What Is the Role of High-dose Chemotherapy and Autologous Marrow Support for Patients With Breast Cancer?

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High-dose therapy is now safer, but more effective regimens are needed to optimize results.

Introduction

I will first focus on the use of high-dose chemotherapy regimens in metastatic breast cancer. With that background, we will be better able to evaluate the adjuvant use of high-dose therapy in the primary disease or adjuvant setting. We have fairly large amounts of data in metastatic disease, though only one randomized clinical trial is completed and published.\(^1\) Outcomes have not changed dramatically in the last five or six years in terms of progression-free and overall survival. More than five years ago, Antman and colleagues\(^2\) developed a database containing voluntarily reported data on patients undergoing autologous bone marrow transplant (ABMT) for metastatic disease. An early hypothesis was that patients who responded to chemotherapy prior to high-dose chemotherapy and ABMT were likely to have a better outcome than patients with advanced refractory disease who were already resistant or cross-resistant to drugs used in the high-dose regimens. Thus, patient outcomes, both immediately following ABMT and two years after the procedure, were compared based on disease status prior to transplant (ie, advanced refractory disease vs partial remission vs complete remission).

In summary, this analysis showed a very low complete remission (CR) rate in patients with advanced refractory metastatic disease prior to transplant (Table). Approximately 20% to 25% of patients in partial remission had CR conversions posttransplant. However, relatively few of these patients remained in remission at the two-year follow-up. In comparison, the two-year progression-free survival in patients with a CR prior to transplant ranged from 25% to 50%.

<table>
<thead>
<tr>
<th>Disease Status Prior to ABMT</th>
<th>CR Post-ABMT (%)</th>
<th>2-year CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced refractory</td>
<td>10 - 20</td>
<td>rare</td>
</tr>
<tr>
<td>PR</td>
<td>20 - 25</td>
<td>5 - 10</td>
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<tr>
<td>CR</td>
<td>90 - 100</td>
<td>25 - 60</td>
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Succeeding this initial collaborative effort has been a series of reports from the Autologous Blood and Marrow Transplant Registry, which has the strength of being based on a consecutive registration of patients treated in participating centers. Once a patient is enrolled in the registry, the center must continue to provide data on that patient. This allows an adequate population for subset analysis to identify groups that are most likely to benefit from high-dose chemotherapy and ABMT. In addition, we should be able to rationally identify appropriate subsets for stratification in clinical trials.

More than 19,000 patients have been enrolled in the ABMT database to date.\(^3\) The primary neoplasms for these patients include non-Hodgkin's lymphoma, myelocytic leukemia, Hodgkin's disease, and breast cancer. Of this overall database, approximately 6,000 breast cancer cases are included as part of a research database, including 1,058 metastatic breast cancer cases with enough follow-up at the time of the initial analysis.\(^4\) Approximately 12% of the patients were less than 35 years of age, which is generally younger than the median age of the overall breast cancer population. A significant percentage of patients had visceral metastatic sites. A substantial number of patients were estrogen receptor-positive. The majority of patients in this analysis underwent transplant prior to 1994; thus, three-year follow-up data are available for many patients.

Results of the analysis of breast cancer cases show that the relative risk of death or progression is lower in patients who were more than two years from the time of diagnosis to metastasis.\(^4\) These patients had the best outcome following ABMT. The reasons for this observation probably relate to the natural history of the disease as well as the tumor sensitivity to chemotherapy. Those patients who develop metastatic disease within 12 to 18 months after completing adjuvant chemotherapy have a
poor prognosis in terms of response to subsequent chemotherapy. The relative risk of progression or death is lower for patients who have bone or bone marrow metastases vs those with predominantly visceral or soft-tissue metastases. This trend was not apparent in previous single-institution studies and warrants further evaluation. Age over 45 years is associated with a higher relative risk of death (RR = 1.23); this could be a confounding variable in terms of other selection criteria. In addition, estrogen receptor-positive patients had a slightly lower relative risk than estrogen receptor-negative patients.

Patients with refractory disease also had a higher relative risk of progression or death, and partial remission did not confer benefit. Only patients in CR had a significantly lower relative risk for progression or death. Data from the registry show that the four-year progression-free survival was 20% and the four-year overall survival was 30% in patients who had a CR prior to ABMT. Therefore, I believe that patients who attain a CR following initial lower-dose chemotherapy are certainly an appropriate subset for routine use of high-dose chemotherapy and marrow rescue as consolidation.

