The Cancer and Leukemia Group B Transplant Committee

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Abstract

The Transplant Committee of the Cancer and Leukemia Group B has a robust portfolio of studies and is poised to make significant contributions to the field. We are working in collaboration with the Cancer and Leukemia Group B Leukemia and Lymphoma Disease Committees and importantly in collaboration with other groups to define the role of both autologous and reduced-intensity allogeneic transplantation in the management of selected hematologic malignancies. Some of our studies have the potential to change the standard of care in areas such as the maintenance therapy for multiple myeloma after autologous transplantation and to generate the data that could lead to acceptance of new approaches to the initial post-remission therapy of older adults with acute myeloid leukemia. The cooperative group setting allows us to advance the transplant field by showing which approaches are successful outside of single institutions and are therefore feasible on a generalized basis.

The Transplant Committee of the Cancer and Leukemia Group B (CALGB) was organized in the mid-1980s at a time when high-dose chemotherapy with autologous bone marrow transplant was being actively investigated as treatment for a number of solid tumors and hematologic malignancies. Preliminary data from single institution studies had generated considerable interest in the use of high-dose chemotherapy and autologous bone marrow transplant for both metastatic and early-stage high-risk breast cancer, so that such treatment was widely employed at many centers despite the lack of definitive evidence from controlled trials that it was efficacious. Therefore, CALGB designed protocol 9082 to definitively test whether high-dose chemotherapy and autologous bone marrow transplant was superior to intermediate dose chemotherapy in women with stage II breast cancer and ≥10 positive axillary lymph nodes (1).

At the time this trial was initiated, the role of autologous transplantation as treatment for high-risk primary breast cancer was a subject of great controversy. Phase II trials suggested a significant benefit from this procedure and led to the widespread application of this treatment in an uncontrolled fashion. Resistance to the use of this treatment was strong among insurance carriers, and litigation was common between payors and patients and their advocates. Insurance companies were seen as denying access to the best possible treatment based solely on financial grounds. From the perspective of insurers, the prospect of widespread application of this expensive treatment to a common cancer was daunting. The question was begging for an answer, and CALGB 9082 was developed to provide a conclusive answer.

There was great debate about many aspects of the trial design. One area of debate was that of eligibility. Patients were eligible if they had high-risk primary breast cancer (defined as ≥10 lymph nodes and stage II or IIIA) and were up to “physiologic age 55.” Although most of the phase II trials had been conducted on younger women, advances in the field and particularly the use of peripheral blood stem cells in addition to bone marrow and improvements in supportive care had reduced the morbidity and mortality of the procedure enough to allow the participation of older women. In this trial, 25% of the women were over age 50, a factor that may have had an effect on the outcome.

A second major topic of debate was the choice of high-dose chemotherapy regimen to be used. There were strong advocates for the use of high-dose “CPB,” which employed cyclophosphamide (7,500 mg/m²), cisplatin (165 mg/m²), and carmustine (600 mg/m²), and this was the regimen ultimately chosen. Advocates for this regimen pointed out the evidence for a steep dose-response curve that provided the scientific basis for the combination, and the fact that the largest published phase II trials at the time used this combination. However, this regimen seemed to be more toxic than alternative chemotherapy programs, both in terms of short-term mortality and delayed pulmonary toxicity, and many transplant physicians were reluctant to accept this increased and perhaps unnecessary toxicity. Ultimately, the choice of high-dose CPB as the chemotherapy regimen may have had a significant effect on the primary study results, given that treatment-related mortality (TRM) was higher than expected at 9% and was especially high (15%) in women over age 50.

A third controversy in the trial design was the nature of the “nonexperimental” arm. Rather than compare a standard chemotherapy approach with the standard plus the addition of high-dose chemotherapy with autologous stem cell support, a decision was made to add to the nontransplant arm a course of “intermediate-dose” chemotherapy using the same CPB agents at reduced doses (36% of cyclophosphamide, 55% of cisplatin, and 15% of carmustine). Proponents of this approach pointed out that this would most directly test the effect of dose escalation. However, this design compared the use of autologous transplant with an approach that had never been previously tested and that has never been in common use. Because the “control” arm in this trial had an outcome better
than predicted, it is possible that this unusual trial design had a significant effect on the study conclusions.

