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Chaos surrounds high-dose chemotherapy for breast cancer

In the past, the American Society of Clinical Oncology has fiercely enforced a policy of no early release of data to be presented at its meetings. But this year, a month before its annual gathering, which starts today in Atlanta, Georgia, ASCO decided to publish abstracts of five randomised trials of high-dose chemotherapy for high-risk or advanced breast cancer: only one reports a statistically significant positive result. High-dose chemotherapy for breast cancer effectively ablates the patient's bone marrow and makes a haemopoietic transplant essential. The technique is dangerous (one study reports 7·4% treatment-related mortality), and any benefit is likely to be small. Releasing and discussing early data from the trials, before the conference, is controversial.

Most probably, ASCO's hand was forced by a strong story in the *Wall Street Journal* in March which said that the studies were expected to be negative. That story followed a February meeting convened by the National Cancer Institute in the USA and attended by breast-cancer advocacy groups.

ASCO stated, when it released the abstracts in mid-April, that definitive conclusions cannot yet be made. Ric Klausner, NCI director, commented guardedly: "high-dose therapy has not yet been shown to be superior". The NCI's head of cancer treatment and diagnosis, Robert Wittes, went further: "the information . . . does not suggest that high-dose chemotherapy with transplants improves survival".

Most of the consumer groups still insist that the high-dose treatment should be available to those women that want it. This is the line taken by, for example, the Susan G Komen Breast Cancer Foundation and the Y-ME Breast Cancer Organization. The National Breast Cancer Coalition takes the opposite view: "the results will not show that this treatment benefits women with breast cancer".

The story of high-dose chemotherapy for breast cancer is turning into a classic example of how not to turn research into practice. Early non-randomised studies gave promising results, and the regimen leaked out into practice before the results of any large randomised phase 3 trials were reported. In Europe, however, oncologists are far more reluctant to give high-dose treatment as routine. The USA has very active breast-cancer consumer groups who aggressively lobby for access to almost any new treatment that offers even the slightest hope. Not surprisingly, many frightened patients decided to gamble on high-dose chemotherapy. As a result, only one in ten US patients who have received high-dose chemotherapy did so within a clinical trial. With so few patients participating in randomised studies, the trials dragged on far longer than expected.

Although ASCO and the NCI must be presumed to have the best of intentions, their management of the release of these latest data has only served to muddle the situation further. Both should have known that the public disclosure of controversial medical information needs careful handling, especially in the extremely politicised field of breast cancer. ASCO failed, when commenting on the five studies, to include the findings of three previous randomised studies. Although all were small, two were negative and the positive trial was from the same South African group that will report positively again at this week's conference.

Cancer professionals still have one chance to restore some scientific dignity and public confidence. While releasing the data early, ASCO sought to hold its position by saying that the data are yet to be "reviewed and discussed in the scientific community". That discussion must look critically at whether the interim analyses presented to date were preplanned in the trial protocols. The investigators must also resist calls for subgroup analyses. Because the trials are so diverse, a meaningful meta-analysis is unlikely, and the opportunity for prospective overviews may have been missed. Rigid adherence to what remains of the principles of good practice for clinical trials will limit the damage already done to the reputation of all those involved in breast-cancer treatment and advocacy in the USA. Then the needs of women with breast cancer will be truly served, and seen to be so.

The Lancet

SPECIAL ARTICLE

PHYSICIANS' REASONS FOR NOT ENTERING ELIGIBLE PATIENTS IN A RANDOMIZED CLINICAL TRIAL OF SURGERY FOR BREAST CANCER

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Abstract We studied the reasons surgical principal investigators chose not to enter patients in a large, multicenter trial sponsored by a cooperative group. In 1976 the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) initiated a clinical trial to compare segmental mastectomy and postoperative radiation, or segmental mastectomy alone, with total mastectomy. Because the low rates of accrual were threatening to close the trial prematurely, we mailed a questionnaire to the 94 NSABP principal investigators, asking why they were not entering eligible patients in the trial. A response rate of 97 per cent was achieved. Physicians who did not enter all eligible patients offered the following explanations: (1) concern that the doctor–patient relationship would be affected by a randomized clinical trial (73 per cent), (2) difficulty with informed consent (38 per cent), (3) dislike of open discussions involving uncertainty (22 per cent), (4) perceived conflict between the roles of scientist and clinician (18 per cent), (5) practical difficulties in following procedures (9 per cent), and (6) feelings of personal responsibility if the treatments were found to be unequal (8 per cent). Further investigation into the behavioral aspects of the investigator–patient relationship is particularly pressing, since fear of change in this relationship was the most common reason given for not entering eligible patients in the trial. (N Engl J Med 1984; 310:1363-7.)

THE National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP), the largest North American cooperative group dedicated to research in breast cancer, was formed in 1958 for the purpose of implementing multicenter randomized clinical trials to evaluate the effectiveness of different treatments of breast cancer.[1] Member institutions are centers that agree to enter eligible patients in collaborative breast-cancer trials.

In 1974 the NSABP completed a randomized surgical trial demonstrating that total mastectomy, with or without radiation, was as effective as radical mastectomy in the primary treatment of cancer of the female breast.[2] Within 38 months (July 22, 1971, to September 6, 1974) 34 of the 75 NSABP institutions entered a total of 1765 patients in this controlled trial.

A follow-up study was initiated to compare treatment outcomes for patients with breast cancer who were randomly assigned to one of three treatment groups: segmental mastectomy ("lumpectomy") without radiation, segmental mastectomy with radiation, or total mastectomy.[3] It was estimated that up to 2500 patients would be required for this study. The number of eligible patients per participating institution could not be accurately predicted. However, on the basis of the success in recruiting patients for the earlier trial and an increase in NSABP membership from 75 to 94 centers, it was projected that the accrual rate for the second trial would be equal to or higher than that in the first trial. At the inauguration of the second trial in April 1976, it was expected that with an accrual rate of 75 patients per month, the trial would take from 2.5 to 3 years to complete.[4] After 44 months, only 519 patients had been enrolled, an actual accrual rate of approximately 12 patients per month, or 16 per cent of the expected rate.[5] To ensure adequate statistical power and validity, it was imperative that a minimal number of patients be admitted to the trial at a specified rate.[6-8] Thus, nonaccrual was threatening the successful completion of the trial.

