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NCI's Initiatives to Save the Breast Cancer ABMT Trials

by James L. Wade III, M.D., F.A.C.P.

Technology moves faster than knowledge, which in turn, moves faster than wisdom. This new dilemma of modern medicine is best epitomized in the use of autologous bone marrow transplantation (ABMT) with high-dose chemotherapy (HDC) for the treatment of women with breast cancer. The ability to treat women with this approach slowly evolved from other malignant disease models such as non-Hodgkins lymphoma and acute leukemia. With the availability of the new hematopoietic stem cell growth factors, the use of this technology in patients with breast cancer has greatly increased. The North American Autologous Blood and Bone Marrow Transplant Registry in Madison, Wisc., has been collecting data from more than 100 institutions since 1989; it captures about 50 percent of patients undergoing this therapy nationwide. Breast cancer represents the fastest growing target disease for this procedure, with more than 1,300 performed each year. Unfortunately, we do not know if this expensive and potentially dangerous procedure works.

Since 1991 the National Cancer Institute has sponsored three large national intergroup prospective randomized clinical trials to answer this question. One of the trials is in women with metastatic breast cancer; the other two trials are in women newly diagnosed with breast cancer that was at such a stage that the patients were at high risk for relapse after initial treatment. Although entry onto these trials is available at many sites, including CCOPs, CGOPs, and member institutions belonging to almost all the cooperative research groups across the country, the accrual has been poor. If these trials are not completed, we will never know if the technology really works, and we will never gain the wisdom needed to treat women afflicted with this disease.

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A HISTORY OF POOR ACCRUAL

A prime reason for poor accrual to these trials has been biased studies and inconclusive results. Studies testing ABMT with HDC in carefully selected women with metastatic breast cancer have been published in phase II trials from single institutions. Early results suggested that about one in five women treated this way would survive several years without the disease returning, and that this outcome was better than that achieved by "historic controls." However, none of these trials was randomized and none had a control arm. This underlying bias was one of the main reasons that deterred accrual. This prejudice affected both physicians and patients. Furthermore, with the advent of colony stimulating factors (CSFs), the preferred method of stem cell procurement has changed. The classic bone marrow harvest done in the operating room under a general anesthetic is now being replaced by peripheral blood stem cell harvesting using leucopheresis after priming with cyclophosphamide or CSFs, or both.

In October 1995 the first prospective randomized trial testing ABMT with HDC in patients with metastatic breast cancer was published from the University of Witwatersrand in South Africa. The 90 women enrolled in this trial were treated with either a "standard" regimen of six to eight cycles of cyclophosphamide, mitoxantrone, and vincristine or high-dose cyclophosphamide, mitoxantrone, and etoposide with stem cell support. The standard group had a complete remission rate of 4 percent and a median survival of 11 months. The experimental group had a complete remission rate of 51 percent and a median survival of 22 months, with about 18 percent alive and disease free at three years. Although these results are encouraging, the standard arm, by U.S. standards, would have been *undertreated*. Current regimens in common use in the United States achieve an 18 percent complete response rate in all comers, which include women too sick or too old to have a BMT. The average survival for a woman in this country treated with standard chemotherapy for metastatic breast cancer is 22 months, a similar number to the transplanted group from South Africa. Therefore, instead of concluding that those who are overtreated do better, an alternative conclusion for this study might be that women who are undertreated do worse.

An even more recent development makes the issue even more murky. In May 1996, Dr. Williams Peters at Duke University presented his latest results from a randomized trial performed in women with metastatic breast cancer. Four hundred and twenty-three patients with hormone-resistant, previously untreated metastatic breast cancer were enrolled in an intensive induction regimen with doxorubicin, methotrexate, and 5-fluorouracil. Of these, 105 (25 percent) achieved a complete remission and were randomized to either an immediate ABMT with HDC or observation only, with ABMT reserved for time of relapse. The median overall survival of the *observed* group was 3.6 years versus 2.3 years for the group in complete remission that went on to immediate transplant. Once patients relapsed after transplant, they did not do well; only 20 percent were alive at five years versus 45 percent for the delayed ABMT group. What was demonstrated was that immediate HDC with ABMT converts patients

