Eur J Cancer Clin Oncol, Vol. 23, No. 3, pp. 263–266, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

Perspectives and Commentaries

Bone Marrow Transplantation for Malignant Lymphoma

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PATIENTS with disseminated malignant lymphoma who have failed first line chemotherapy are unlikely to be cured with further chemotherapy or radiotherapy delivered at conventional doses. Based on the success of high dose chemo-radiotherapy and marrow transplantation as treatment for patients with relapsed leukemia, a similar approach has been taken for patients with relapsed lymphoma. A paper by Armitage *et al.* summarizes the experience at two institutions treating patients for recurrent diffuse large cell lymphoma with high-dose therapy and autologous transplantation [1]. At the time of their report, 6 of 29 patients were alive disease-free resulting in a 20% probability of disease-free survival 24 months after treatment. These results are similar to a number of other phase II studies of high-dose therapy followed by marrow transplantation for recurrent lymphoma, all of which illustrate that a small but definite proportion of patients become long-term disease-free survivors following such treatment [2–9].

In thinking about ways to improve upon these results, it is useful to examine reasons for treatment success and failure. Such an analysis is difficult because of the heterogeneity of treated patients imposed by differing disease histologies, stages, and prior treatments, different transplant regimens, and, in some studies, different sources of marrow. Nonetheless, there are some common threads running through these reports. In virtually all of these studies, including the one reported by Armitage *et al.*, the most common reason for failure has been disease persistence or recurrence. The relapse rate following allogeneic and autologous transplantation is similar, illustrating that the reason for disease recurrence in the vast majority of cases is the inability of the preparative regimens to eradicate the disease [8]. Occasionally, as pointed out by Armitage *et al.*, patients treated with autologous marrow relapse early with disseminated marrow and peripheral blood disease suggesting that reinfusion of tumor in an apparently remission marrow may sometimes contribute to relapse. In addition to disease recurrence, other less common but still significant causes of death are infection, interstitial pneumonia, and, following allogeneic transplantation, graft-vs.-host disease.

In the study reported by Armitage *et al.*, complete responses were seen more frequently in patients with a good performance status, a history of complete remission with initial chemotherapy, without bulky tumor, and in those treated with a total body irradiation (TBI) containing preparative regimen. In a recent review of the European experience by Singer and Goldstone, better results were also seen in patients treated during remission and in those treated with TBI-containing regimens [10]. In an analysis of 100 consecutive patients treated in Seattle (all of whom received TBI), we also found improved results in those treated in second (or subsequent) remission or in untreated first relapse without bulky disease. In addition, we found that patients who had not been previously treated with radiotherapy to the chest did better than those who had [8].

Accepted 30 July 1986.
This investigation was supported by PHS Grant Numbers CA 18029, CA 15704, and CA 18105 awarded by the National Cancer Institute, DHHS. Dr. Thomas is the recipient of Research Career Award AI 02425 from the Institute of Allergy and Infectious Diseases.

The observation of improved results in patients transplanted in first relapse or second remission compared to patients with more advanced disease appears to be consistent; such patients tolerate the transplant procedure better and have a lower incidence of post-transplant relapse. The only reason not to carry out transplant at first relapse or second remission would be if salvage chemotherapy programs offered an equivalent or better chance for cure. In our experience and that of others, transplantation for recurrent lymphoma at first relapse or second remission results in a 2 year disease-free survival of approx. 40%. In their review, Singer and Goldstone examined a number of recent salvage chemotherapy studies for recurrent non-Hodgkin's lymphoma (NHL) and could identify only 11 of 398 patients (2.8%) alive in complete remission 2 years after treatment [10]. Similarly, patients with Hodgkin's disease who relapse either during or soon after completion of primary therapy have a poor prognosis. Thus, currently available data suggest little reason to delay transplantation beyond first relapse or second remission. A reasonable approach is to follow patients during and after initial therapy carefully. When relapse is first detected, if the extent of relapse is not great, immediate transplantation should be considered. Patients with extensive disease at the time recurrence is detected may benefit from several cycles of chemotherapy prior to transplantation. While this seems to us to be a reasonable approach, it should be noted that there has not been a prospective randomized study of salvage chemotherapy vs. salvage marrow transplantation. Some might argue that the retrospective differences seen are so large a prospective trial is unnecessary. However, almost all reports of salvage chemotherapy and of transplantation involve small numbers of patients and may be subject to strong patient selection bias. Further, many of the patients entered into these studies were not treated initially with chemotherapy regimens currently used. Thus, the results of a prospective trial would be of interest. Transplantation for very high risk lymphoma patients during first remission is an appealing idea but there are at present insufficient data to recommend such an approach although several trials are under way.

Improved preparative regimens are obviously needed. Among those regimens for which results are available, those containing TBI appear to be more effective than those based on chemotherapy alone with 2 possible exceptions. Patients with Burkitt's lymphoma may do as well or better if treated with chemotherapy-only regimens containing high doses of alkylating agents. Patients who have previously been treated with chest radiotherapy have a high incidence of fatal interstitial pneumonia following TBI-containing regimens. If this is a result of cumulative radiation damage to the lungs, then chemotherapy-only preparative regimens or lung-shielding may be of benefit to this group of patients.