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METHODS

To examine factors influencing the accrual rate, the NSABP surveyed the principal investigators at all 94 member institutions in February 1980. A questionnaire was designed to examine the process of entering patients in a trial — a procedure whose outcome is critical to the success of randomized clinical trials.[9]

The sample frame included all principal investigators at the 94 hospitals in the NSABP, representing a census of NSABP institutions. Although a total of 235 surgeons were registered as active participants in the cooperative group, the self-administered questionnaire was designed for completion by the 94 principal investigators and was pretested on a group of surgical oncologists in the Montreal area. It was expected that these senior members, who were not assumed to be representative of all participating surgeons, would be the strongest supporters of the clinical trial.[10-12] All respondents were male principal investigators: 84 (89 per cent) were from the United States and 10 (11 per cent) were from Canada, with a mean postresidency status of 14.2 years. The institutions they represented ranged from large teaching hospitals (59) to smaller community-based institutions (32).

The questionnaire was divided into three sections. In the first, surgeons were asked whether they entered all, some, or none of their eligible patients in the trial. In the second section, they were asked to comment on the appropriateness of the scientific design of the trial, including whether or not they had established segmental or total mastectomy as the treatment choice. The third section addressed the issue of informed consent as a possible obstacle to accrual. Was there a problem in telling the patient she would be randomly assigned to a treatment group or in having to explain that the surgeon did not know which procedure was best? Space was provided for open-ended responses in addition to the closed-ended answers.

Because of the descriptive intent of the survey, raw frequencies

and percentages have been used to present the analyzed responses. The chi-square test of significance has been used to examine hypotheses of independence between accrual and factors that may have had an influence on it. When expected cell values were less than 5, the chi-square statistic was computed by applying the continuity correction.

Results

A 97 per cent response rate (91 of 94 principal investigators) was achieved after a single mailing of the questionnaire. Each reply contained answers within each of the categories of specific queries, as well as extensive written comments, although not all respondents answered all questions within a category. For example, a respondent may not have noted a concern about scientific design but may nonetheless have cited a preferred treatment. Even though it was optional to do so, all 91 investigators identified themselves on the questionnaire.

The responses to specific questions are presented in Table 1. The open-ended comments, which were coded, grouped, and tabulated, are shown in Tables 2 and 3. Over one third of the principal investigators did not enter any patients in the trial, and 38 per cent stated that they enrolled only a portion of their eligible patient population. None of the surgeons who expressed reservations in any of the six categories of concern identified by the open-ended responses (Table 3) entered all eligible patients in the trial. Of the 91 respondents, 19 declared a preferred operation and 8 indicated a concern with the scientific design of the trial. Obtaining informed consent was noted as a difficulty by 25 surgeons. Ten said that telling a patient she would be randomly assigned was an impediment to treatment, and 15 were bothered by being unable to recommend one operation over another; 20 surgeons gave both reasons.

Obstacles to accrual, as determined from the open-ended responses, are shown in Table 2. Five surgeons said they would feel personal responsibility if one treatment were shown to be superior, and six indicated that the increased time required to follow a patient in the trial was an obstacle. Twelve cited a perceived conflict between the traditional therapeutic, individualized approach to patient care and the benefit to the public good implicit in the clinical trial. Fifteen surgeons indicated their discomfort with frank discussions of uncertainty — an integral part of patient enrollment in randomized clinical trials. Finally, 2 respondents indicated problems with informed consent, and 48 referred to their uneasiness with a doctor–patient relationship in which the patient becomes a research subject.

Table 1. Frequency of Responses by 91 Principal Investigators to Specific Questions from a 1980 NSABP Survey.

Statement	Frequency of "Yes" Response	
	no.	%
Enrollment of eligible patients		
All	25	27
Some	34	38
None	32	35
I am concerned with the scientific design of the trial.	8	9
Patient should not be treated by segmental mastectomy.	16	18
Patient should not be treated by total mastectomy.	3	3
I have trouble with informed consent.	25	27
The trouble is telling the patient she will be randomly assigned to treatment.	10	11
The trouble is telling her I don't know which operation is better.	15	17
Physicians who responded "yes" to both statements.	20	22

Table 2. Obstacles to Accrual, According to Open-Ended Responses from 66 of 91 Surgeons Who Did Not Enter All Eligible Patients in the Trial.

Reasons for Not Entering Patients (Rank Ordered)	Frequency of Response	
	no.	%
Concern with doctor–patient relationship in a randomized clinical trial	48	73
Trouble with informed consent	25	38
Dislike of open discussions about uncertainty	15	23
Conflict between physician as clinician and as scientist	12	18
Practical difficulties in trial procedures	6	9
Feelings of personal responsibility if treatments are unequal	5	8

Discussion

An analysis of questionnaire responses suggests that there were six distinct, although interrelated obstacles to enrollment of patients in the trial.

Doctor–Patient Relationship

Forty-eight of the 66 physicians (73 per cent) who did not enroll all patients made some reference to their relationship with the patient. Studies of traditional doctor–patient relationships indicate that the primary basis for the authority of physicians has been their expert knowledge and individualized decision-making power.[13-15] A second basis has been the belief that physicians will try to do what is best for the particular patient.[16-18] Finally, there has been a strong element of charismatic authority, since medical practitioners are engaged in an activity of symbolic importance.[19] Participation in a clinical trial has been described as potentially compromising the authority of the physician.[20,21] Such a situation may put pressure on the doctor–patient relationship, and many of the respondents cited this factor as a deterrent to enrollment.

For example, nine surgeons complained that patients' preferences had been so influenced by the me-

Surgeons Enterin
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All (n = 25)
Some (n = 34)
None (n = 32)

Total (n = 91)

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6	9
5	8

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Table 3. Association between Accrual and Six Categories of Concern Expressed by Surgeons.

Surgeons Entering Stated Proportion of Eligible Patients	Category of Concern 1: Doctor–Patient Relationship		2: Informed Consent		3: Discussing Uncertainty		4: Clinician vs. Scientist		5: Practical Difficulties of Trial		6: Personal Responsibility	
	yes	*no*	*yes*	*no*	*yes*	*no*	*yes*	*no*	*yes*	*no*	*yes*	*no*
All (n = 25)	0	25	0	25	0	25	0	25	0	25	0	25
Some (n = 34)	25	9	16	18	7	27	2	32	2	32	0	34
None (n = 32)	23	9	9	23	8	24	10	22	4	28	5	27
Total (n = 91)	48	43	25	66	15	76	12	79	6	85	5	86
Chi square (2 df)	38.52		16.03		7.41 *		14.88 *		4.21 *		10.37 *	
P value	<0.005		<0.005		0.01<P<0.025		<0.005		0.10<P<0.25 †		0.005<P<0.01	

...lated with the continuity correction.

†Not significant.

