

subclass. They also identify other subgroups with poor-risk for event-free survival, including patients from each AML subclass with pretreatment transcript ratios greater than the 75th percentile. By deduction, all postconsolidation patients studied had pretreatment ratios lower than 75th percentile and this group was enriched for APL cases, raising some concern that analyses including postconsolidation data might partly involve a comparison of APL with low transcript ratios to the other 2 subclasses with higher transcript ratios and poorer clinical outcome. How the “new score” relates to relapse-free survival with longer follow-up seems of particular interest, since its potential clinical value will pertain only to patients who do not suffer an “event” before completing consolidation therapy.

Surprisingly, the investigators conclude that individual patient monitoring seems a more promising application of RQ-RT-PCR. This is partly based on analysis of 15 cases, in which an increase from a previous negative RQ-RT-PCR assay was demonstrated in all 8 patients who relapsed within 6 months. This limited data set does not specify individual assay sensitivities, and the reported 2000-fold ABL transcript variation could affect data subsets, especially at/near zero during the postconsolidation period, even though no overall correlation between transcript ratios and ABL transcript numbers was found. One hopes that a forthcoming report⁵ and future trials will address essential RQ-RT-PCR standardization requirements to derive reliable predictive values for both cohort and individual case analyses.

In answer to the title-posed question: not quite yet.

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Multicentric Castleman disease: viral and cellular targets for intervention

Kaposi sarcoma (KS) is now the most common malignancy in much of sub-Saharan Africa, due to widespread infection with KS-associated herpesvirus (KSHV, also known as human herpesvirus 8) and human immunodeficiency virus (HIV). Two rarer but nonetheless serious neoplasms, primary effusion lymphoma (PEL) and plasmablastic multicentric Castleman disease (MCD), also are caused by KSHV and markedly augmented by HIV.

Patients with MCD have lymphadenopathy typically with hepatosplenomegaly. Many are severely ill with chronic or intermittent malaise, fever, weight loss, night sweats, respiratory symptoms, peripheral edema, and skin rashes. Anemia, thrombocytopenia, elevations of γ -globulin and acute-phase reactants, hypoalbuminemia, and proteinuria occur in the majority of patients. About one quarter develop central nervous system disease. Especially with HIV coinfection, a substantial fraction progresses to PEL, plasmablastic, or anaplastic large-cell lymphomas.¹⁻³

MCD and PEL arise from B cells, the primary reservoir for KSHV. In MCD-affected lymph nodes, KSHV-latent nuclear antigen can be detected consistently in immunoglobulin M (IgM)-expressing, λ -light-chain-restricted B-cell plasmablasts in the

mantle zone.² Interleukin-6 (IL-6) is a potent growth factor for plasmablasts and both human (huIL-6) and KSHV (vIL-6) homologues may contribute to its pathogenesis.³

Vinca alkaloids and other cytotoxic agents, with or without high-dose corticosteroids, produce frequent but short-lived responses. Similarly, treatment with an anti-huIL-6 monoclonal antibody temporarily relieved the signs and symptoms of MCD but not its underlying pathophysiology.⁴ Cidofovir has potent in vitro activity against KSHV replication, but no MCD responses have been reported.

MCD exacerbations are correlated with huIL-6, IL-10, and C-reactive protein serum levels and with the level (viral load) of KSHV DNA in peripheral blood cells. One patient obtained complete relief of severe MCD symptoms for at least 14 months following one dose of rituximab, an anti-CD20 monoclonal antibody.⁵ Rituximab targets B cells, a KSHV reservoir and probably a major source of the IL-6 and other soluble mediators of MCD. In the current issue, Marcelin and colleagues (page 2786) report on treating 5 more MCD patients with rituximab, 2 of whom died quickly with MCD complications and other conditions. The other 3 patients experienced complete clinical remissions of MCD that lasted 3, 6, and 12 months, respectively, after receiving 4 doses of rituximab. Peripheral blood B-cell and C-reactive protein levels fell abruptly in responding patients, whereas KSHV viral load declined inconsistently, illustrating the presence of non-CD20 viral reservoirs.

Some patients developed MCD despite complete suppression of HIV with highly active antiretroviral therapy (HAART) and CD4 counts above 200 cells/ μ L. Rituximab apparently had no drug interactions with HAART, nor did it have any effect on HIV viral load or CD4 count. However, because KS worsened in 2 patients, the risk of de novo or worsening KS in other rituximab-treated patients should be evaluated.