The most commonly used TBI-containing preparative regimen has included high-dose cyclophosphamide. Since virtually all first line chemotherapy programs for non-Hodgkin's lymphoma include cyclophosphamide, albeit at lower doses, the use of an alternative alkylating agent seems worthy of investigation. Initial results substituting melphalan for cyclophosphamide do not yet suggest an advantage [1]. Since results of standard chemotherapy studies demonstrate that combination chemotherapy is, in general, more effective than single agent chemotherapy, another logical approach is to study the addition of drug combinations to TBI. Although the numbers so far are small, the addition of high-dose cytarabine to cyclophosphamide and TBI as reported by Armitage *et al.* has not yielded results much different from those we have seen with cyclophosphamide alone with TBI [1, 8]. Many relapses initially occur at sites of previous bulk disease. This observation suggests that the addition of local "boost" radiotherapy, in addition to the preparative regimen, might be of benefit. Whether boost radiotherapy is best given before or after treatment and whether it contributes to improved survival is, as yet, unknown. Studies by Phillips *et al.* suggest that pre-transplant boost radiotherapy can be given with relative safety and may contribute to improved survival for patients with Hodgkin's disease but does not clearly benefit patient with non-Hodgkin's lymphoma [11].

Altered drug and radiation schedules are the subject of a number of current clinical trials. Several new approaches to improved regimens have been developed in the laboratory and will soon be tested in the clinic. One such approach is to combine beta-emitting radioisotopes with monoclonal antibodies reactive with tumor cells in order to deliver increased amounts of radiation to areas of tumor with less radiotoxicity to normal organs. Investigations both in the mouse and the dog demonstrate that this approach is feasible and human studies with unlabeled antibody show that tumor localization is achievable [12, 13].

While most relapses are due to the inability of currently-used preparative regimens to eradicate the tumor, in the setting of autologous transplantation some recurrences may be the result of reinfusion of tumor with the remission marrow. We have seen similar relapse rates following syngeneic or allogeneic transplantation (where tumor is not reinfused with the marrow) and autologous transplantation suggesting that relapse due to

tumor reinfusion must be either uncommon or it occurs in the same patients destined to relapse because of tumor resistant to the preparative regimen [8]. However, if transplants are carried out earlier in the patient's course and if preparative regimens improve, the role of *in vitro* marrow treatment may become both clearer and more important. The two most commonly used approaches (*in vitro* chemotherapy or *in vitro* treatment with monoclonal antibodies plus either complement, toxins, or physical agents such as magnetic beads) can be made to work in animal model systems and can remove several logs of cells which are apparently malignant. However, the clonogenic stem cell of spontaneously-arising human tumors cannot be identified morphologically or functionally so that the utility of *in vitro* marrow treatment cannot be assayed in the laboratory and, as already mentioned, the similarity in relapse rates following allogeneic and untreated autologous marrow transplantation make an informative clinical trial impossible to construct. Thus, the value of marrow purging techniques at present must be taken as an article of faith. Such faith is relatively easy to maintain as long as the method used does not significantly interfere with engraftment or immune reconstitution, but this concern should not be taken lightly. In the study of Armitage *et al.*, 14% of patients died with septicemia while pancytopenic. Further delays in engraftment could increase this proportion. Assuming that some method of marrow manipulation will be required for optimal autologous transplantation, a possibly attractive alternative to trying to kill or remove each and every tumor cell is, instead, positive selection of normal hematopoietic stem cells. In a canine model, we have successfully engrafted animals following otherwise lethal TBI with as little as 5×10^6 cells/kg by positively selecting Ia+ cells using an immunoadsorption column (Berenson *et al.*, unpublished). As our knowledge of antigens found only on human hematopoietic stem cells or very early myeloid precursors increases, this approach becomes more feasible.

While transplantation early in the disease course and the use of TBI-containing transplant regimens have been, in general, associated with improved outcomes, several pre-transplant characteristics have not yet shown a major influence on outcome including disease histology and marrow source. Admittedly, there are few studies which have treated sizable numbers of patients having different disease histologies using a constant preparative regimen, but in the few available reports, there are, as yet, no striking differences in the outcome among patients transplanted for intermediate grade lymphoma, high grade lymphoma, or Hodgkin's disease [8]. The European transplant registry suggested a slightly, but not significantly, better outcome for patients with lymphoblastic lymphoma [10]. A group for which there are very little data at present is the indolent lymphomas. Some have suggested that since this group is incurable with conventional chemotherapy, there is little reason to believe that higher-dose treatment will be curative. However, chronic myelogenous leukemia (CML) is incurable with conventional chemotherapy and is regularly curable with high-dose chemoradiotherapy and marrow transplantation [14, 15]. The analogy is obvious and this is a group for which the outcome of transplantation will be of interest.

In our experience, the source of marrow has not had a significant impact on the incidence of long-term disease-free survival. Autologous marrow has the obvious advantage of avoiding graft-vs.-host disease and based on this fact some have argued that this is the preferred approach [16]. Allogeneic transplantation, however, has several possible advantages including assurance that the marrow is tumor free, a potential graft-vs.-lymphoma effect, and reconstitution with marrow previously unexposed to chemotherapy and presumably immunologically intact. Following allogeneic transplantation for lymphoblastic leukemia, a graft-vs.-tumor effect has been documented [17]. Whether such an effect occurs following transplantation for malignant lymphoma is unproven, but at least in the case of Hodgkin's disease, is certainly possible. Reed–Sternberg cells are strongly Ia positive and therefore should make excellent immunologic targets. Patients with Hodgkin's disease are thought, in some cases, to have a life-long immunologic defect. Use of allogeneic rather than autologous marrow might provide a method not only of curing the disease but also of reversing this defect.

Although advances have been made in the primary treatment of malignant lymphoma, the treatment of patients with recurrent disease has led to few long-term disease-free survivors. Although much is yet to be learned about transplantation, the results to date merit consideration of this approach in any patient who fails first line therapy. Definite conclusions regarding the utility of various treatment regimens, with or without marrow transplantation, will require careful analysis including long-term follow-up of 5 years and more to determine the true incidence of cure.

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