...hat random assignment was a difficult task. One ...on stated:

...ts now have a strong conviction with respect to retention of ...east, because of the lay literature. Some eligible patients refuse ...l; others will accept only partial. With such a controversial ...col you cannot expect a high rate of participation from physi... ...or patient.

...rthermore, 15 surgeons believed that their rap... with patients might be jeopardized by enrollment ...e trial. The following response was typical: "At ...nt there appears to be reduced credibility in the ...of the public — for example, the push for a second ...on. It seems that adding further questions and ...vation will just further disturb my rapport with ...patients."

...leven surgeons were concerned that morale might ...owered if patients were subjected to the indecision ...licit in the trial. One respondent said: "Were I to ...r my patients into the trial, I might undermine the ...ients' trust and faith, which are an important part ...he cure itself."

...ome respondents believed that participating in a ...nical trial would necessitate a major change in the ...aditional physician–patient interaction. Fears ex...ressed were often anticipatory or theoretical in na...re but were nevertheless cited as a reason for not ...tering patients in the trial. Of the 48 surgeons who ...edicted a problem with the physician–patient rela...nship, none entered all their patients in the trial, 25 ...2 per cent) entered some, and 23 (48 per cent) en...ed no eligible patients. Of the 43 surgeons who did ...t cite jeopardy to the doctor–patient relationship, 25 ...58 per cent) entered all their patients in the trial, 9 ...21 per cent) entered some, and 9 (21 per cent) en...ed no patients (Table 3).

These data suggest that surgeons may enroll a sub...t of eligible patients not expected to have problems ...ith the ensuing doctor–patient relationship. In fact, ...x surgeons who enrolled all their eligible patients ...dicated that they would enroll some rather than all, ...they encountered difficulty with the doctor–patient ...lationship. It appears that concern about relationships with patients had a major impact on enrollment in the trial.

Informed Consent

In addition to other reasons for nonenrollment, 25 respondents cited trouble with informed consent. Enrollment of a patient in a randomized trial suggests that the patient has signed a document confirming her understanding of the disease, its risks, and possible side effects of any therapy, and has agreed to be randomly assigned to treatment. Twenty-five respondents complained that obtaining informed consent was an arduous task. The following comment was typical:

> It is very difficult for me to present this protocol to my patients. I know the study is important, and I support it vigorously at meetings, yet I just can't ask my patients to join. I try . . . I say . . . the next eligible one . . . and then I look at the informed consent sheet which is far in excess of what is appropriate, and that's it.

None of the 25 surgeons who had difficulty with obtaining consent entered all their patients in the trial, 16 (64 per cent) entered some, and 9 (36 per cent) entered no patients. Of the remaining 66 who did not cite trouble with informed consent, 25 (38 per cent) entered all their patients in the trial, 18 (27 per cent) entered some, and 23 (35 per cent) entered no patients (Table 3).

The need to obtain informed consent before participating in a randomized clinical trial has been cited as an obstacle to recruitment of patients.[22-26] Furthermore, there has been speculation that differing legal requirements may result in concerns peculiar to physicians in the United States, as compared with their Canadian counterparts.[23] Although only a small proportion (11 per cent) of the respondents were Canadian, informed consent appears to have posed a greater problem for them (5 of 10, or 50 per cent) than for their American counterparts (20 of 81, or 24 per cent), but the difference was not significant at the 0.05 level (P = 0.0739, by Fisher's exact test).

Two unexpected findings emerged from close examination of the data. First, of the 25 physicians citing

problems with informed consent, 9 (36 per cent) did not enter any patients in the trial. Of the 66 who did not cite problems with informed consent, 23 (35 per cent) also entered no patients. This suggests that should the requirement for informed consent be removed, surgeons might still not enter patients in the trial. Second, although it is not surprising that none of the 25 respondents who had difficulty with informed consent enrolled all their patients, it is notable that 16 of the 25 (64 per cent) did enroll some patients. The physicians may have selected out patients they predicted would have difficulty with informed consent.

Discussing Uncertainty

Fifteen principal investigators expressed difficulty in telling patients that they did not know which operation was better. Although they admitted that the same uncertainty exists for surgeons not entering patients in clinical trials, they were unaccustomed to including the patient in frank discussions about the controversy over treatment. This concern was aggravated by an inability to suggest a treatment of choice, as is evident from this typical response: "How can I possibly tell the patient that I don't know which operation is better? I am not uncomfortable telling her there are two options . . . but then she says, 'Well . . . what do *you* think?' And then what do I say?" None of the respondents who were concerned about the public admission of uncertainty implicit in the accrual process entered patients in the trial.

The randomized clinical trial highlights the conflict of having to say, "We don't know," rather than the more familiar, "I think this is the best thing to do."[27,28] The responses to our questionnaire suggest that for surgeons accustomed to the classic organization of medical practice, the clinical trial with random assignment to treatment is an unfamiliar and disquieting process often prompting nonparticipation. Of the 66 surgeons who did not enter all eligible patients in the trial, 15 (23 per cent) made some reference to this conflict.

Physician as Clinician versus Scientist

A complex set of responses to the survey addressed the tension between the surgeon as scientist and the surgeon as clinician. Twelve of the 66 surgical oncologists who did not enter all patients in the trial argued that they were pragmatists, often relying on their own observations in the face of controversial evidence and apt to tinker if the desired results could not be obtained by conventional means. This behavior was contrary to the terms of participation in the trial. The following comment is representative of this conflict: "I would probably enter more patients in the trial if I weren't so concerned that if they 'go sour' I will then have to follow instructions or withdraw them from the trial." Five respondents said they preferred to trust firsthand experience, even when it conflicted with evidence. This attitude led them to believe that they had definitive a priori knowledge about which operation was correct, thus obviating the need for scientific investigation. The following response is an example of this barrier to enrollment of patients in the trial:

> The majority of surgeons in my hospital are convinced that modified radicals are the procedure of choice. A smaller group feels just as strongly that wide local excision with radiotherapy is the best treatment. Neither group feels the need, nor are they willing, to randomize their patients and put them into a trial. Why should they? Each group feels they have the right answer.

Surgical tradition appeared to be another strong motivating force against enrollment. Six investigators referred to this obstacle. One stated, "I have done modified radicals on hundreds of patients over the last thirty years. Why should I stop now when they cannot give me any evidence of an improved cure rate with lesser surgery?" Another wrote, "What do you expect me to do? I live in Halsted City." Of the 12 physicians who adopted a clinical rather than a scientific approach to the surgical question, 2 entered some patients in the trial, and 10 entered no patients; none of the 12 entered all patients (Table 3).