Although it is apparently effective and relatively safe, rituximab does not eliminate KSHV infection and almost certainly does

not cure MCD. Rather, as with MCD responses following splenectomy or excision of a lymph node mass,⁴ rituximab reduces the burden of KSHV-infected cells and B-cell growth factors, particularly IL-10. More experience in treating MCD with rituximab is needed before it can be considered the standard of care.

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Stem cells stat, please!

Over the past decade, cytokine-mobilized peripheral blood stem cells have largely replaced bone marrow as a source of stem cells for both autologous and allogeneic stem cell transplantation. Only 2 cytokines, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage-CSF (GM-CSF), have been approved by the Food and Drug Administration (FDA) for stem cell mobilization. Their use for stem cell mobilization is limited by their cost, the need for multiple injections, toxicity to the donor (bone pain), and most importantly by their failure to mobilize a minimum number of progenitors (2×10^6 CD34⁺/kg) necessary for consistent and rapid engraftment of neutrophils and platelets from difficult-to-mobilize patients. The addition of chemotherapy to cytokines has enhanced mobilization but is also limited by significantly greater cost and morbidity to the donor. Over the past decade we have witnessed the death of many exciting new cytokines that

were marketed and tested as stem cell mobilizing agents. These include stem cell factor, daniplestim (interleukin 3 [IL-3] agonist), chimeric cytokines, thrombopoietin analogues, and flt-3 ligand and analogues. Their impact on mobilization has either been modest at best or they have been associated with unexpected toxicities. Chemokines such as IL-8 have been shown to rapidly (within 1-4 hours) induce the mobilization of hematopoietic progenitors in mice and nonhuman primates but directly activate mature myeloid effector cells, limiting their potential in human clinical trials due to the possibility of excessive toxicity. Liles and colleagues (page 2728) used AMD3100, a novel reversible bicyclam antagonist of CXCR4 (the receptor for stromal cell-derived factor 1 or SDF-1/CXCL12) to rapidly (3-9 hours) mobilize CD34⁺ progenitors in a dose-dependent manner from a series of healthy human volunteers. The circulating CD34/mL increased 10- to 20-fold within 6 to 9 hours after a single injection of the highest dose of AMD3100 (240 μ g/kg) tested. These single injections were associated with minimal toxicities and were sufficient to mobilize enough stem cells for a stem cell transplantation after a single apheresis.

This exciting report raises many questions. Although comparable numbers of CD34 are mobilized 6 to 9 hours after a single subcutaneous injection of AMD3100 and after 5 days of G-CSF in healthy donors, will the same effect of AMD3100 be seen in patients who have impaired marrow reserves? Preliminary studies in patients with myeloma and non-Hodgkin lymphoma (NHL) are currently underway and the results are anxiously awaited. Since 20% to 40% of heavily pretreated patients with NHL and Hodgkin disease fail to mobilize using G-CSF, it will be extremely important to demonstrate that AMD3100 has an additive or synergistic effect with G-CSF on stem cell mobilization. Previous data¹ suggest that AMD3100 acts synergistically with G-CSF in a murine model of stem cell mobilization. Finally, are stem cells mobilized more rapidly by AMD3100 compa-

rable or better than stem cells mobilized more slowly by G-CSF? Can dosing of AMD3100 be effectively performed in a repetitive fashion with respectable toxicities? Although initial trials in humans may provide some insights, only preclinical competitive repopulation studies in the mouse will be able to appropriately assess the short-term and long-term multilineage engraftment potential of stem cells mobilized with AMD3100 and G-CSF. Will AMD3100 be an option for the mobilization of allogeneic donors? Since CXCR4 is expressed on many cells, including CD3⁺ T cells, it is conceivable that AMD3100-mobilized T cells may alter graft-versus-host disease (GVHD) and graft-versus-leukemia (GVL) in positive or negative ways. Again, preclinical studies using AMD3100 in the allogeneic setting will be necessary prior to any future clinical trials using AMD3100 as an allogeneic stem cell mobilizing agent in humans.

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Shear madness in TNF- α signaling

During the past decade it became evident that shear stress in the vasculature modulates gene expression of endothelial cells and thus the endothelial phenotype. The observed changes included adhesion molecules and chemokines involved in the recruitment of leukocytes.¹ The differential gene expression under various shear rate conditions offered an explanation for why some sites in the vasculature may be more suited for leukocyte extravasations and why atherosclerotic lesions develop mainly in the regions of disturbed flow.² The as-yet-unidentified mechanotransducing receptors were proposed to be either integrins³ or stretch-activated calcium channels.⁴