CALGB 9082 randomized 785 women to the high-dose versus intermediate-dose CPB arms after they had received three cycles of standard CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) adjuvant chemotherapy. Subsequent therapy included chest wall irradiation and tamoxifen (if the tumor was positive for hormone receptors). The patients had a median age of 44 years (range, 22–66 years), with 25% over age 50. The primary outcome, event-free survival, was not significantly different between the two arms (61% versus 58%). Similarly, overall survival did not differ between the treatment arms and was higher than expected with an overall 5-year survival of 71%. An unplanned subset analysis suggested a possible benefit for women younger than age 50 (P = 0.02) based on a lower relapse rate than was not offset by high TRM. Older women had no significant decrease in relapse and experienced a high TRM of 15%.

As discussed above, the results of this and several other trials effectively ended the use of this procedure for women with breast cancer in the United States, and no further trials have been initiated or planned in this country. Investigators in Europe have continued to study the question using less toxic regimens and more usual trial designs and have suggested benefit. However, given the results of CALGB 9082 and their reception in this country, it will take an overwhelming positive outcome to resurrect interest here.

In view of the curative potential for allogeneic stem cell transplant for acute and chronic leukemias and other primary bone marrow disorders and advances in our understanding of the biology of bone marrow transplantation, the major research focus of the CALGB Transplant Committee during the past 5 years has shifted to exploring the use of reduced-intensity regimens for allogeneic stem cell transplantation.

CALGB 90003 was designed to confirm in the cooperative group setting the results of the National Cancer Institute program of allogeneic therapy in the treatment of renal cell carcinoma (2). We used the same preparative regime as reported by the National Cancer Institute investigators (3). We used the combination of tacrolimus plus low-dose methotrexate for graft-versus-host disease (GVH) prophylaxis, which has become the standard backbone of GVH prophylaxis in our studies but took a more aggressive approach to tapering off of immunosuppression based on the observation at the National Cancer Institute that only patients with overt GVH had tumor responses. This protocol was closed after 22 of the planned 36 patients were accrued with no objective responses observed in 20 evaluable patients. All but one of the patients engrafted, and median CD3+ donor chimerism was 99% at day +90. The safety profile was very acceptable, with only one TRM by day +100. Acute GVH was seen in 50% and extensive chronic GVH in 65% of evaluable patients. This study showed that although the treatment program is feasible and safe at approved cooperative group transplant centers, the initial results from the National Cancer Institute could not be reproduced. The most likely explanation is that only very carefully selected patients can benefit from this approach. Further refinements of the adoptive immunotherapy approach will be needed before future efforts are launched in this area.

CALGB 109901, which has completed its accrual, evaluated the role of reduced-intensity sibling allogeneic transplant for low-grade lymphoid malignancies, including chronic lymphocytic leukemia. Patients were eligible up to age 70 with low-grade lymphoid malignancies beyond first remission. The majority of patients had follicular lymphoma and had failed at least one prior regimen. One third of the patients had high-risk chronic lymphocytic leukemia with progression after primary therapy. Of the 45 patients entered, there were no treatment-related deaths at 6 months, showing a high degree of safety of this approach in the cooperative group setting. Longer follow-up will be needed to fully assess the effect of this strategy.

CALGB 100002, a nearly completed study, has tested whether reduced-intensity allogeneic transplant from sibling or unrelated donors can be carried out with acceptable safety and feasibility in the setting of patients with treatment failure after a prior autologous transplant. For patients with matched sibling donors, we used a standard preparative regimen of fludarabine plus reduced-intensity busulfan and a standard GVH prophylaxis with tacrolimis and mini-methotrexate. For patients with matched unrelated donors, we modified the preparative regimen to add rabbit ATG to reduce the risk of graft rejection. We also developed a novel regimen for GVH prophylaxis adding micophenylate mofetil to the backbone.

At this time, 90% (72 of 80) of the patients have been accrued, and 46 patients have been followed for longer than 6 months. Treatment-related mortality at 6 months is 9%, and overall TRM is 15%. TRM is equivalent in sibling and unrelated donor transplants.

Chimerism assays have yielded some important and interesting information. Patients with unrelated donors have achieved a high rate of full donor chimerism (defined as ≥90% donor CD3 cells). For unrelated donor patients, 78% have achieved full donor chimerism by day +30 and 86% by day +90. In contrast, patients with sibling donors have a reduced probability of achieving full donor chimerism, only 15% by day +30 and 40% by day +90. Because the hypothesis behind this treatment is that it is the alloimmune effect, which can control diseases that were not controlled by maximal doses of chemotherapy, and because there is strong evidence that it is necessary to achieve full donor chimerism to manifest this graft-versus-malignancy effect, future studies will be designed with this chimerism data in mind.