Practical Difficulties in Trial Procedures

In discussions of barriers to accrual, some physicians have voiced concern with the additional time required to follow a patient enrolled in a trial.[26] Six NSABP principal investigators alluded to particular features of the trial as a barrier to enrollment of patients. The time required to explain procedures to patients, the rigid rules governing eligibility, the inflexibility of the prescribed treatment formulas — all designed to ensure scientific rigor and generalizability of results — were described as insurmountable barriers to enrollment. In a typical comment one surgeon wrote:

> I do not have the time it requires to explain to a patient about entering the protocol. If in the future there were a faster, more efficient way of doing it, I think I would enter a lot more patients. To try to talk a patient into entering adds three quarters of an hour to a consultation when one has just had to tell the patient she has breast cancer. This is a major deterrent to participation.

Four of the six respondents citing problems with the practical application of trial procedures did not enroll any patients, and two enrolled some; none enrolled all eligible patients (Table 3).

Personal Responsibility

A final obstacle to entering patients in the trial, cited by five surgeons, was fear of feeling personal responsibility should one treatment be more successful. This fear was expressed by advocates of both partial and total mastectomy. The following comment is an example of the concern expressed by those who preferred a total mastectomy:

> I don't fear the remorse of removing a breast unnecessarily as I do the remorse of losing one patient unnecessarily because of the trial. A patient who could have been cured may die, if the partial mastectomy fails to meet the cure rate of the total mastectomy, and who will bear the responsibility? Me!

In contrast, the feelings of the surgeons who advocated segmental mastectomy are well illustrated by this response:

I have performed the segmental mastectomy over the last few years and have no reason to regret the operation. If I honestly believe that there is no choice between the operations and that I do not know which is better, then why, obviously, should my patients subject themselves to the mutilating mastectomy? I have no answer for this. I do not want to be responsible for causing my patients to undergo unnecessary surgery, if as I believe, the results will show they could have done just as well with the smaller operation.

None of the five surgeons entered patients in the trial.

Conclusions

The traditional role of physician as individualist, particularly in relation to therapeutic decision making, is being challenged by the popularity of randomized clinical trials as an effective and reliable method of generating new medical information.[20,27,28] Physicians have been accustomed to a certain degree of authority, which has shaped their relationship with patients and given them ultimate responsibility in treatment choices. Clinical trials have necessitated a dramatic change.[29] For example, the uncertainty formerly implicit in many therapeutic decisions is now acknowledged openly, and the consent form highlights this uncertainty. The new medical setting inevitably alters the way physicians relate to patients.[21] The obstacles to accrual posed by both difficulty with informed consent ($P<0.005$) and concern with the doctor–patient relationship ($P<0.005$) reflect this observation (Table 3).

Despite numerous classic studies in the behavioral literature describing the doctor–patient relationship, the additional complexity of interaction within the clinical-trial setting is a relatively new phenomenon and has received little attention.[30,31]

The current analysis provides a view of surgeon participation in clinical trials, but it also raises critical questions. For example, besides addressing the issue of accrual, the replies to the questionnaire suggest that results of clinical trials may be selectively incorporated into the surgeon's decision-making process. A further question raised as a consequence of these findings concerns the impact of a randomized clinical trial whose participants do not enter all eligible patients. In addition, in the NSABP trial, proponents of each surgical approach appeared to have a predictable "cancer philosophy," which was rooted less in scientific fact than in a commitment to a particular task, with substantial implications for surgeon behavior. Additional information could prove to be of value to an oncology community dedicated to generating new medical information of benefit to patients with breast cancer, while maintaining a humanistic, individualized approach to patient care.

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Business Thrives on Unproven Care, Leaving Science Behind

By GINA KOLATA
and KURT EICHENWALD

For years, Dr. Larry Norton tried to conduct a medical study to determine, once and for all, whether bone marrow transplants could really save the lives of women desperately ill with breast cancer.

His efforts — and those of dozens of other doctors — were largely futile. Year after year, few women were willing to participate in the clinical tests, which, to be scientifically valid, required patients to be randomly assigned to either the experimental treatment or standard chemotherapy.

Many believed the experimental treatment was their only hope, and were unwilling to leave anything to chance. So most chose to get transplants from a growing number of hospitals and cancer centers that are part of a multimillion dollar industry that sells experimental treatments. There, for more than a decade, many women were told that the procedure was the only thing that could save their lives — when, in fact, no one knew for sure whether it was better or worse than the standard treatment.

"I got so angry," Dr. Norton said. "Fifty years from now, we will look at this period with horror and say, 'How could this have happened.' "

But Dr. Norton, head of the division of solid tumor oncology at Memorial Sloan-Kettering Cancer Center in New York, said he understood why the women refused to join the study: Few patients, faced with advanced and likely fatal disease, would risk passing up a supposedly cutting-edge treatment simply to advance scientific knowledge.

Experts say that tens of thousands of such personal decisions, made under enormous emotional strain, are significantly slowing the search for cures for dire diseases like cancer. The wide availability of unproven procedures sops up the vast majority of potential test subjects, they say, making it difficult, or impossible, to assess which treatments work and which do not.

HOPE FOR SALE

A special report.

An increasing number of untested treatments are being sold to desperate patients with ailments like cancer, heart failure and Parkinson's disease. Today, experimental procedures can be purchased outright from community hospitals, university medical centers and even from publicly traded companies.

To better understand the workings of this system, The New York Times examined one of the most widely offered procedures — bone marrow transplants for solid tumor cancers like breast cancer. The examination found that this procedure entered the medical marketplace in the 1980's before studies to test its effectiveness had even begun. By the time testing was under way, the business had taken on a life of its own. Patients were unavailable and tests were delayed for years or had to be abandoned.

The issue arises because medical procedures, like the bone marrow transplants or new surgical techniques, are not regulated, reflecting the Government's usual reluctance to interfere with doctors' practice of medicine. By contrast, Federal rules require that new drugs or devices like a heart valve be proven safe and effective before being sold to the public.

Doctors, of course, can voluntarily regulate themselves and those in one tiny specialty, pediatric cancer, have done so. These doctors have agreed to provide experimental procedures only to patients who participate in valid research. In that specialty, new ideas for treatments are rapidly tested, allowing them to be adopted nationwide if they work, or tossed aside if they prove useless. As a result, the advances in this field have been phenomenal, far outracing anything seen in adult medicine.

"Too often people have access to therapies that are not proven," said Fran Visco, president of the National Breast Cancer Coalition, a patient group. "As a result, we don't get enough individuals to participate in the clinical trials, so it takes a long time to get answers, or we never get answers."