During the past five years, the stem cell source used for transplants has changed. Peripheral blood stem cells (PBSC) are used in the vast majority of transplants for breast cancer performed today. The theoretical advantage of PBSC is that these cells contain a higher ratio of multipotent and lineage-restricted cells compared with marrow. This, plus growth factor mobilization, translates into a shorter time to engraftment. Time to engraftment of 25 to 30 days to reach an absolute neutrophil count (ANC) of 500 cells/mm$^3$ reported in previous years with marrow source has been reduced to under 14 days in most series with PBSC.

In addition, by using large-volume leukopheresis in growth factor-stimulated patients, we are now able to obtain an adequate number of PBSC for transplant with one leukopheresis session in 90% of patients. The time to engraftment is short (10 days to an ANC of 500 cells/mm$^3$ and a median of 11 days to an ANC of 2,000 cells/mm$^3$) following stem-cell reinfusion. The number of platelet transfusions and the duration of time they are required also have been reduced by using PBSC.

The morbidity, mortality, and cost of autologous transplantation for breast cancer have been significantly reduced over the last five years. The 100-day mortality rate following autologous transplants decreased dramatically from 1989 to 1993 and is now 6% for patients with advanced primary and metastatic disease. Some of this improvement may reflect patient selection since many early phase I and II trials enrolled patients with more advanced disease at the time of transplant. However, a majority of this improvement is related to improved supportive care techniques.

The dominant question we must now ask is what extent of benefit we can expect to achieve with high-dose vs lower-dose chemotherapy in the adjuvant setting? In the metastatic setting, up to one third of patients who respond to lower-dose chemotherapy will achieve and remain in CR for two years following high-dose chemotherapy. In the adjuvant setting, Bonadonna et al demonstrated that approximately one third of patients who would otherwise develop metastatic disease will remain progression-free at 20 years with adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil). Thus, a reasonable expectation for high-dose chemotherapy in the adjuvant setting would be to prolong the time to metastatic disease by two years in approximately one third of the patients who would eventually relapse. The value of this benefit for the entire population treated depends on the prognosis for the particular primary disease subgroup selected (Figure).

Clinical Trials

**DR HORTON**

What are the advantages and drawbacks of the current clinical trials comparing high-dose chemotherapies with lower-dose therapies?

**DR VAUGHAN**

The first trial that will be reported in metastatic disease is the Cancer and Leukemia Group B (CALGB) trial, which compares cyclophosphamide/doxorubicin/5-fluorouracil (CAF) followed by conventional-dose cyclophosphamide/cisplatin/carmustine vs CAF followed by high-dose cyclophosphamide/cisplatin/ carmustine (STAMP I).

Although randomized clinical trials are the gold standard to scientifically answer clinical questions, I believe there is a significant risk to performing premature randomized trials. For example, in terms of high-dose chemotherapy regimens, it is difficult to identify a “standard” regimen against which to compare many of the new regimens. This adds to the confusion about high-dose chemotherapy for breast cancer.

It may be too early to undertake a large phase III randomized trial and expect it to be definitive. My view is that we need more and better phase I and II trials, such that we may be better able to identify therapies that show a high benefit in a small number of patients and can adequately design further studies based on these early data.

**DR SLEDGE**

The Eastern Cooperative Oncology Group (ECOG) trial is evaluating CAF followed by either observation or combination high-dose chemotherapy using...
cyclophosphamide plus thiotepa. Though initially slow, accrual on this and the CALGB trial has increased in the last year. The Philadelphia group has opened a trial evaluating CAF followed by cyclophosphamide/thiotepa/carboplatin (STAMP V) in metastatic disease. In addition, the Intergroup has recently opened a trial evaluating sequential administration of three cycles of doxorubicin followed by three cycles of cyclophosphamide with granulocyte colony-stimulating factor (G-CSF) vs CAF followed by high-dose chemotherapy and peripheral stem-cell transplantation.

**DR VAUGHAN**

Patient selection is an issue in these trials in that the patient population is very restricted. For example, in the CALGB trial, eligible patients include only those with greater than 10 positive lymph nodes but not defined as stage IIIB. There are similar strict eligibility criteria for the trials that include only women with four to nine positive lymph nodes. These strict criteria may be shifting both arms of the studies towards a more favorable prognosis.

**DR HORTOBAGYI**

One additional issue with all of these trials is that patient selection is now determined not only by clinical criteria but also by specific tests to rule out metastatic disease or to better define the patients functional status. For example, Crump and associates demonstrated that approximately 30% of patients who were referred to their practice for high-dose chemotherapy were excluded from the trial because they were found to have either micrometastatic disease or obvious metastatic disease during staging. Therefore, 25% to 30% of patients with high-risk primary breast cancer may be excluded from trial eligibility because of micrometastasis. If one expects a 10% to 30% survival benefit from high-dose chemotherapy, then the exclusion of 30% of patients complicates the power calculation of these trials. If the magnitude of the benefit from high-dose therapy is similar to the magnitude of the fraction of patients who are excluded, how certain can one be of the significance of the benefit? Furthermore, when these results are compared with nonrandomized controls that have not gone through the same staging process, how much of the theoretically achieved benefit is real and how much is due to patient selection?

