Innovations in Autologous Transplantation for Hematologic Malignancy

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INTRODUCTION

Improvements in supportive care and the use of peripheral blood stem cells have increased the safety of autologous transplantation, making it an effective therapy for more patients with hematologic malignancies and some solid tumors. Although more patients, including older patients, are successfully undergoing transplantation, the major obstacle to long-term success remains relapse. In addition to relapse, there are some unresolved questions concerning the optimal timing of transplantation (first remission versus relapse) and the type of regimen (radiation based or chemotherapy based). Although short- and long-term complications are less common after autologous transplantation compared with allogeneic transplantation, myelodysplasia remains a unique and troublesome late effect, particularly for patients with lymphoma and Hodgkin lymphoma [1-3]. This session will focus on the current status of autologous stem cell transplantation for hematologic malignancy, with emphasis on strategies being explored to help reduce the chances of relapse, the major impediment to long-term survival for patients undergoing treatment.

NON-HODGKIN LYMPHOMA

The initial report of successful high-dose therapy in transplantation in 1978 from the National Cancer Institute in patients with very advanced disease was followed by reports from Philip et al. [4,5] of a cure rate of 35% to 40% in patients with relapsed chemosensitive diffuse aggressive lymphoma. These results were confirmed in 1995 with a multinational PARMA trial in which patients were randomized to receive second-line chemotherapy with cisplatinum, cytosine arabinoside, and dexamethasone with radiotherapy or the same regimen combined with high-dose BCNU, etoposide, ara-C, and cyclophosphamide. The 5-year event-free survival was 46% for transplanted patients versus 12% for chemotherapy-only patients [5]. After this, many studies, including single-institutions and cooperative groups, have shown that approximately 50% of patients with relapsed large cell lymphomas that are sensitive to chemotherapy can be cured [6-9]. This figure does not include patients who do not achieve a remission with initial treatment or who are refractory to chemotherapy, thus leaving considerable room for improvement in all groups of patients. Innovations in transplantation for lymphoma have focused on more effective transplantation regimens, mobilization and collection of stem cells free of contamination by tumor cells, and, more recently, the development of immunotherapy as a component of the treatment.

Theoretically, a larger proportion of patients will have relative, rather than absolute, drug resistance earlier in the course of their disease; thus, trials were conducted with high-dose therapy in poor-risk patients during their first response or remission [10-12]. Subsequently, this concept has been tested in multiple clinical trials that differ in patient selection, pathologic subtype, choice and extent of induction therapy, time and selection for randomization, and statistical power to observe treatment effects. Thus, several trials have reported a benefit where others have not [13,14]. In general, patients with poor prognostic features at the time of diagnosis have been those for whom these trials have shown benefit. Recently, results have been reported in adult patients with untreated aggressive lymphoma with a low, low-intermediate, and high-intermediate risk of death according to
an age-adjusted international prognostic index and who then received treatment with cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone [CHOP] followed by either observation or autologous stem cell transplantation after high-dose chemotherapy [15]. The estimated event-free survival at 5 years was significantly higher among patients who received high-dose therapy than among those who received CHOP (55% versus 37%; \( P = .037 \)). Among patients with a high-intermediate risk of death, according to the age-adjusted international prognostic index, the 5-year survival rate was significantly higher after high-dose therapy than after CHOP (74% versus 44%; \( P = .001 \)). This trial, although optimistic and consistent with other reports, did not include rituximab as part of the transplantation regimen or, more importantly, as part of the chemotherapy, and this may have affected the results. In addition, changes in the initial treatment of large-cell lymphoma, including the use of anti-CD20 antibody and a shortened interval between cycles of CHOP, can affect the control arm of the study, thus making such trials limited by the control arm [16,17]. Currently, US cooperative groups are testing the hypothesis that high-intermediate–risk and high-risk patients who respond to a full course of CHOP would benefit from early autologous transplantation versus autologous transplantation at relapse, and they include anti-CD20 antibody as part of the treatment program.

To address the major problem of relapse, investigators have explored means of augmenting the dose of antineoplastic therapy delivered to the tumor. This includes the addition of etoposide to the standard regimen of total body irradiation and cyclophosphamide, and excellent results have been obtained in the cooperative group setting. Press et al. [18] pioneered the use of high-dose radioimmunotherapy in conjunction with autologous hematopoietic cell transplantation. After demonstration of the safety and efficacy of iodine 131 linked to the anti-CD20 antibody tositumomab, the radioimmunoconjugate was combined with Etoposide and Cyclophosphamide followed by autologous transplantation and seemed more effective than the historical control. Subsequently, Vose et al. [19] safely escalated iodine 131–tositumomab with full-dose BCNU, etoposide, cytosine, arabinoside, melphalan (BEAM) before transplantation. More recently, Nademanee et al. [20] successfully escalated yttrium 90 chelated with ibritumomab, a murine anti-CD20 antibody, in combination with Etoposide and Cyclophosphamide, with excellent results and good tolerance. These studies suggest that targeted radiation may be more effective and better tolerated than full total body irradiation or non–total body irradiation–based regimens. Antibody targeting has also led to the exploration of T cells genetically modified with an antibody-based immunoreceptor to recognize the CD19 or CD20 antigen on lymphoma cells (see below) [21].

