparent that patients with chemosensitive disease before transplantation had superior PFS and OS compared with chemoresistant patients. In addition, although the overall TRM at one year was 17%, TRM was significantly lower in the chemosensitive versus chemoresistant group (2 [7%] of 28 vs 7 [27%] of 26, respectively). These data imply that only patients with chemotherapy-sensitive disease should be considered for this regimen.

I anticipate that future trials will further identify those individuals (early treatment, chemosensitive; perhaps chromosome 13 abnormalities) who may benefit from this approach. Only time will tell if the current “fashion statement” using a combined autologous/mini AlloTx will result in improved survival and, dare I state, be curative! This concept will be further evaluated in the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial comparing tandem AHSCT with autologous/mini AlloTx.

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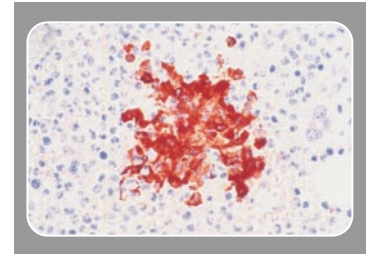
1. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003; 348:1875-1883.
2. Blade J, Vesole DH, Gertz M. Transplantation for multiple myeloma: who, when, how often? *Blood*. Prepublished on July 31, 2003, as DOI 10.1182/2003-01-0073.
3. Badros A, Barlogie B, Siegel E, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. *J Clin Oncol*. 2002;20:1295-1303.
4. Giralt S, Aleman A, Anagnostopoulos A, et al. Fludarabine/melphalan conditioning for allogeneic transplantation in patients with multiple myeloma. *Bone Marrow Transplant*. 2002;30:367-373.

HES and SMCD-eos: birds of a *FIP1L1-PDGFR* feather

The development of the tyrosine kinase inhibitor imatinib mesylate has led to rational targeted therapy for chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) based on inhibition of *bcr-abl* and altered *c-kit*. Given its potential to also inhibit the PDGF receptor (PDGFR), imatinib then proved itself effective in CMML harboring translocations involving this kinase (particularly *ETV6-PDGFRβ*)¹ and subsets of GIST lacking *c-kit* mutations.² Clinical observations of imatinib response in hypereosinophilic syndrome (HES) led to a search for an inhibited molecular target, now identified as the *FIP1L1-PDGFR* fusion tyrosine kinase.³

Known to be associated with altered *c-kit*, systemic mastocytosis (SMCD) was an additional hematologic disorder explored for potential imatinib sensitivity; however, an association with the imatinib-insensitive Asp816Val enzymatic site *c-kit* mutation made benefit seem less likely.⁴ Pardanani and colleagues nonetheless recently reported activity of imatinib in a subset of SMCD patients,⁵ and, in this issue of *Blood* (page 3093), add another chapter to the story by further defining a subgroup of SMCD patients with eosinophilia (SMCD-eos) harboring a *FIP1L1-PDGFR* fusion tyrosine kinase. Loss of fluorescence in situ hybridization of a probe developed against the deleted region on 4q12, cysteine-rich hydrophobic domain 2 (*CHIC2*), provided surrogate identification of *FIP1L1-PDGFR* fusion, and was found in imatinib-

sensitive SMCD-eos patients. In one patient, *FIP1L1-PDGFR* fusion was confirmed with



polymerase chain reaction performed on eosinophil and neutrophil populations. Although common to both HES and SMCD-eos, eosinophilia did not necessarily predict deletion at *CHIC2*, consistent with this group’s prior demonstration of potential for response to imatinib in SMCD without eosinophilia.

Definitions and treatment of disorders such as those mentioned above will certainly change in the era of targeted therapy and with the ability to identify, through molecular techniques, abnormalities common among divergent diseases. In this case an imperfectly predictive clinical link, eosinophilia, hints at a molecular link, *FIP1L1-PDGFR*, now made more easily identifiable and useful in screening for and predicting the response to therapy in SMCD.

Such important links, like the naked eye aided by binoculars, enable us to tell when birds of a feather really do fly together.

1. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. *N Engl J Med*. 2002;347:481-487.
2. Heinrich MC, Corless CL, Duensing A, et al. PDGFRα activating mutations in gastrointestinal stromal tumors. *Science*. 2003;299:708-710.
3. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRα and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348:1201-1214.
4. Ma Y, Zeng S, Metcalfe DD, et al. The c-KIT mutation causing human mastocytosis is resistant to STI571 and other KIT kinase inhibitors; kinases with enzymatic site mutations show different inhibitor sensitivity profiles than wild-type kinases and those with regulatory-type mutations. *Blood*. 2002;99:1741-1744.
5. Pardanani A, Elliott M, Reeder T, et al. Imatinib for systemic mast-cell disease. *Lancet*. 2003;362:535-536.

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