In breast cancer, testing of bone marrow transplants took twice as long as anyone expected. Throughout the 1990's, doctors and hospitals reported to a national registry that about 15,000 women had purchased bone marrow transplants for treatment of breast cancer. Medical experts said that the voluntary reporting system missed about half of the women who actually received the procedure. Yet, while as many as 30,000 women had bone marrow transplants for breast cancer, only 1,000 participated in the scientific studies.

In ovarian cancer, it proved impossible to even conduct a trial of bone marrow transplants. Doctors at more than 100 medical institutions nationwide spent two and a half years seeking 285 women who would participate. They enlisted just 25. Last April, researchers admitted defeat. The ovarian cancer trials collapsed.

Those who sell experimental procedures have a different view. They say they are helping patients who have run out of options and that researchers who are only focused on determining whether a treatment works are out of touch with the needs of patients suffering with a disease now.

"These are not guinea pigs, this is not a fascist society," said Dr. William H. West, chairman of Response Oncology, a publicly traded, for-profit company that sells the procedure. "We are an open marketplace, and that's true in clinical trials."

But other experts point out that the same arguments could be made about drugs and medical devices. In those cases, the Government has decided that treatments must be proven safe and effective before they are offered on a large scale. Abandoning that standard for procedures, these experts said, is perilous.

"Physicians must demand the same high standards of science for new procedures as we do for new medicines,' said Dr. C. Warren Olanow, professor and chairman of the department of neurology at the Mount Sinai School of Medicine in New York. "The alternative is uncontrolled human experimentation."

Today, in bone marrow transplants, the uncertainty lives on, tearing at women as they face the decision of whether to undergo this difficult procedure. With so many years having passed since the idea of bone marrow transplants first emerged, they struggle to understand how a medical system so advanced could not yet answer a question so basic: does the treatment work?

Many doctors, like Dr. Maurie Markman, director of the Taussig Cancer Center at the Cleveland Clinic, were unable to enroll a single patient despite monumental efforts.

"It's a tragedy that we can't do a randomized trial in the United States to answer this," Dr. Markman said. "Unfortunately, if someone says they can cure you and I say I can't, it is very logical that people will drift to those who can give you hope."

New York Times
Sunday
Oct. 3, 1999

Senator, Mike DeWine, a Republican. The aide in turn reached Mrs. Hartmann's insurance company. In addition, Mrs. Hartmann and 20 of her friends wrote pleading letters to her insurer. Three months later, on Valentine's Day last year, the company agreed to pay. Mrs. Hartmann had her transplant.

Her cancer returned within nine months.

Under pressure from doctors and patient groups, Congress even mandated in 1994 that insurers for Federal employees pay for bone marrow transplants for women with breast or ovarian cancer. Soon, lobbied by doctors, hospitals and patient groups, about a dozen states adopted their own mandates that the experimental procedure be covered.

Lost in the rush to offer the treatment to more cancer patients with solid tumors was the fact that the procedure still had not been shown to work even for breast cancer, where it got its start.

"It evolved into a standard of care," said Dr. John Glick, director of the Cancer Center at the University of Pennsylvania. "It isn't."

The Patients

Rejecting Trials In Quest for a Cure

The poison seeped through the catheter implanted in Deborah Holmes's chest, slowly destroying cells throughout her body. The bone marrow transplant was painful and experimental, but Ms. Holmes believed it her only real hope of beating her ovarian cancer. With it, the doctors performing the procedure assured her, she had a 30 percent chance of wiping out the malignancy; without it, they said, she would probably die.

After being assured that her insurance company would pick up the $150,000 bill, Ms. Holmes traveled halfway across the country for the treatment, from her home in Hamden, Conn., to the hospital in Zion, Ill., operated by Cancer Treatment Centers of America. To Ms. Holmes, it was worth the trip. "There was so much hope there, so much positive energy down to the nurses and the doctors," Ms. Holmes said.

At Brown University in Rhode Island, a 90-minute drive from Ms. Holmes's home, the mood was far less positive. Despite the happy assurances of 30 percent cure rates at places like Cancer Treatment Centers, researchers at the university knew the truth: No one could say whether this procedure worked for ovarian cancer patients like Ms. Holmes.

Brown was part of a consortium of institutions scouring the nation for just 285 women with ovarian cancer to participate in research to determine whether bone marrow transplants prolonged lives. But with so many desperate patients like Ms. Holmes flying anywhere to get the experimental treatment, finding test subjects was almost impossible. On April 25, after two years of trying to enroll women, researchers admitted defeat.

Ms. Holmes, unaware of the national clinical trial, believed what Cancer Treatment Centers of America had told her — that transplants could cure women like herself. When her cancer returned last November, five months after her transplant, Ms. Holmes said she guessed she was just one of the unlucky ones.

She died on Aug. 14.

The collapse of the ovarian cancer trials underscores the problems with the current system for selling unproven medical procedures. Even though there may be plenty of patients eligible to join such studies, they may be unwilling to participate when they can obtain the procedure elsewhere.

Breast cancer clinical trials had begun several years before, in 1990, but struggled to find patients. There were two national trials: one for women whose breast cancer had spread throughout their bodies and another for women whose cancer had spread to at least 10 of the lymph nodes under their arms. Researchers expected it would take about three years to enroll about 1,000 women in the two studies. Instead it took seven years. For every 10 women who could have been in a clinical trial, 1 actually enrolled, Dr. Norton said.

That is not so surprising, Dr. Henderson said. Patients in the clinical trials must sign a consent form spelling out their grim prognosis and stating that there is no evidence that bone marrow transplants are any better than the standard therapies.

To enter the trial, he said, "you have to face these realities, which is never easy."

But if the patient has a transplant outside a trial with a control group of patients, known as a randomized trial, enthusiastic doctors may tell her that a transplant could save her life. Although patients "have a right to the truth," Dr. Henderson said, they understandably "are not going to go to doctors who take away hope"

Medical centers had to make a choice: Offer only the randomized clinical trials — and watch patients leave in droves — or offer bone marrow transplants outside the randomized trials for those who would not participate in the research studies.

Dr. Andrew L. Pecora, chief of the adult blood and marrow stem cell transplant program at Hackensack University Medical Center in New Jersey, gave women an option of having a transplant outside a randomized trial. "I offered the clinical trial to every patient," he said. "But I did not force them to do it." Few entered the trial, he said.

Dr. Norton refused to provide transplants outside the trial. His patients went elsewhere. "I was disheartened but I wasn't surprised," he said.

As the business was booming and the trials staggering, Dr. Hortobagyi, one of the pioneers who had helped get transplants started, was having second thoughts. Those initial stunning results he and others had reported were with carefully selected patients younger than 60 and otherwise healthy — no heart disease, no emphysema, nothing that might make the high doses of drugs even more risky.

