Review Article

The role of autografting in lymphoma

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Introduction

The malignant lymphomas were the first solid tumours demonstrated to be curable by chemoradiotherapy. Despite the evolution in the last 20 years of more intensive and more successful chemotherapy schedules, about 30% of patients with Hodgkin's disease^{1,2} and at least 50% of those with intermediate and high-grade non-Hodgkin's lymphoma,³ will die of their disease.

It has been appreciated for some time that patients receiving suboptimal therapy for lymphoma fare less well than those receiving full treatment, and thus dose escalation to eradicate resistant or relapsed tumour has some theoretical merit. A significant increase in dose intensity cannot be achieved without potentially lethal prolonged bone marrow failure. This may be prevented by aspirating some of the patient's bone marrow and re-infusing this following chemoradiotherapy conditioning. Autologous bone marrow transplantation (ABMT) was first attempted in the 1950s, but results were poor due partly to inadequate dosage escalation to eradicate tumour and partly because techniques of bone marrow harvest and cryopreservation were ill-understood.⁴

The development of allogeneic bone marrow transplantation in the 1970s, with the realization that cryopreserved marrow could successfully be used to salvage patients receiving massive conditioning therapy, led to a re-awakening of interest in ABMT in lymphoma. In 1978, Appelbaum *et al.*,⁵ in Seattle reported successful results of ABMT in some patients with resistant malignant lymphoma. Following this a large number of reports have appeared on the use of ABMT both in Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL).^{6–9} A unifying feature of most of the reported data is that the results have generally been compared with historical controls and prospective

randomized trials are lacking. Despite the lack of compelling scientific support there has been considerable interest worldwide in ABMT. A survey of autotransplantation activity in the 1980s showed that more than 1,200 autotransplants were performed in 1987, of which nearly 40% were for lymphoma.¹⁰

Hodgkin's disease

Approximately 30% of patients with Hodgkin's disease are not cured by conventional treatment. These may be divided into three groups: primarily resistant patients, those relapsing within 12 months of treatment and those relapsing beyond 12 months. In a study of patients with primarily resistant and relapsed resistant lymphoma the University College Hospital, London Group¹¹ demonstrated a 50% complete response to ABMT using BEAM conditioning (BCNU, etoposide, cytosine arabinoside and melphalan). A subsequent report from the same centre¹² reported a 50% disease-free survival for a mixed group of 155 Hodgkin's patients at 5 years. These results are similar to those obtained by others^{13,14} and the European Bone Marrow Transplant Group.¹⁵ There has only been one published prospective randomized study of ABMT compared with chemotherapy.¹⁶ The British National Lymphoma Investigation examined the use of either BEAM and ABMT or 'mini-BEAM' (that is, BEAM in doses not requiring bone marrow support). This study was stopped prematurely because of the difficulties in obtaining the patients' agreement to participate in the non-transplant arm. Despite this the results have shown a significant reduction in relapse risk following ABMT but as yet no survival advantage. The German Hodgkin's Disease Group is currently coordinating a similar study with the European Bone Marrow Transplantation Group to demonstrate whether these encouraging findings can be confirmed in a larger study. Features at the time of transplant which are generally agreed to be

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associated with an adverse outcome are masses > 10 cm,¹² elevated lactic dehydrogenase¹⁷ and number of previous regimens.¹⁴ Most authors find that lack of chemosensitivity before ABMT is also predictive of a poor outlook,^{18,19} although others disagree.²⁰

There is, however, now broad agreement on the indications for ABMT amongst Centres reporting substantial series of patients.²¹ These are: (a) failure to achieve first complete remission with satisfactory induction therapy; (b) relapse within 6 months of attaining complete remission with conventional first line therapy; and (c) failure to maintain remission after treatment with two different modalities of therapy, that is, either relapse from second remission or failure to achieve a second remission after relapse from first remission.

In addition most centres would regard relapse following an alternating schedule such as MOPP/ABVD or LOPP/EPAP as having failed two modalities and be candidates for ABMT.

What of ABMT in first remission? This approach has been advocated by Carella in Italy²² and the Scottish and Newcastle Lymphoma Group.²³ The rationale here lies in the ability to identify those patients who achieve a complete remission but have a high probability of relapse. The problem with this is that the prognostic indices at diagnosis may be most predictive of failure to achieve a complete remission rather than subsequent relapse. The Genoa Group²² have, however, identified that a cohort of patients with bulky stage IVB disease, pulmonary involvement, extra nodal involvement and a high lactic dehydrogenase would have only a 30% chance of survival after attainment of remission. This comprises only a small group of patients. If all stage IV patients were offered ABMT in first complete remission, considerable numbers of patients already potentially cured, would receive high-dose chemotherapy with its attendant risks. In a hypothetical cost-benefit analysis of ABMT in first complete remission Goldstone and McMillan²⁴ calculated that 40 additional transplant procedures would potentially produce only three additional long-term survivors.

Non-Hodgkin's lymphoma (NHL)

High-grade NHL

Despite improvements in the treatment of high-grade non-Hodgkin's lymphoma, only 30–50% of patients are cured with primary therapy. Of the patients requiring further treatment, about one-third have primary resistant disease and the remainder relapse having achieved a complete remission. Conventional salvage therapy is poor in

this group of patients and ABMT has been extensively studied.