Although most studies have focused on the use of autologous stem cell transplantation for large cell lymphoma, studies on the other subtypes of lymphoma, particularly mantle cell and indolent lymphoma, have also been conducted. The recognition of a different clinical biology of this disease has led to different and, in some ways, more intensive approaches, including the use of cyclophosphamide, hydroxydaunomycin, vincristine, dexamethasone, methotrexate, cytosine arabinoside (hyperCVAD) for induction therapy and the early use of autologous transplantation for mantle cell lymphoma. The data suggest that, for mantle cell lymphoma, autologous stem cell transplantation in first remission is associated with improved outcome, whereas patients who undergo transplantation after first remission rarely benefit by such an approach and are more often candidates for allogeneic transplantation [22,23]. For patients with relapsed low-grade lymphoma, a comparative clinical trial of autologous transplantation versus reduced-intensity allogeneic transplantation is being conducted by the Transplant Clinical Trials Network.

**MULTIPLE MYELOMA**

The improvements in supportive care and the development of specific regimens for myeloma have expanded the therapeutic potential in a disease that is more commonly seen in older patients. Although not curative in most patients, autologous stem cell transplantation improves the likelihood of a complete response and of prolonged disease-free survival and overall survival, and it is a major advance in myeloma treatment [24]. Most trials have indicated that prognosis is determined according to whether patients are able to achieve a complete response. The most commonly used treatment regimen is melphalan at 200 mg/m² given on either 1 or 2 days, and this has replaced other regimens, particularly those that combine chemotherapy with radiation. Some controversy remains about the overall role of autologous stem cell transplantation, particularly in patients already responding to therapy, and whether it needs to be performed as part of the up-front treatment or whether it can be delayed until patients show evidence of disease progression [25].

On the basis of these observations and the lack of a survival plateau in patients undergoing autologous stem cell transplantation, tandem autologous transplantation was developed to improve complete response rates. In a randomized trial conducted in France, event-free survival and overall survival were significantly better among recipients of tandem transplants than among those who underwent a single autologous stem cell transplantation, particularly for pa-
patients not in remission after the first cycle [26]. However, preliminary data from other randomized trials have not shown a convincing improvement in overall survival among patients undergoing tandem transplantation, although the follow-up is too short to make any definitive conclusions [27].

Similar to regimens for lymphoma, alternative regimens are being developed to improve the antitumor response. These include the use of bone-seeking radioactive holmium and samarium [28]. In addition, an increasing number of new medications are being developed for myeloma that will likely change not only the treatment for relapse, but also the up-front treatment, including the use of lenalidomide and bortezomib [29,30]. Given that the patient’s disease burden at the time of transplantation affects disease-free survival, it is likely that an improved up-front treatment will also affect transplant results.

Allogeneic transplantation is also re-emerging as an option for patients with multiple myeloma; it is based on the facts that the graft is not contaminated with tumor cells and that the graft-versus-myeloma effect has been demonstrated [31]. This, combined with new approaches to performing allogeneic transplantation by using immunosuppressive medications to facilitate engraftment, is allowing successful transplantation in older patients [32]. Currently, a trial designed by the Transplant Clinical Trials Network at the National Institutes of Health comparing autologous transplantation followed by either a second autologous transplantation or a mini-allogeneic transplantation is being performed. One novel aspect of this trial is the use of post-tandem autologous transplantation treatment to address minimal residual disease with dexamethasone and thalidomide and may serve as a model for future innovations.

HODGKIN LYMPHOMA

With increasing innovations in the use of up-front chemotherapy and radiation therapy, the vast majority of patients with Hodgkin disease can be cured with initial therapy. Thus, transplantation studies in Hodgkin lymphoma have been conducted in patients who either do not achieve a complete remission or who relapse after achieving 1 or more remissions [33,34]. The most common regimens have been the combination of Cyclophosphamide, BCNU and VP-16, BEAM, and total body irradiation-based regimens. A large number of variables associated with the outcome of autologous transplantation have been identified, including (1) bulky or minimal disease after transplantation, (2) the amount of therapy before transplantation, (3) performance status, (4) duration of initial remission, (5) extranodal disease at relapse, (6) systemic symptoms at relapse, (7) chemotherapy resistance, (8) age, (9) stage at relapse, (10) progressive disease at relapse, and (11) lactic dehydrogenase level at transplantation [35,36]. On the basis of these considerations, attempts have been made to understand treatment results according to patient characteristics at transplantation. Such analyses reveal actuarial survivals that vary from as high as 80% to as low as 15%. Most studies show that extensive therapy before transplantation, poor performance status, chemotherapy resistance, and active disease at the time of transplantation are predictive of a poor outcome after autologous transplantation [37,38].