Based on the strong interest and encouraging results of this trial, we have developed a successor study. To enhance donor engraftment in the sibling group, we will add rabbit ATG in a dose of 3 mg/kg to the preparative regimen. For the unrelated donors, we will reduce the dose of rabbit ATG from 10 to 6 mg/kg. This reduction is based on evidence that show that 10 mg/kg of rabbit ATG may lead to excessive immunosuppression and risk of opportunistic infection. We will need to ensure that these treatment changes do not result in a higher rate of TRM than we have seen in the past.

### Ongoing Studies

CALGB 100101 explores the role of pentostatin in the treatment of chronic GVH disease. Chronic GVH disease has become a problem of increasing importance in the field of transplantation. Both the use of peripheral blood stem cells and the treatment of an older population of patients are likely
important contributors to the increasing incidence of chronic GVH.

CALGB 100103 will be conducted in collaboration with the Bone Marrow Transplant Clinical Trials Network and will study the potential role of reduced-intensity allogeneic transplant as the initial post-remission therapy for older patients with acute myeloid leukemia. The outcome of these patients (age over 60) with acute myeloid leukemia in first remission is very poor, with long-term survival of <10%. In the extensive CALGB database, even the most favorable subset of these patients still has a poor prognosis. From the last several CALGB chemotherapy studies addressing these groups of patients, we identified 236 patients who were between age 60 and 75 years who entered first complete remission and who were subsequently randomized on phase III trials and received their first course of post-remission therapy. This group will approximate the group of patients who are eligible for this study. For this cohort of patients, the 2-year disease-free survival was 24%, and the 3-year disease-free survival was 17% (4). There are no current chemotherapy approaches, which seem to substantially improve on these outcomes.

This protocol will test whether we can achieve a 2-year disease-free survival of >40% in this group, a result that would represent a significant improvement over other strategies. A total of 61 patients will be enrolled, and both sibling and unrelated donors were allowed.

CALGB 100104 is being conducted in collaboration with Eastern Cooperative Oncology Group and will test whether maintenance therapy with lenalidomide (Revlimid) will improve results of autologous transplantation for multiple myeloma. Lenalidomide is a derivative of thalidomide, which is both more active against myeloma as well as significantly less toxic than the parent compound. The drug has recently been approved for use in myelodysplasia and will likely be approved soon for use in relapsed myeloma. Multiple myeloma is the single most common indication for autologous stem cell transplantation in the United States. However, the treatment is rarely curative and produces a treatment-free interval of between 2 and 3 years. The major question now facing the field is how to further build on these results. CALGB 100001 is testing the aggressive approach of tandem transplant with autologous followed by reduced-intensity allogeneic transplant. This approach entails a high degree of risk and is most suitable for young patients with aggressive multiple myeloma who have matched sibling donors.

This study will interest the much larger group of patients who either did not have suitable donors or are not interested in a high-risk approach. After a standard autologous transplant using a preparative regimen of melphalan (200 mg/m²), patients will be randomized to lenalidomide or placebo. The goal will be to significantly prolong time to progression without compromising the quality of life. If this can be accomplished, this study would change the standard of care for this disease.

**Future Plans**

We will soon be activating CALGB 100102, a study of reduced-intensity transplant using haploidentical donors who are KIR mismatched with the recipient. The KIR receptors on natural killer cells provide a mechanism of inhibition of natural killer cell function. Donor-recipient pairs in which the donor natural killer cells are not inhibited by shared class I HLA antigens in the recipient allow for the expression of antitumor effects of the donor natural killer cells. We will use rigorous T-cell depletion to avoid post-transplant immunosuppression and hence allow the KIR-mismatched natural killer cells to exert a graft effect against the malignancy.

We are currently developing CALGB 100502, a study of cord blood transplantation using a reduced-intensity approach. This study is based on encouraging pilot data with a program that has reduced TRM to 14%, a level much lower than most other programs. The use of cord blood donors promises to increase the applicability of allogeneic transplant, especially to minorities.

**References**

Clinical Cancer Research

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