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The contribution of autologous transplant in lymphoma

One of the very first diseases treated with high dose therapy and autologous hematopoietic stem cell transplant was lymphoma. Since the initial report in 1957[1] this approach has been used for literally thousands of lymphoma patients and, in certain circumstances, has become the standard of care. This editorial will review the current status of autologous transplantation for the several diseases that are categorized as lymphoma.

Hodgkin's disease

Specific scenarios often encountered along the course of this disease have been regarded as possible indications for the introduction of high dose therapy (HDT) and autologous hematopoietic stem cell transplantation. However, the available literature does not currently answer all of the questions regarding the specific indications for HDT. Because this disease is often cured with first line conventional dose radiation and/or chemotherapy that has less potential for morbidity and mortality, intuitively HDT should not be considered as first line therapy for these patients unless there is a very high risk that their disease will fail to respond completely to conventional dose treatment or they have a high probability of relapse. However, no randomized prospective studies regarding the use of high dose therapy for patients with high risk Hodgkin's disease as initial therapy are available. Transplantation in this setting, while not considered standard of care, is being investigated currently in clinical trials for potential usefulness.

Two randomized prospective trials of HDT and transplantation have been reported for patients with relapsed Hodgkin's disease. The first is a British trial, reported in 1993.[2] Patients who had not achieved a complete remission after first line conventional dose chemotherapy or who relapsed within a year of therapy or who were in second or greater relapse were randomized to receive either up to three courses of mini BEAM (carmustine, etoposide, cytarabine and melphalan in robust but less than transplant-requiring doses) if needed to achieve a complete response or to receive BEAM (the same drugs but in marrow-ablative doses) followed by autologous bone marrow transplantation. Because the trial was closed earlier than originally planned due to the reluctance of patients to undergo randomization rather than proceeding directly to HDT and transplantation, only 20 patients were randomized to each arm, thus supplying low power to detect a modest difference in outcomes. At a median follow up time of 34 months, the event-free survival was significantly better for the transplant group although there was no significant difference with regards to overall survival between the two groups. One factor that may be partially responsible for the lack of any significant difference in overall survival is that four of the patients who relapsed after treatment with mini BEAM were subsequently treated with high dose therapy and autologous bone marrow transplantation. This study also demonstrated that higher doses of the same chemotherapy provide better tumor killing. The second trial is a German one, first reported in 1997.[3] This study differed from the British trial in that eligibility requirements included the achievement of a complete response to first line standard dose chemotherapy prior to relapse. At relapse, patients were randomized to treatment with aggressive conventional dose chemotherapy or high dose therapy and autologous peripheral blood stem cell transplantation. The report described the outcomes of the first 101 of 146 eligible patients accrued to the trial. After randomization, all patients received two cycles of non-marrow ablative chemotherapy (DexaBEAM or dexamethasone, carmustine, etoposide and cytarabine). Patients whose disease did not respond to Dexa BEAM were removed from the study. The 79 responders were then treated according to their original assignment of either two more cycles of DexaBEAM or BEAM and autologous peripheral blood stem cell transplantation. After two years of follow up, with the analysis based on the intent to treat assignment, the transplant group had a better failure-free survival but this group had no statistically significant overall survival advantage.

Two additional studies without a randomized prospective design but with important implications were also reported in 1997 and 1999. In the earlier study,[4] the authors reviewed the outcomes of 60 Hodgkin's disease patients who were refractory to first line therapy or in first relapse and were treated with HDT and autologous peripheral blood stem cell transplantation at Stanford University Medical Center between 1988 and 1993. The outcomes of these patients were compared to those of a case-matched group of 103 similar patients treated with conventional dose salvage therapy between 1976 and 1989

at the same institution. At four years post treatment, the transplant group had a significantly better event-free survival but, again, there was no statistical difference in the overall survival rate. The more recent study[5] considered 86 patients with refractory disease to first line conventional therapy, subsequently treated with HDT and autologous hematopoietic stem cell transplantation whose treatment data were reported to a French transplant registry. These cases were matched with 258 conventionally treated patients obtained from two international data bases. At a median follow up of 22 months, the six year overall survival rates of the transplanted patients just approached statistical significance compared to the case controls; 38% survival for the transplanted patients and 29% for the controls (p = .058). These four studies of relapsed or refractory Hodgkin's disease patients each suggest that HDT and autologous transplantation offer a significantly longer event-free survival than standard dose salvage chemotherapy and/or a trend toward better overall survival that is not statistically significant. Each of these studies included a small transplant sample size, providing insufficient power to detect modest differences in outcome. If more patients had been entered, the overall survivals of the transplant groups might have achieved statistical significance.