An important issue in autologous transplantation for Hodgkin disease is the appropriate timing of transplantation during the course of the disease. Although some patients who have an isolated lymph node recurrence and a long initial progression-free survival can be treated with either chemotherapy or involved-field radiation, patients who do not attain an initial complete remission or who have a short first remission after combination chemotherapy and second or subsequent relapse are very appropriate candidates for this treatment. In each of these situations, data support the use of autologous transplantation to prevent relapse [39].

There are considerably fewer data to evaluate or support autologous stem cell transplantation for patients with high-risk disease during first complete remission. These single-center reports, which are focused on patients who had poor prognostic signs at the time of diagnosis and who had responded to therapy, show very good survival, but comparative trials are lacking [40,41]. To improve outcome, pilot trials have been performed to determine the potential efficacy of tandem autologous transplantation in patients with advanced poor-risk Hodgkin lymphoma [42,43]. In one study of a group of 49 patients with refractory disease who had either primary induction failure or a short remission, tandem autologous transplantation resulted in a 3-year event-free survival of 50% [43]. The concept will be tested in a phase II Southwest Oncology Group study to determine its overall effect, particularly in poor-risk patients.

The therapeutic options for patients with relapsed Hodgkin lymphoma have not changed significantly over the past decade, and, in contrast to Hodgkin lymphoma, no immunotherapeutic approach has been developed that has proven to be effective. The CD30 antigen was defined by the monoclonal antibody Ki1 in 1982 and as a structural protein in the membrane of Hodgkin lymphoma in 1985 [44]. It is expressed at only very low levels in T and B cells but is consistently expressed in Reed-Sternberg cells found in Hodgkin lymphoma and in lymphoma cells of patients with anaplastic large cell lymphoma, T-cell type. The presence of CD30 on Reed-Sternberg cells makes it an attractive target for immune-mediated therapy using CD30 antibodies, immunotoxins, and radioimmuno-therapy.
ACUTE MYELOGENOUS LEUKEMIA

Interest in autologous transplantation has increased substantially, in part by the limited success of standard-dose chemotherapy in achieving long-term, disease-free survival for the vast majority of patients with acute myelogenous leukemia (AML). The results of trials using autologous hematopoietic cells in patients with AML in first complete remission vary from 34% to 70% according to the patient’s age, duration of remission before transplantation, and, most importantly, cytogenetic evaluation at the time of transplantation [45-47]. The role of autologous transplantation in second remission is better defined, because the cure rate with conventional chemotherapy is extremely low. Trials using unpurged marrow demonstrate a 20% to 40% disease-free survival, and this is an alternative for patients who lack a related or unrelated donor [48]. For patients with acute promyelocytic leukemia, the outcome of autologous transplantation with a polymerase chain reaction–negative graft is excellent [49]. For patients in whom polymerase chain reaction negativity of the graft cannot be obtained, allogeneic transplantation is the preferred therapy.

Currently, studies are ongoing to address the major problem of relapse in patients undergoing autologous transplantation. These include the exploration of mini–allogeneic transplantation for older patients with AML and the inclusion of radioimmunoisotopes as part of the preparative regimen to better target sites of disease and improve the effect of treatment for both autologous and allogeneic transplantation regimens [50,51]. Other investigators are exploring the use of posttransplantation immunotherapy or immunization to specific antigens to induce an immune response to treat minimal residual disease [52].

Some patients with secondary AML arising out of myelodysplasia who achieve a remission have undergone autologous transplantation. Although some studies, particularly those in Europe, have shown some beneficial results in patients, these are a highly selected group of patients who achieve a remission with chemotherapy, with negative cytogenetics and normal blood counts, and are able to have adequate stem cells collected [53]. They represent a small minority of patients who develop AML after myelodysplasia—a population of patients best treated with an allogeneic approach.

ACUTE LYMPHOBLASTIC LEUKEMIA

Development of an effective autologous transplantation regimen for acute lymphoblastic leukemia (ALL) has been difficult. In general, the results with allogeneic transplantation for patients with poor-risk disease, including those in second remission, have made it the preferred treatment approach [54]. A recent update of the French LALA trial suggests that allogeneic stem cell transplantation improves disease-free survival for high-risk ALL in first remission and that autologous stem cell transplantation does not confer a significant benefit over chemotherapy for high-risk ALL [55]. This is similar to the preliminary result from the Eastern Cooperative Oncology Group/Medical Research Council trial [56]. On the basis of this result, most current trials are pilot studies designed to augment the efficacy of the regimen by using radioimmunotherapy, infusion of genetically modified T cells designed to treat minimal residual disease, or imatinib (Gleevec; Novartis, Basel, Switzerland) for patients before and after transplantation with Philadelphia chromosome–positive ALL.

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