To the editor:

Measles in bone marrow transplant recipients

Machado et al. should be congratulated on seizing the opportunity of the 1997 measles outbreak in São Paulo, Brazil, for learning about measles in marrow transplant recipients. Per the report, only 8 of 156 patients (5.1%) developed measles, and only 1 patient (0.6%) had a severe disease (measles pneumonia). But both the incidence and the severity of measles were likely underestimated. Measles was defined by seroconversion (appearance or 4-fold rise of specific antibodies). A significant fraction of transplant recipients cannot seroconvert (reviewed in Storek and Witherspoon2 and in Parkman and Weinberg3). In the São Paulo study, patients with symptoms or signs of measles who did not seroconvert were considered to be patients without measles. The immunity of the patients who could not seroconvert was probably more compromised than the immunity of the patients who could seroconvert. Therefore, the incidence of measles in the patients who could not seroconvert may have been high and the course of the disease in these patients may have been severe. Thus, substantially more than 5.1% transplant recipients may develop measles during an out-

break, and substantially more than 0.6% patients may have a severe course.

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To the editor:

Treatment options in chronic myelogenous leukemia

The perspective “Chronic myelogenous leukemia: current treat-

ment options”1 provides a succinct, direct, and evenhanded ap-

proach to a complex topic, for which I congratulate the authors. I have a lone concern with the final aspect of the review, the dependence on age to determine the recommended treatment option.

As the authors state, scoring systems devised by Sokal and Hasford can be used to predict survival for individual patients receiving nontransplant therapy. Similarly, Gratwohl’s scoring system estimates survival after allotransplantation; the reliability of this scoring system was recently confirmed by the International Bone Marrow Transplant (IBMT) Registry.2 Advanced age is a poor prognostic factor for all patients, whether they undergo transplantation or receive nontransplant therapies. The other variables used in these scoring techniques are necessary to estimate outcome.

Recipient age may influence outcome in adults undergoing allogeneic transplantation for chronic myelogenous leukemia (CML) to a lesser degree than is commonly thought. Bolwell recently summarized relevant data and concluded that the inclusion of pediatric patients (grouped with young adults) in many studies has led to the impression that older adults fare far more poorly with transplantation than do younger adults.3 He found only a slightly higher risk of transplantation-related mortality in older compared to younger adults. Data from Seattle4 and our own center,5 among others, indicate that conventional allogeneic transplantation can be performed safely in older patients. Data from the same institutions suggest that transplantation less than 6 months4 and 3 months5 from diagnosis can further improve results, including in older patients.

Thomas et al.’s original report of allogeneic transplantation in CML found a direct relationship between mortality rate and interval from diagnosis to transplantation and an association between older age and longer interval from diagnosis to transplantation.6 Delaying transplantation in older patients contributes to a higher mortality rate. The fact that every study does not demonstrate a significant influence of this interval on outcome does not prove a lack of influence any more than studies that fail to demonstrate an adverse influence of older age prove the absence of an adverse affect. These studies are not appropriately designed to detect the absence of such differences.

Last, results at specific institutions, often with large patient numbers, are clearly better than overall IBMT Registry results. Many studies with favorable results have included large numbers of patients and have utilized similar approaches. Using targeted busulfan and cyclophosphamide, the Seattle group reports one-year transplantation-related mortality rates of approximately 10% and rare relapses. Institutions with poor results should consider referring patients to centers consistently achieving favorable results.

We can all agree that the decision can best be made by a well-informed patient; that patient depends on clinicians to provide an accurate, fair, and complete description of his or her options.

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Age and chronic myelogenous leukemia treatment algorithm

Our recent perspective tried to balance the benefits and risks of treatment with STI571 (imatinib mesylate) against the benefits and risks of early allogeneic stem cell transplantation (SCT) for patients with chronic myelogenous leukemia in chronic phase. Dr Copelan feels that we have ascribed undue importance to age in guiding decision-making. Regarding transplantation, he refers to published and unpublished data from single centers in which the transplantation-related mortality (TRM) does not differ greatly between younger and older patients.

As noted, in both the Sokal and Hasford systems for estimating survival with nontransplant therapy, older age is a negative prognostic factor. Thus, older patients would more likely fall into their intermediate- and high-risk categories. According to our algorithm, we would tend to favor transplantation options for these patients.

In all published series of unrelated allogeneic SCTs, including single-institution studies, age is indisputably the most important factor in predicting survival. In the Seattle experience, age over 50 years was associated with a greater than 60% mortality rate at 2 years after transplantation. In patients under age 50 receiving transplants within the first year of diagnosis, the 5-year survival rate was 74%. The HLA sibling transplantation experience is a bit more complicated and may relate in part to the conditioning regimen. In particular, the use of busulfan and cyclophosphamide, as opposed to cyclophosphamide and total body irradiation, may have a lower mortality rate. Whether this will also apply to unrelated transplantsations is unknown. But this may account for some of the variability reported by individual centers.

Despite this, even sibling transplantations carry a significant mortality rate in the first 2 years following transplantation. For a Sokal or Hasford low-risk patient of older age, for whom median survival with nontransplant therapy may approach 10 years, we would be less likely to consider transplantation as initial therapy. Ultimately of course, the final decision will be the patient’s.

John M. Goldman and Brian J. Druker

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To the editor:

The common pathways, but different outcomes, of apoptosis induced by extracorporeal photopheresis and in vivo chemotherapy may reinforce the important immunomodulatory effect of monocytes

Stahnke et al discussed the mechanisms associated with the apoptosis of lymphoid cells following in vivo chemotherapy. Their observations showed striking similarities to those of early apoptotic lymphocytes induced by extracorporeal photopheresis (ECP). ECP therapy involves exposing cells, separated by leukopheresis, to 8-methoxypsoralen (8-MOP) and ultraviolet A (UVA). Treated cells are subsequently reinfused. Like in vivo chemotherapy, ECP induces a rapid increase in lymphocyte apoptosis following treatment. The apoptosis is independent of subtype: CD4+ and CD8+ lymphocytes are similarly affected. As early as 12 hours following in vivo chemotherapy, an increase in Bax expression was observed, but p53 remained undetectable. Immediately following ECP, exposed lymphocytes also demonstrate no increase in p53 expression but do show a reduction in Bcl-2/Bax ratio. Early loss in mitochondrial function also links the 2 treatment modalities: both therapies demonstrated early loss of mitochondrial membrane potential (∆ψm). Immediately after ECP the apoptosis was caspase independent, and Stahnke et al also indicate that, in some patients, apoptosis was independent of caspase activation. Only after prior in vitro stimulation did chemotherapy induce apoptosis by a CD95- or p53-dependent mediated pathway, 2 mechanisms not observed in the early stages after ECP; these pathways are only observed after a prolonged incubation in culture after ECP (Yoo et al7 and J.B., manuscript submitted, November 2001).

These observations may indicate a common pathway for the early induction of apoptosis in lymphocytes following treatment with DNA-damaging agents. Rather than an arrest of cell cycle and an increase in p53 expression, these cells become apoptotic...
Treatment options in chronic myelogenous leukemia

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