The researchers had compared their outcomes with the outcomes with conventional chemotherapy for all women with advanced breast cancer, even though most breast cancer patients were older and sicker than those who had transplants. Dr. Hortobagyi decided to go back and compare the outcomes in the women who had transplants with those of women who were just as young and healthy but who had conventional chemotherapy.

The women, he discovered, did just as well when they had conventional chemotherapy. The women he had provided with transplants did not survive in greater numbers because of the procedure. They survived because they were healthier to begin with.

It was a hard fact to face.

In promoting transplants, "we deceived ourselves and we deceived our patients," Dr. Hortobagyi said. "We oversold it."

But that realization came too late.

The Future

Dismay as Results Prove Disappointing

Last May 17 a crowd of breast cancer specialists filled a conference room half the size of a football field at the Georgia World Congress Center in Atlanta. Those who came too late to get seats spilled into two smaller rooms nearby with closed circuit television screens. Few at the annual meeting of the American Society of Clinical Oncology wanted to miss this moment when the leaders in their field would present the long-awaited data from clinical trials of bone marrow transplants for women with advanced breast cancer.

Five studies had been completed — two large clinical trials from the United States, two large trials from Europe, and a small one involving 154 women from South Africa. In all, about 2,000 women had been randomly assigned to have the experimental procedure or conventional chemotherapy and enough time had elapsed to ask if the women who had transplants lived longer than those who did not have them.

The results were not the triumph that many had hoped for.

In four of the five clinical trials, there was no difference in survival between women

Catherine Porter, 44, who has breast cancer that has spread to other parts of her body, is among those wondering. Seven years ago, Mrs. Porter, of Imlay City, Mich., had a breast removed to combat her cancer. She felt certain she had been cured. Then, recently she learned the cancer was back, worse than ever. Figuring she would take a gamble, she elected to have a bone marrow transplant two weeks ago at the Barbara Ann Karmanos Cancer Institute in Detroit.

Last week, she arrived home. Now, she waits, wondering if the experimental treatment she received will help her, and why medical science still cannot answer that question for so many thousands of women.

"Something has got to be done," she said, "So we don't have to keep doing this."

The Procedure

Early Success Leads to Competition

Dr. Gabriel Hortobagyi was something of a rebel.

In 1979, when the options for treating breast cancer were limited, Dr. Hortobagyi was one of a handful who ventured into uncharted territory: treating the cancer with a bone marrow transplant. When the first patient appeared to do well, Dr. Hortobagyi offered the procedure to another woman, and another.

It was not an easy procedure. Known within the field as high-dose chemotherapy followed by bone marrow transplant or stem cell rescue, the experimental treatment is based on a simple concept: if a little chemotherapy killed some of the cancerous cells in a woman's body, a lot might kill them all.

So doctors remove some bone marrow or red blood cells from the patient, then load her with huge amounts of toxic drugs, quantities that destroy the bone marrow. The hope is that the high doses will eliminate the cancer and that the saved bone marrow, when returned to the body, will grow back quickly enough so that the patient does not die from infection. A version of the procedure, using donations of bone marrow, had long been established as effective for blood cancer, but solely because the cancer was in the marrow that was being replaced. The use of the treatment for breast cancer involved a completely different — and untested — reasoning.

Even though Dr. Hortobagyi and a handful of other pioneers at academic centers selected patients who were young and otherwise healthy, they could not save some from the terrible effects of the powerful anticancer drugs. Fifteen to 20 percent of the women in those early days died from the harsh drugs alone; others had permanent injuries, including hearing loss, nerve damage and heart damage.

The outlaws became heroes by the late 1980's, when they began announcing what looked like amazing outcomes. The data were not scientifically valid proof that the treatment worked — each medical center looked at less than a few dozen patients and had to infer how they would have fared without a transplant.

But the data appeared to make a startling point. Women with advanced breast cancer who had had transplants experienced remission rates of 50 to 60 percent. The general population of women with advanced breast cancer who had received conventional chemotherapy had remission rates of just 10 to 15 percent.

"Those of us who were involved got very very excited," Dr. Hortobagyi said. "We told our patients, 'Look at the results we're getting.' "

The patients were not the only ones who looked. With the apparent success of the bone marrow transplants, a new business had been born.

"It seemed so logical," Dr. Norton said. "It started getting accepted without clinical trials."

Data from a voluntary registry, the Autologous Blood and Bone Marrow Transplant Registry of North America, show the growth in the popularity of this procedure. The registry, which records about half of the bone marrow transplants in the United States, found that 271 women with breast cancer had transplants in 1989. Two years later the number had jumped to 749. By 1997 there were 2,853 bone marrow transplants for breast cancer reported.

For-profit corporations offering bone marrow transplants emerged by the late 1980's. Response Oncology, one of the first, started offering the procedure in 1989 as part of what it called a "clinical trials program."

That program involved only trials that gave everybody the procedure and watched how they fared. These studies cannot be used to demonstrate whether the procedure is any better than the standard treatment, because there is no comparison group of similar patients. Therefore, there is no way of knowing how the patients would have fared with conventional treatment.

But the trials did help Response Oncology earn profits. Dr. West, the chairman of the company, said the profit margin from bone marrow transplants is 15 percent. All told, Response Oncology brought in $128 million in revenue in 1998, largely from its cancer centers providing bone marrow transplants.

In large part, the company, based in Memphis, approached the sale of the experimental procedure like any other business. It undercut potential competitors on price, charging $80,000 per transplant at a time when others were charging $200,000.

"We've been a very competitive force," Dr. West said. "What happened was a battle over the franchise — who owns high-dose chemotherapy?"

Private hospitals also joined the fray. Institutions like a hospital in Zion, Ill., owned by Cancer Treatment Centers of America advertise heavily for patients and even pay for patients to travel there for the procedure. Hospitals associated with giant for-profit chains, including the Columbia/HCA Healthcare Corporation and Tenet Healthcare, opened bone marrow transplant programs that offered the treatment to women with breast cancer.

But the academic medical centers — even those trying to recruit patients for clinical trials — did not stand aside and let all the profits go elsewhere. By the early 1990's virtually every major medical center was offering bone marrow transplants for breast cancer patients and a growing number of community hospitals were offering them as well.

At academic centers, bone marrow transplant programs quickly became "the cash cow for the cancer service," said Dr. William McGuire, an ovarian cancer specialist at Mercy Medical Center in Baltimore.

The doctors who provided transplants were rewarded with money and prestige.

"Bone marrow transplanters are kings," said Dr. I. Craig Henderson, a breast cancer expert at the University of California at San Francisco. "They usually get a higher salary, they usually get more money. And more important, they have security and power."

