Graft Purging in Autologous Bone Marrow Transplantation: A Promise Not Quite Fulfilled

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The analysis, "Graft Purging in Autologous Bone Marrow Transplantation: A Promise Not Quite Fulfilled," by Drs. Joseph Alvarnas and Stephen Forman, is very timely. The authors' conclusion is succinctly presented in their title. For about a decade late in the 20th century, the merits—or in some cases, the absolute necessity—of purging autologous bone marrow harvests prior to transplantation were fervently presented by various authors. Target diseases included leukemias, lymphomas, myeloma, and breast cancer. It was suggested that the transplantation of unpurged autologous bone marrow harvests might even be considered unethical. As noted by Alvarnas and Forman, several (phase I) studies demonstrated the feasibility of removing or reducing the number of tumor cells in autologous bone marrow harvests. Unfortunately, the clinical benefits of purging harvests were not always obvious and became increasingly controversial.

Appropriate Time for Reassessment

Proponents of purging and their opponents became increasingly polarized. For reasons that are not entirely obvious, a little over 5 years ago the passion and heat generated by this topic began to dissipate, and recently, debate on the purging front has been relatively cool, possibly because of a shift in interest, as the authors note, toward the use of reduced-intensity allogeneic (mini-allo) transplants. Consequently, this is a most appropriate time for a dispassionate presentation and analysis of the available data—a service provided by Alvarnas and Forman's excellent review. The emphasis of the review is hematologic diseases but the authors' conclusions on the clinical impact of graft purging likely applies to all diseases in which this approach has been attempted. For efficiency, this commentary focuses on lymphoma as the target disease. As the authors claim, there is at a minimum indirect evidence that tumor cells contaminating grafts can contribute to relapse posttransplantation. As they also note, the relative contribution to relapse of infused tumor cells vs tumor-surviving therapy is much less clear. This remains an unanswered theoretical question, although in a clinical context it is of little importance.

Purging Techniques

Alvarnas and Forman present a detailed review of purging techniques. A more critical analysis of the possible consequences of purging techniques might also have value. As they note, "Interest in graft purging was dramatically stimulated by the 1991 publication of a Dana-Farber Cancer Institute trial that evaluated the course of 114 patients with follicular NHL." This trial employed a very novel biologic purging technique that induced B-cell death using monoclonal antibodies and baby rabbit complement.[1] Removal of tumor cells was documented using bcl-2 polymerase chain reaction (PCR) analysis. More recent purging approaches largely employ the physical removal of tumor cells, eg, antibodies attached to magnetic beads[2] or purification of stem cells. The importance of this distinction is that the major determinant of clinical outcomes in lymphoma is disease sensitivity vs resistance to therapy. Patients whose lymphoma does not show a major response to frontline chemotherapy have poorer outcomes.[3] The biologic purging technique employed in the original Dana-Farber trial likely not only purged lymphoma cells from the harvest, but potentially also identified patients with sensitive (ie, purged to negativity) vs resistant disease. In retrospect it was the ideal technique. Consequently, the clinical outcome of this trial was likely the best that could ever be expected. On the one hand, this maybe lead to exaggerated expectations of purging technologies. At the same time, it may eventually have promoted despair at the failure to replicate this clinical success. It is interesting that chemopurging trials that also have a biologic component have produced limited benefits, albeit most evident in subgroup analyses.[4] Purely physical approaches to purging tumor cells from harvests generally have not demonstrated clinical benefits.[2] Future Trials

Despite these reservations, as Alvarnas and Forman note, "the concept of graft purging is seductive." A number of phase II studies and a registry analysis[5] have suggested a clinical benefit,
but phase III trials are lacking. As the authors point out, this in part reflects organization, technical aspects, quality control, and cost issues involved in developing complex large multicenter trials of purging technologies.[2] Furthermore, since purged harvests are classified as "more than minimally manipulated," the regulatory issues are increasingly daunting. Given the evidence that the biologic component of purging is important-potentially critical—we agree entirely with Alvarnas and Forman that in vivo purging, in contrast to in vitro approaches, appears to offer significant promise but is presently unproven. We fully support their proposal for the development of phase III purging trials. In such trials there would be concern over the use of an "unpurged" control arm if the hypothesis is that purging is beneficial. We suggest that a randomized trial directly addressing the question of the relative roles of purging tumor cells from the harvest vs minimizing the tumor burden in the patient should have a general design comparable to that of trials of rituximab (Rituxan) in lymphoma. The ex vivo purging arm would treat the harvest only with rituximab followed by its transplantation. The in vivo purging arm would treat the patient and thereby the harvest with rituximab followed by harvest and transplant. The third arm would employ an unpurged harvest transplanted to a patient receiving rituximab after harvest as part of the transplant regimen. Individual arms of this trial have been attempted or are in progress. Unfortunately, given the likely magnitude of benefit associated with purging, this trial would have to be very large and is unlikely to be undertaken. Rather, we accept the likelihood (as proposed by Alvarnas and Forman) of the evaluation of various immunologic therapies including mini-allo transplants and potentially even autologous transplant followed by mini-allo transplant. Nevertheless, we acknowledge concerns over treatment-related mortality of allogeneic transplants[5] and the recent evidence that allograft-vs-lymphoma effects may be less potent than anticipated.[6] We support a structured approach to the application of these procedures, so that the risks may be matched to the anticipated benefits. In this regard, autologous approaches such as interleukin-2 (Proleukin), adoptive immunotherapy, or vaccination are likely best suited to patients with minimal tumor burdens. Mini-allo transplants as suggested by Alvarnas and Forman should be initially piloted in high-risk patients. **Conclusions**

The true benefits of graft purging may never be discerned. Its role may be simply one step in history on the way to newer therapies. This review will be important if it helps move the debate from the point of "to purge or not to purge" to the question, "can (and how can) purging be incorporated into trials to improve clinical outcomes?" This might lead to novel lymphoma trials and provide new options for the treatment of acute myelogenous leukemia and multiple myeloma.

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