It is likely that the results of every randomized clinical trial can be questioned because the target is moving. However, this is true for all clinical trials, and though it makes analysis of true benefit difficult, it does reset the standard each time. If the high-dose therapy trials that are being completed show a 10% to 15% improvement over standard therapy, I think this will be important and will show that this is a therapeutic effect, not simply patient selection or bias. Alternatively, if these ongoing trials show no statistically significant difference with high-dose therapy, the concept of high-dose therapy is not necessarily disproved. It will just be a very strong signal to the oncology community that we have a concept that may be valid but for which the evaluated regimens do not demonstrate a substantial benefit.

I think we can agree that the current generation of high-dose therapy trials has one major deficiency, which is the poor efficacy of these cytotoxic regimens, regardless of high- or low-dose administration. One of the interesting observations about the regimens included in the transplant registry is that the majority contain cyclophosphamide. The existing evidence for cyclophosphamide suggests that a dose of 600 mg/m² is more effective than lower doses. However, there is very little additional evidence that cyclophosphamide doses higher than 600 mg/m² are more or less effective.

**DR VAUGHAN**

There is no question that a dose-response curve exists for the majority of these agents. The issue for the clinician is how much of that range is accessible in a given patient. With regard to cyclophosphamide, the majority of patients I see for transplant have previously received the drug and may already have specific inducible enzymes for cyclophosphamide resistance. Thus, when cyclophosphamide is administered in combination with thiotepa, the thiotepa dose must routinely be reduced (eg, to 500 mg/m² in the STAMP V regimen). In the original phase I thiotepa trials, outcomes in patients who received more than 900 mg/m² were significantly better compared with those whose dosages were lower. From these observations, it would be interesting to design a regimen based on thiotepa 900 mg/m² and identify what agents can safely be added.

The Southwest Oncology Group trial is important because it is evaluating the efficacy of the maximally aggressive nontransplant regimen available today vs a standard transplant-based regimen. This is an important clinical question that differs from the questions being asked in the CALGB and ECOG trials, where there is no intention to maximize the intensity of the nontransplant arm.

**DR SLEDGE**

In the metastatic setting, I think that we would all agree that if high-dose chemotherapy improves the percentage of long-term disease-free survivors by a third, then too few transplants are being performed. Similarly, if the percentage of long-term disease-free survivors is increasing by only 1%, then too many transplants are being performed. Thus, the comparative trial setting becomes vital to identify whether high-dose chemotherapy significantly increases the percentage of long-term disease-free survivors compared with our best standard therapy. That is the test that transplant, both in the metastatic and adjuvant settings, has not yet passed.

**Timing of Treatments**

**DR VAUGHAN**

The timing of high-dose treatments for breast cancer is controversial. It is unclear how much chemotherapy should be administered prior to high-dose therapy. Adjuvant treatment initiated beyond six months after diagnosis has little effect. Timing is also an issue in the advanced primary nonresectable patients where the surgeon or radiologist may request the medical oncologist to give just enough chemotherapy to shrink the tumor. I advocate three to four months of CAF followed by high-dose chemotherapy, because we are treating metastatic disease. At that point, I recommend mastectomy as definitive therapy for local disease. We are using this strategy at my institution, although it is not accepted in the community.

**Future Roles for High-Dose Chemotherapy**

**DR SLEDGE**

When I look at the registry data, I am not convinced for metastatic disease that there is anything approaching a plateau in terms of disease-free survival (and therefore cure) for the general group of patients treated. I think it is reasonable to identify the attributes of high-dose therapy in this population. We know transplant is excellent at inducing CR in a significant number of patients. In the future, we may use high-dose chemotherapy as the launching platform on which to add biologic therapies aimed at preventing micrometastatic disease regrowth. Each of these may not be curative alone, but together may prevent regrowth of micrometastatic disease.

**DR HORTOBAGYI**
I agree. High-dose chemotherapy may be the surgery of the next century. It may be possible to achieve a very effective surgical resection chemically by a single-cycle high-dose chemotherapy administration. In fact, we have shown that posttransplant chemotherapy actually results in additional responses and apparent prolongation of remission duration.\textsuperscript{22} It may be that in 10 years, breast cancer will be treated initially by the radiologist, followed by one or two high-dose chemotherapy regimens, followed by chemoprevention.

References