

blood

2004 103: 371-372
doi:10.1182/blood-2003-10-3660

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published semimonthly by the American Society of Hematology, 1900 M St, NW, Suite 200, Washington DC 20036.
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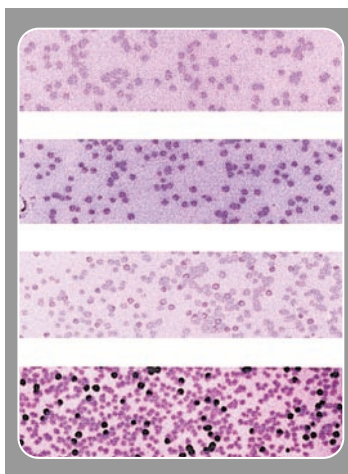
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New insights into the knowledge of graft-versus-myeloma

Application of chemo(radio)therapy at doses requiring hematopoietic stem cell support has been challenging in multiple myeloma (MM). Extensive clinical trials conducted over the last decade and involving many thousands of patients have shown the ability of high-dose therapy to overcome, at least in part, chemoresistance, thereby increasing the complete remission (CR) rate up to the 40% to 50% range and providing a survival prolongation of 12 to 15 months in comparison with conventional chemotherapy.¹

Compared with autologous transplantation, allogeneic stem cell transplantation in patients with MM has been reported to effect more frequent molecular remissions, approaching 50%,^{2,3} and more durable duration of disease control. Based on these

observations, the existence of an allogeneic immune response against residual myeloma cells in vivo (graft-versus-myeloma [GVM]) has been postulated. Direct evidence for a GVM effect came from clinical studies of donor lymphocyte infusion(s) (DLI) in patients relapsing after a T-cell-depleted allogeneic transplantation. In several of these studies, re-



sponse (both complete and partial) to DLI occurred in 35% to 50% of patients and was more frequently, albeit not always, associated with the development of acute and chronic graft-versus-host disease (GVHD). Disappointingly, most CRs were not durable and the probability of these patients remaining alive and free of disease at more than one year after DLI was less than 20%. Efforts to increase the efficacy of GVM and to separate the benefits of the immune response from the toxicity of GVHD should be made in an attempt to improve the outcome of patients receiving allogeneic stem cell transplantation.

In this issue, Bellucci and colleagues (page 656) provide new insights into the knowledge of the immunologic mechanisms and target antigens of the GVM response. To address these issues, the authors screened a cDNA expression library with serum samples from 4 patients who underwent T-cell-depleted allogeneic bone marrow transplantation (BMT) for relapsed MM and attained CR following the subse-

quent prophylactic infusion of CD8⁺ T-cell-depleted donor lymphocytes. Library screening with early and late post-DLI serum from these patients resulted in the identification of a panel of 13 antigens representing a diverse set of cellular proteins. High-titer antibody response against these proteins was detected in all 4 patients who responded to DLI, but was absent in their serum taken before BMT or DLI. However, no or minimal reactivity was detected in serum from healthy individuals, from MM patients who failed to respond to DLI, from patients who did not receive DLI after BMT, or from patients with either acute or chronic GVHD. Testing of serum samples from DLI responders showed that antibody response to the antigens was closely associated with the time of best antitumor response, suggesting that these proteins were potential targets of the immune response. Of these antigens, 5 were detected in more than 1 patient in CR following DLI. Using Northern blot analysis and oligonucleotide microarrays, the authors found that the corresponding genes were expressed in MM primary cells and in myeloma cell lines at higher levels than in plasma cells from healthy individuals or from patients with monoclonal gammopathy of undetermined significance.

The advent of DLI and the documented effect of the allogeneic immune response against residual tumor cells in vivo have brought about a shift in the field of allogeneic stem cell transplantation for the treatment of hematologic malignancies. Nonmyeloablative conditioning regimens that reduce the early complications and mortality of transplantation while retaining an immune response sufficient to induce remissions are increasingly used and increase the number of candidates for allogeneic transplantation. In MM, preliminary reports are promising, particularly if allogeneic transplantation is applied front-line, following an autologous transplantation to reduce the tumor burden.⁴ Such treatments are frequently combined with DLI. Immunogenic antigens that are highly expressed in primary myeloma cells, such as those characterized by Bellucci et al and reported in

this issue, might be appropriate targets for potential immunotherapies aimed to enhance the antimyeloma activity in the near future.

