A Dramatic Story of Hope and Reality

Edward A. Stadtmauer, Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA

In the late 1980s and early 1990s, high-dose chemotherapy and autologous stem-cell transplantation seemed to be so promising for patients with metastatic breast cancer. Advanced breast cancer was a devastating disease with limited treatment options. Though responses were frequent, long-term remissions were generally uncommon, and median survival was perceived to be short. Conventional-dose chemotherapy and radiation therapy were inadequate and surgery of limited practicality.

Attempts to improve outcome focused on the growing body of evidence at that time that increased dose intensity could overcome inherent tumor resistance, particularly with alkylating agents. A strong relationship of dose to response was demonstrated both in vitro and in early clinical trials in various solid tumors, but, ultimately, dose escalation was limited by bone marrow destruction and the resultant increased likelihood of infection and bleeding. The 1980s saw the development and accessibility of the necessary technology of hematopoietic stem-cell collection, cryopreservation, and storage. Advances in supportive care for patients with prolonged cytopenia and transient organ dysfunction also allowed for the widespread use of high-dose alkylating agent regimens and autologous stem-cell transplantation.

This approach was applied to various chemotherapy-responsive malignancies, particularly leukemia, lymphoma, germ cell cancer, ovarian cancer, and breast cancer. Preliminary results showed high response rates, even in patients with relapsed chemotherapy-resistant breast cancer, with relatively low rates of morbidity and mortality when the dismal prognosis of this group of patients was taken into consideration. A number of prominent cancer centers began to focus on this approach for breast cancer, and a number of moderately sized phase II trials were reported suggesting long-term survival that appeared superior to reported historical data. The degree of evidence for benefit was at least as extensive as many prior established therapies, and high-dose chemotherapy and autologous stem-cell transplantation were well on their way to becoming a standard of care for women with metastatic breast cancer. Both the medical community and patients and their caregivers were understandably hopeful about a new level of success for the treatment of a serious disease.

There were, however, barriers to the establishment of this therapy as the standard therapy for all patients with poor-prognosis breast cancer. First was the cost. With tens of thousands of women per year as potential candidates for this treatment approach that required intensive and costly inpatient and outpatient care, an incremental financial burden of billions of dollars was anticipated, which raised concerns from the insurance industry. Most insurers demanded further proof of benefit before routinely covering this procedure for this indication. Additionally, patients and their advocacy groups were at times hesitant to subject themselves to such intensive and potentially toxic therapy; yet, they were incensed by decisions being made by third-party payers or government regulators rather than through physician and patient discussion. Finally, oncologists were hesitant to send their patients for this procedure without prospective comparative data to prove superior outcome with high-dose therapy.

In light of these issues, a number of comparative trials were initiated throughout the world, with random assignment of patients to either conventional dose therapy or to high-dose therapy and autologous stem-cell transplantation. These trials were straightforward, asking an important clinical question and requiring accrual of only a small minority of all the patients who were undergoing the procedure at the time. Nevertheless, these trials accrued slowly, with up to a decade for completion and analysis of data; many were terminated prematurely because of slow accrual. The reasons for this were manifold, but included many issues that are still applicable today. Insurers frequently denied coverage for the clinical care of patients enrolled on these trials, declaring that they would change their policy once the clinical trials were completed and showed a positive outcome. This was a classic “Catch 22.” Patients and their physicians were also frequently hesitant to enroll on these trials, concerned that the assigned treatment was based on random choice rather than thoughtful consideration of pros and cons by patient and physician. This insertion of controversy throughout the entire health care system put insurers, patients and their advocacy groups, and physicians at odds, when in fact, a collaboration of these constituencies towards rapid accrual to these clinical trials and answers to these questions were necessary. To this day I remain impressed and profoundly grateful, not only to the women who participated in these trials, but also to the referring physicians and insurers who understood their importance. These are truly the unsung heroes of this story.

The end result of the nearly two decades of research on this topic is now well known and confirmed by the report by Crump and his colleagues from the National Cancer Institute of Canada reported in this issue of the Journal.1 There are now at least six randomized studies that have examined the effects of high-dose chemotherapy in patients with metastatic breast cancer: the Philadelphia Bone Marrow Transplant Group/Eastern Cooperative Oncology Group PBT-1 trial, the French Pegase 03 and 04 studies, two trials from Duke University, and the Canadian MA16 trial reported here.2-7 All show similar results to the Canadian study. Following
initial response to conventional-dose chemotherapy including anthracycline- or taxane- based induction therapy, 224 patients were randomly assigned to either high-dose alkylating agent chemotherapy and autologous stem-cell transplantation or to the standard dose therapy to which they were already responding. With a median follow-up of 4 years, no difference in median overall survival (approximately 2 years) was seen for each arm. In this study, as well as a few of the other studies, a mild improvement in progression-free survival (11 v 9 months) was seen with the high-dose chemotherapy arm, but this did not translate into an improvement in overall survival in this disease.

This report, taken together with the results of numerous prior trials, led us to definitively conclude that a high-dose of alkylating agents with autologous stem-cell transplantation, when given in the setting of responding metastatic breast cancer, does not lead to improved overall survival. Many reasons for these results have been suggested, including patient selection, choice of the high-dose chemotherapy regimen, choice of the conventional-dose chemotherapy regimens, or sample sizes leading to a lack of statistical power. One large nonrandomized study comparing patients in a bone marrow transplant registry to similar patients treated with conventional-dose chemotherapy protocols, also failed to show significant benefit. It is unlikely that further meta-analyses of all these clinical trials will lead to a different conclusion.

The story of high-dose therapy for metastatic breast cancer has been dramatic and has recently resulted in the publication of a book recounting the story. Fraudulent results, legislative battles, and health care financing all came into play. This story clearly demonstrates the practical importance of the timely conduct of well-designed clinical trials. These trials must be financed adequately without undue burden to the remarkable patients and physicians who are trying their best to improve treatment outcome from serious diseases. The story of high-dose chemotherapy and autologous stem-cell transplantation for breast cancer was not one of false hope. Instead, it was one of real hope and was a rational idea based on promising preliminary data. Subsequent studies have now shown that though patients who have undergone stem-cell transplantation can do well, these patients do not have a survival that is superior to those who undergo other therapies. It is time to move on to the future, but remember the lessons of the past.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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