Every entity offering the experimental procedure tried a different sales pitch. Some promoted the prestige of their institutions, others the convenience of their locations, others their caring attitudes and patient support, and others, like Response Oncology, their lower prices.

Soon, with competition red hot, a new business spinoff emerged: Doctors, hospitals and companies began selling bone marrow transplants to patients with other types of tumors, like ovarian and brain cancers. But if the breast cancer treatments were based on a theory, these new uses were theories on a theory.

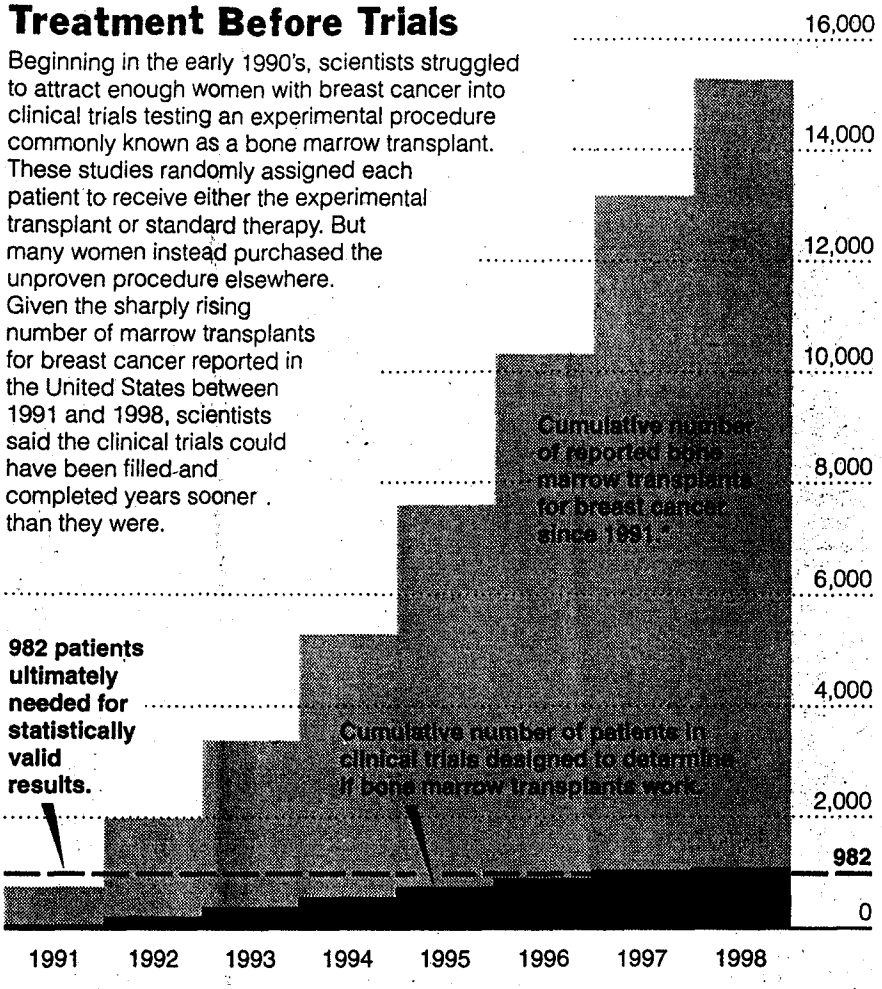
"It is a technology based on a hypothesis," Dr. McGuire said.

Paying for the procedures turned out not to be a problem for many patients: Their insurance companies ended up footing the bill. The insurers at first refused, pointing out clauses in their policies saying they would not pay for experimental procedures. But under pressure from patients, doctors, lawyers and lawmakers, most insurance companies gave in.

Take the case of Rita Hartmann, a 60-year-old elementary school teacher from Wooster, Ohio. When her ovarian cancer recurred, Mrs. Hartmann and her husband agonized over what to do. Cancer Treatment Centers of America told her she had a 30 percent chance of a cure if she had a transplant, but her insurance company said it would not pay. Mrs. Hartmann's husband wanted to mortgage their house, sell all they owned to raise the money. But Mrs. Hartmann held back. "I said, 'That's too traumatic,' " she said.

Treatment Before Trials

Beginning in the early 1990's, scientists struggled to attract enough women with breast cancer into clinical trials testing an experimental procedure commonly known as a bone marrow transplant. These studies randomly assigned each patient to receive either the experimental transplant or standard therapy. But many women instead purchased the unproven procedure elsewhere. Given the sharply rising number of marrow transplants for breast cancer reported in the United States between 1991 and 1998, scientists said the clinical trials could have been filled and completed years sooner than they were.



*Since reporting by doctors and hospitals is voluntary, medical experts said about twice as many women actually received the procedure as a treatment for breast cancer. Figures for 1998 are preliminary.

Sources: Statistical Center of the Autologous Blood and Marrow Transplant Registry (reported transplant data); Eastern Cooperative Oncology Group and Dr. William Peters of the Karmanos Cancer Center at Wayne State University (clinical trial data)

The New York Times

who had transplants and those who had conventional therapy.

Only in the South African study did the women who received bone marrow transplants outlive the patients in the group who received standard therapy. But on closer inspection of the data, even that success seemed suspect: the women who had transplants lived about as long as the women in the other studies. But the women who had conventional chemotherapy in the South African study did far worse. The results did not indicate that transplants improved survival, but that the outcomes for the control group were poor.

No one on the podium that day claimed that the studies showed that transplants were a triumph. Indeed, the trials' failure to show the expected benefits of transplants gave rise to a troubling question: When the best available data provided no evidence that bone marrow transplants were any better than conventional chemotherapy, should transplants continue to be promoted and sold?

For the National Breast Cancer Coalition, which represents cancer patients, the data spoke for themselves: Bone marrow transplants had been tested and had failed.

"How can anybody look at these data and think this is something we should continue doing or that they are inconclusive?" asked Ms. Visco, the coalition's president. The group put out a news release saying, "It is time to move beyond the infrastructure" created around transplants.

But cancer specialists were less definitive. Many said they still saw promise in transplants, arguing that it was too soon to say for sure that the procedure offered no benefits. They urged that nothing change for the time being while the women in the studies were followed for longer periods to see if those who had transplants eventually did better. They also said that chemotherapy had improved over the last decade and because the studies used older drugs, it remained possible that bone marrow transplants with new drugs might be better than conventional chemotherapy.

Reflecting these views, the American Society of Clinical Oncologists put out a news release saying that the papers presented at the meeting "report mixed early results" and that more years of study are needed.