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Unrelated cord blood stem cell transplantation for AML

Postremission therapy for acute myeloid leukemia (AML) generally includes either consolidation with chemotherapy used in induction, or intensification using non-cross-resistant agents. Of approximately 60% of patients younger than 55 years who attain first remission with standard induction therapy, projected disease-free survival (DFS) rates range from 20% to 40%. Allogeneic transplantation performed in first remission can provide long-term DFS approximating 65% in young adults with histocompatible sibling grafts, with inferior outcomes observed in patients with advanced age (> 30 years), advanced disease, or infusion of unrelated adult or partially matched donors. Unrelated umbilical cord blood (UCB) has therefore been explored as a potential alternative graft source for AML patients lacking a sibling donor. However, low nucleated cell doses contained in a single UCB unit have limited its widespread use, particularly in adults, and initial reports of high-risk patients enrolled in phase 1 trials demonstrated inferior survival rates compared with conventional grafts.¹

In this issue, Ooi and colleagues at the University of Tokyo (page 489) report clinical outcomes in 18 adults with de novo

AML, of whom 14 were beyond first remission. These patients were treated with fully ablative total body irradiation (TBI)-based conditioning and infusion of allogeneic unrelated cord blood transplantation. The median age of the patients in this series was 43 years. No patient had a related or unrelated bone marrow donor available at the time of cord blood transplantation. Each patient received a single UCB unit thawed and infused without prior ex vivo expansion. Median cryopreserved UCB graft nucleated cell dose was $2.5 \times 10^7/\text{kg}$. Of these 18 adult patients, 17 demonstrated sustained donor engraftment, and median day to absolute neutrophil count of $0.5 \times 10^9/\text{L}$ was 23 days. In the 17 patients demonstrating myeloid reconstitution, chimerism analyses confirmed full donor engraftment. On day 27, 1 patient died with organ toxicity, and 3 patients relapsed within the first 2 years after transplantation. The remaining 14 patients are alive and free of disease for up to 48 months of follow-up, and probability of DFS at 2 years was 76.6%. Further observations outlined in this issue parallel those reported in other adult patient series, that use of unrelated cord blood has been associated with a low incidence of severe acute and chronic graft-versus-host disease (GVHD). The majority (17) of these patients received standard cyclosporine + methotrexate as GVHD prophylaxis. One patient demonstrated severe (> grade II) acute GVHD and 3 patients demonstrated extensive chronic GVHD. All patients who are alive and disease-free received cord blood grafts containing more than 2×10^7 nucleated cells per kilogram, attributable in part to the shorter stature of these Japanese patients (median weight, 55.2 kg). These results confirm the importance of cord blood graft cell dose in determining optimal engraftment rates and survival in adults.

Recent advances in AML pathophysiology and proposed new therapeutic strategies include the following: identification of overexpressed differentiation antigens as targets of graft-versus-leukemia effect,² fms-related tyrosine kinase 3 (Flt3) mutations, and antibody-targeted chemotherapy with immunoconjugates of cali-

cheamicin (gemtuzumab ozogamicin). Despite these advances, a large proportion of patients treated for AML succumb either to the disease or to complications related to its treatment. As outlined by the study reported by Ooi et al, the use of banked unrelated cord blood as an alternative allogeneic graft source results in durable remissions for adults with de novo AML, elicits low rates of severe GVHD, and is associated with acceptable survival rates. Further studies are warranted to determine the impact of improved HLA matching and higher graft cell dose threshold ($> 2 \times 10^7/\text{kg}$) on unrelated donor UCB stem cell transplantation outcomes in adults with AML.

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BAFF and related proteins: a new therapeutic target for B-cell malignancies

For many years, investigation of new therapeutic agents for multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) has been limited to empiricism based in part on our lack of understanding of the pathogenesis of each disease. During this time period, basic laboratory studies have led to a better understanding of the pathways that promote normal immunologic function in nontransformed B cells and how these pathways are effectively perturbed in the malignant transformed B-cell counterpart to promote the manifestations of disease. Such work has led to identification of several molecules that promote survival, including members of tumor necrosis factor superfamily ligand family B-cell-activating factor (BAFF) (also known as BlyS or B-lymphocyte stimulator) and a proliferation-inducing ligand (APRIL). BAFF and APRIL serve to enhance normal B-cell response to antigens, production of antibodies, and survival.¹ In several autoimmune