Aggressive non-Hodgkin's lymphoma

In contrast to Hodgkin's disease, there is some evidence that HDT and autologous hematopoietic stem cell transplantation may be useful as first line therapy for certain patients with high-risk aggressive non-Hodgkin's lymphoma (NHL). In 1997, a group of Italian investigators randomized patients with newly diagnosed aggressive B-cell NHL but without bone marrow metastases to either 12 cycles of conventional dose chemotherapy (MACOP-B or methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin) or high dose sequential chemotherapy and autologous peripheral blood stem cell transplantation.[6] The high-dose sequential therapy included all drugs in MACOP-B except bleomycin plus etoposide, melphalan and TBI or mitoxantrone. Patients with less than an 80% reduction in tumor size after either MACOP-B or high-dose sequential chemotherapy and transplant were crossed over to the opposite treatment regimen as a salvage therapy. At seven years post initial treatment, the event-free survival was statistically better for the transplant group and the overall survival showed a trend toward improved event-free survival that was not statistically significant (p =.09). However the lack of significant difference may be due to the low numbers of patients studied.

A second study conducted by French investigators considered the value of HDT and autologous bone marrow transplantation for newly diagnosed patients with aggressive NHL and no marrow metastases.[7] After induction therapy with either mitoxantrone or adriamycin-based induction therapy, patients who achieved a complete response were then randomized to receive consolidation therapy with either conventional doses of ifosfamide, etoposide, asparaginase and cytarabine or high doses of cyclophosphamide, carmustine and etoposide followed by autologous bone marrow transplantation. Disease-free survival was no different between the two groups but a retrospective subset analysis of patients with high risk or high intermediate risk disease according to the international prognostic index,[8] showed a superior disease-free survival and a trend toward a superior 5 year overall survival (p = .06) in the transplant group. This trial and the Italian study described above suggest that patients with newly diagnosed poor risk aggressive NHL and no marrow metastases might benefit from the incorporation of HDT and autografting after achieving a complete response with standard dose first line chemotherapy.

The Parma study (named after the city in which the first meeting was held to design the trial) was designed to show whether HDT and autologous bone marrow transplantation was useful for patients with aggressive NHL who had relapsed after first line conventional dose chemotherapy.[9] Two hundred and fifteen relapsed patients with no evidence of marrow metastases were treated with two courses of conventional salvage therapy. One hundred and nine patients responded and were randomized to receive four courses of conventional dose chemotherapy and radiation to areas of bulky disease or radiation to bulky disease followed by HDT and autologous bone marrow transplantation. After five years, the event-free survival and overall survival were statistically better for the transplant group. Recently, these data were updated in a 1998 abstract which showed continued superiority of the transplant patients' outcome after eight years.[10] Thus, for patients with relapsed aggressive NHL not involving the bone marrow that is responsive to chemotherapy, HDT and autologous hematopoietic stem cell transplant has become a standard treatment provided the patient is otherwise well enough to undergo the procedure.

Follicular (low grade) lymphoma

The value of HDT and autologous hematopoietic stem cell transplantation in the management of follicular lymphoma is unknown. No published randomized studies are available for review. However, several studies from single institutions have been reported which consider the outcomes of patients with follicular lymphomas who received autografts. These reports usually describe some patients who have experienced long-term event-free survival. Because this disease is considered to be incurable with standard chemotherapy regimens, the possibility exists that HDT could have some value. A recently reported series of 100 such patients treated at the University of Nebraska Medical Center described an eight year fol-

low-up with some surviving patients still free of disease.[11] However, the event-free survival curves showed continued relapses and no plateau, suggesting that cure may be unlikely even if survival is improved. Additional follow-up is needed to assess the value of HDT and autologous transplantation in this disease.

Lymphomas with bone marrow metastases

Essentially all of the published randomized trials examining the usefulness of HDT and autologous hematopoietic stem cell transplantation in patients with lymphoma have excluded patients with biopsy proof of bone marrow metastases from participation. Since lymphomas commonly involve the marrow, an important subpopulation of patients with these diseases has not been studied in regards to the suitability of the approach. The exclusion of marrow biopsy-positive patients was necessary prior to the early 1990's when peripheral blood had not yet become an accepted source of cells for hematopoietic transplantation. Since 1994, peripheral blood stem cell autografts have been used nearly to the exclusion of marrow autografts. Whether HDT and autologous hematopoietic stem cell transplant should also be considered as standard therapy for patients with relapsed aggressive lymphoma and marrow involvement has not been investigated. One retrospective study suggests that long-term disease-free survival is possible and at least as likely in these patients as in patients without marrow involvement.[12] Other series have described Hodgkin's disease[13] and follicular lymphoma patients[11] with marrow involvement who have experienced long-term event-free survival after HDT and autografting, providing only proof of principle. Systematic studies of the issue are not available and nor are they underway.

Summary

High-dose therapy and autologous hematopoietic stem cell transplantation has been followed by long-term disease-free survival for some patients with relapsed Hodgkin's disease and follicular lymphoma. For patients with aggressive non-Hodgkin's lymphoma who have experienced a chemotherapy sensitive relapse, HDT and autotransplant is an approach considered to be the standard of care. Studies continue to determine the exact role, if any, in the management of other lymphomas.

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