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who are in complete remission to cure only 20 percent of the time. What was not tested was whether standard dose chemotherapy given at time of relapse would have done just as well as those receiving the ABMT with HDC. Standard dose chemotherapy in patients with hormone refractory breast cancer yields a historic 2 to 4 percent long-term survival and these results are prior to the introduction of new agents such as paclitaxel, docitaxel, vinorelbine, dexrazoxane, gemcitabine, etc.

The second reason for poor accrual was the reimbursement system. Insurance companies, in an effort to curtail costs, began to insert exclusions in health insurance policies in the early 1990s that eliminated coverage if the treatment was administered as part of a clinical trial. The National Blue Cross/Blue Shield Association established a demonstration project, which, if the local BC/BS plan agreed, would cover the cost of a BMT on an NCI study. Unfortunately, only fifteen of the seventy BC/BS plans throughout the country agreed to participate. Patients referred to a transplant center would discover that their transplant would be covered, paradoxically, as part of standard medical care if they were not on the trial and thus not part of a research study.

The dependence on third-party coverage led to a third reason why accrual to these trials suffered. Some transplant centers learned that their revenue would certainly improve if all patients were transplanted, rather than just half if they were on the NCI study. Some centers implemented their own phase II trials that would not include randomization. Patients who came to learn about the NCI trial would be offered instead a newer, "better" study where all patients received the life-saving transplant. Patients thought they were still contributing to science by receiving their transplant while the center contributed to the bottom line.

By spring 1995 all three trials were in trouble with accruals, and it seemed doubtful that they would ever be completed or that the research questions would ever be answered. In March 1995 Jeffrey Abrams, Michael Friedman, and Mary McCabe convened the first HDC with ABMT for breast cancer strategy meeting. Included in that first meeting were experts in the biology of breast cancer; bone marrow transplanters; representatives from community oncology centers, the health insurance industry, and NCI; health care outcomes analysts; and leaders of patient advocacy groups. Notable participants included Sharon Green, Y-Me National Breast Cancer Organization; Elizabeth Hart, The Komen Foundation; Carolyn Harvey, National Black Leadership Initiative on Cancer; Amy S. Langer, National Coalition of Breast Cancer Organizations; Ellen Stovall, National Coalition for Cancer Survivorship; and Fran Visco, J.D., National Breast Cancer Coalition.

This day-long symposium bracketed the major underlying issue: We do not know if this procedure works, and the only way to learn if it does is to complete the NCI trials in progress. The meeting truly aligned for the first time the patients, the doctors, NCI, the universities, and the payers. Each group left the meeting with specific tasks aimed primarily at educating their respective constituencies about the pivotal importance of completing these three trials.

In May 1995 NCI conducted a series of interviews and educational sessions with community oncologists who were attending the American Society of Clinical Oncology meeting in Los Angeles. The report, published in August 1995, summarized many of the barriers to completing the studies, including physician bias about the best treatment, patient reluctance about randomization, regulatory hurdles for community cancer research, and the profitability of the status quo.

IMPROVEMENTS IN ACCRUAL

In October 1995 the Division of Cancer Treatment/Office of Cancer Communications of the National Cancer Institute proposed a special educational and promotional plan. By that time the accrual was starting to improve. The randomized trial for women with metastatic breast cancer PBT01 had entered 305 patients with a target accrual of 549 and a projected completion date of November 1997. The two trials testing BMT in the adjuvant setting were doing better. Both trials were in women who historically had the highest risk for recurrent disease, namely that ten or more lymph nodes were involved with malignancy at the time of diagnosis. INT-0121, which tests BMT after standard adjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide chemotherapy had entered 265 patients with a goal of 536 and a projected completion date of December 1996. The CALGB trial INT-0163 compares a potent adjuvant chemotherapy regimen given either at a standard dose or at a much higher transplant dose. That trial had randomized 500 patients of a total target accrual of 800 with a planned completion date of March 1997.