The majority of reports of high-dose chemotherapy and marrow rescue have been on heavily pretreated patients. A number of studies with a variable duration of follow-up,^{6,8,25,26} indicate disease-free survival after ABMT of approximately 30–60%. The pooled European Bone Marrow Transplantation experience¹⁵ of over 300 patients has demonstrated that the most important prognostic criterion for success after ABMT is the disease status at the time of transplant. Other prognostic factors, which may be important, are tumour bulk, the number of prior regimens received and performance status.^{26–28} Whereas in Hodgkin's disease there is still debate as to the predictability of outlook after ABMT in patients with chemo-resistant disease, it is clear in NHL that such patients do uniformly badly and most centres will only offer ABMT to patients with chemo-responsive tumours.

Although comparison with historical data suggests that ABMT may confer a survival advantage for patients with high-grade NHL who have achieved a second complete response or have responding disease, there are no published data from randomized prospective trials to confirm these findings. The Parma study²⁹ which randomizes patients with responding relapse to either additional conventional treatment or ABMT is attempting to answer this difficult question.

Since it is apparent that patients with advanced disease do less favourably, ABMT is being explored earlier in the treatment of NHL. Encouraging results have been obtained in a number of non-randomized studies³⁰ and two prospective randomized trials are underway in Europe for high-risk high-grade non-Hodgkin's lymphoma and lymphoblastic lymphoma.

Low-grade NHL

Low-grade lymphoma is usually a disease of the elderly. It has an insidious course characterized by repeated responsiveness to chemotherapy or radiotherapy, but relapse and eventual death from tumour is inevitable. The median survival is quite long at about 10 years.^{31,32} In older patients a conservative approach is justified but younger patients may warrant more experimental aggressive therapy. Early results of ABMT are encouraging^{23,33} with transplanted patients doing more favourably than historical age- and disease-matched controls (Rohatiner, 1993, personal communication). A European trial of ABMT versus further conventional treatment for younger poor-risk patients with follicular lymphoma has recently commenced.

Transplant-related mortality

ABMT has frequently been offered to heavily pretreated patients with advanced disease. In these circumstances it is not surprising that a transplant-related mortality of up to 31% has been reported.⁷ The principal causes of death are sepsis and pneumonitis. Pneumonitis is particularly troublesome in patients who have already received mediastinal radiotherapy.⁸ Overall, the transplant-related mortality is approximately 10%, although in some centres with good-risk patients, the mortality can be as low as 2%.²³

Haemopoietic growth factors

The recent clinical availability of recombinant human haemopoietic growth factors (GM-CSF, G-CSF) together with more experimental cytokines (for example, IL3, IL6 and stem cell factor) has generated considerable interest in the stimulation of haemopoietic recovery following ABMT. Although it seems clear that the use of G- or GM-CSF results in about a 7-day reduction in the time to achieve a neutrophil count of $0.5 \times 10^9/l$ after ABMT,³⁴ evidence is mixed that this is translated in significant clinical benefit.^{35,36} The most significant impact of the currently available growth factors may be to permit easier mobilization of peripheral progenitor cells which may be used to repopulate the marrow.

Peripheral progenitor cell transplants

It has been appreciated for some years that part of the mononuclear fraction of peripheral white blood cells following recovery from intensive chemotherapy has the ability to repopulate the marrow.³⁶ This technique was originally used primarily to reduce potential contamination of the graft with malignant cells. This is speculative, since it is not clear whether circulating progenitor cells are devoid of tumour cells with clonogenic potential. Using chemotherapy alone to mobilize cells is cumbersome and engraftment unpredictable. The

situation has dramatically changed with the combination of G- or GM-CSF and chemotherapy (usually cyclophosphamide) to mobilize progenitor cells. Large numbers of progenitors can be harvested and their use results not only in a very considerable reduction in the duration of neutropenia, but also very rapid megakaryocyte engraftment.³⁷⁻³⁹ Research is currently in hand to establish the most effective mobilizing schedules and many groups can harvest adequate cells with only one apheresis. The impact on clinical practice has been considerable. Most patients can now be discharged within 14 days of transplantation and it is likely that, despite the additional costs of growth factors and apheresis, progenitor cell transplants are considerably cheaper than ABMT.⁴⁰

Conclusion

The last 10 years has seen an explosion of interest in the use of high-dose chemotherapy and marrow rescue in the management of malignant lymphomas. The development of peripheral progenitor cell transplants, which promote rapid engraftment, with the promise of reduced morbidity and costs has further accelerated the trend to more intensive treatment. It should not be forgotten, however, that progenitor cell transplantation is only a tool to allow simpler exploration of the efficacy of dose escalation. It remains to be proved whether, in the context of chemotherapy, that more is necessarily better. These questions can only be answered in well-designed, prospective, randomized clinical trials. Experience to date suggests that such trials present ethical dilemmas both to physicians and patients, and accrual of adequate numbers may be difficult because of a widespread perception, possibly fallacious, that transplantation is better than the best available conventional salvage treatment.

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