Three general efforts are now underway to help complete these important studies.

1. *NCI is helping heighten awareness about these trials within the health professional community.* The myth that we already knew the answer is being dispelled. Alliances with other organizations, such as the Association of Community Cancer Centers, are helping spread the word that the problem is not yet solved and the trials need help. The cooperative group chairs are now more closely monitoring their member institutions' participation in and accrual to these trials as a number one priority that takes precedence over any internal phase II studies.

2. *NCI, in partnership with patient advocacy groups, is educating its members (specifically breast cancer patients) that the role of BMT is not yet confirmed in the fight against their disease.* In May 1996 the Office of Cancer Communications completed its second report on the accrual to these trials; the study summarized interviews with twenty-nine women with breast cancer who were involved in the NCI trials. This report, "The Road to an Autologous Bone Marrow Transplant Trial: Breast Cancer Patients' Decision-making Process," concluded that patients relied on information and opinions obtained from their medical oncologist and advice from their families. In addition to the uncertainty of randomization, the biggest barriers were financial and insurance coverage. Patients are being encouraged by their support groups and through the cancer survivor organizations to participate in these trials rather than BMT off a study. NCI is helping supply accurate information to the media to better inform the general public about the urgent need to solve this problem by using the

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clinical trial process.

3. *NCI is working with the insurance industry to explore if a policy that defines coverage for patients on a clinical trial can be defined.* NCI has intensified its dialogue with HMOs and large insurance companies, including CHAMPUS, which insures members of the military and Department of Defense employees and their dependents. This spring NCI and the Department of Defense completed a landmark agreement that virtually guarantees that beneficiaries of the Department's health plan will have ready access to all NCI-approved phase II and phase III treatment trials, even if they include a BMT.

By February 1996 the accrual to PBT01 had risen to 396 patients. The accrual to INT-0121 and to INT-0163 had also increased to 353 and 642 patients, respectively. With the current transplant trials back on track, NCI is now looking to the next high-risk patient group, namely women with breast cancer and four to nine lymph nodes involved with malignancy. This trial will compare HDC with stem cell support versus intensive sequential chemotherapy given over 16 weeks.

Accrual has also been helped by large private companies who are offering to reimburse for treatment costs of their employees who participate in clinical trials. In May 1996, for example, Caterpillar, Inc., the giant world-wide earth moving equipment company, announced a new special benefit plan for its employees. Wayne Zimmerman, vice president for human services, reported that the company, which is self-insured, will cover the treatment costs of women entered on the high-priority adjuvant trials.

When the trials were introduced, many researchers thought that they already knew the answers. It is now clear that we do not yet have the knowledge about the value of this new tool. Until we develop that knowledge, we will never really know how well HDC with BMT works, or in whom, if anyone, should it be used. Only when the trials are completed and the results analyzed, we will then gain the wisdom needed to better treat those afflicted with the disease.

SUGGESTED READINGS

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IN THE NEWS

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Occupational therapy can be a valuable stratagem for distracting patients from focusing on the disease, symptoms, and emotions.

Patients with fatigue should be encouraged to develop their own coping mechanisms, such as pacing themselves, delegating activities, altering activity/rest patterns, setting up an activity or walking program, and using sedentary distractions such as listening to music, watching television, and reading.

"Currently, physicians and HMOs are looking at the efficacy of cancer therapy not only by objective response criteria, but also by quality of life indicators. Fatigue is certainly one indicator and should be included in the physical symptom listings of quality of life instruments," Piper suggested.

[1] Piper BF, SL Dibbie, MJ Dodd. The revised Piper Fatigue Scale: Confirmation of its multidimensionality and reduction in number of items in women with breast cancer. *Oncology Nursing Forum* 23(2):350, 1996.

PROFESSIONAL OPPORTUNITIES