Dr. Allen S. Lichter, the departing president of the society and dean of the University of Michigan Medical School, urged that nothing change for the time being while new studies get under way and the women in the initial studies continue to be followed.

"As a nontransplanter and a keen observer of this research, I don't think there is enough information to say it should die," Dr. Lichter said. He also said that because not every woman is eligible for a clinical trial or has ready access to one, transplants should still be available outside trials. "I for one am not ready to say that this should only be done in a clinical trial," Dr. Lichter said.

Dr. West of Response Oncology said his company intended to keep selling transplants. Calls to stop offering them are "an oversimplification," he said, because the trials were not definitive. More trials and years of further study are needed, he said.

At bottom, he said, critics are missing the point. What matters, he said, is not whether the treatment has been shown to work but whether studies are producing more knowledge.

"You could say there was only one important question and you didn't answer that one," Dr. West said. "I know you want to think of it as a drug that either works or doesn't. I think of it more as a platform that needs to be modified and studied."

So now oncologists and companies say they will press ahead, continuing to sell a painful, expensive procedure that the best available science says is no improvement over standard care, which is less traumatic. Some patient advocates and doctors find this a troubling abandonment of the rigors of science.

"I don't have a problem with oncologists who say, 'We really have to do something for these patients, they are facing a terribly short future,' " said Dr. Alan Garber, a professor of medicine at Stanford University. "The problem is when they start to do things that have been tested and have not proven effective. Then you are leaving the arena of science and going into blind faith."

4

Section 1

Editorials

HIGH-DOSE CHEMOTHERAPY PLUS AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR METASTATIC BREAST CANCER

IN this issue of the *Journal*, Stadtmauer et al. present the results of a clinical trial in which conventional-dose chemotherapy was compared with high-dose chemotherapy plus autologous bone marrow transplantation (hematopoietic stem-cell rescue) in patients with metastatic breast cancer.[1] In this trial, 553 women with previously untreated metastatic or locally recurrent breast cancer were initially treated with conventional multidrug chemotherapy; patients who had a response, according to predefined objective criteria, were then randomly assigned to receive either maintenance chemotherapy at standard doses or high-dose chemotherapy plus an autologous bone marrow transplant. In this randomization phase, a total of 199 women were assigned to the two treatment programs. The results of the study were negative with respect to improvement in disease-free or overall survival attributable to the high-dose regimen at three years. None of the usual methods of analysis identified any group of patients who benefited from the more aggressive treatment.

Some may look for reasons why the data from this study may not apply to the general population of women with metastatic breast cancer, but those reasons are not obvious. However, the number of patients who underwent randomization while in complete remission is relatively small, so it is at least possible to imagine that there was insufficient statistical power to detect a small benefit in women who received high-dose chemotherapy plus hematopoietic stem-cell rescue. Several other studies of this issue have also been negative. The only purportedly positive study has, shockingly, been thoroughly discredited due to major irregularities to be reported soon.[2] The major impetus for rigorous prospective analyses of the potential benefits of high-dose chemotherapy followed by hematopoietic stem-cell rescue came from a large series of phase 2 investigations in which rather astounding benefits were claimed when the data were compared with outcomes in historical controls. Detailed analyses of selection bias that could have affected the entry of patients into those studies[3,4] revealed the impossibility of drawing valid conclusions from such uncontrolled phase 2 trials. In fact, careful reading of those reports reveals the extent to which the outcome for women with metastatic breast cancer can be predicted on the basis of known prognostic factors. These analyses show, among other things, that when disease stages are determined more thoroughly, women at every stage do better, but there is no effect on overall survival. In these uncontrolled phase 2 studies, the early detection of small metastases in women with no intercurrent illnesses and no brain metastases not only clearly identifies a group of women who tend to do better than the entire population of women with metastatic breast cancer, but also makes historical comparisons impossible.

The results of the study by Stadtmauer et al. might have been anticipated from the outcome of a very large trial of adjuvant chemotherapy for breast cancer, in which two or even four times the usual combined dose of alkylating agents had no advantage over conventional doses of these drugs[5]; this finding suggests that there is a plateau effect for dose escalation with some chemotherapeutic agents. Similarly, the Cancer and Leukemia Group B 1993–1994 trial showed that increasing the dose of doxorubicin to the maximally tolerated amount also failed to improve the outcome in metastatic breast cancer.[6] The use of high-dose chemotherapy plus bone marrow rescue as adjuvant therapy — that is, soon after surgical removal of the tumor — has also been found ineffective in multiple American and European randomized trials, though in this setting there remains a potential for some advantage, since follow-up may not have been long enough and improvements in supportive care may reduce early mortality related to therapy.[7]

The disappointing results with high-dose chemotherapy plus bone marrow transplantation for metastatic breast cancer in no way indicate that variations on this theme may prove unsuccessful. These different approaches include tandem (successive) transplantations, new preparative or induction regimens, immune modulation, and in vitro purging of malignant cells from the patient's bone marrow. The negative results reported to date should not suggest any lack of enthusiasm for the prospective evaluation of genuinely different methods. However, such approaches are experimental and should be validated only in appropriately designed trials conducted at centers prepared to analyze and report their results. They can neither be justified nor supported outside of clinical trials. It is important to stress that the negative results found with high-dose chemotherapy and stem-cell rescue should not dampen funding by insurance companies for well-designed clinical trials pursuing new ideas under the aegis of institutional-review-board approval.

Advocates of high-dose chemotherapy plus autologous bone marrow transplantation for metastatic breast cancer contend that since this treatment is unproven, its use is justified outside of a trial — that is, because they think it might be helpful, they should be allowed to use it. We should now acknowledge that, to a reasonable degree of probability, this form of treatment for women with metastatic breast can-

cer has been proved to be ineffective and should be abandoned in favor of well-justified alternative experimental approaches.

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UNDERLYING CAUSES AND SURVIVAL IN PATIENTS WITH HEART FAILURE

HEART failure is a major health problem in the United States. It is estimated that 4.6 million Americans are currently treated for heart failure and that approximately 550,000 new cases are diagnosed each year.[1] Despite advances in therapy, including the widespread use of angiotensin-converting–enzyme inhibitors and the introduction of beta-adrenergic antagonists, mortality associated with heart failure remains high.[2] In a recent community-based survey, one-year and five-year survival rates after the onset of heart failure were 76 percent and 35 percent, respectively.[3] In 1998, heart failure contributed to 260,000 deaths in the United States.[1]

The accurate assessment of prognosis in heart failure is critical to the care of patients, but current methods are limited. Retrospective data from population-based studies and controlled clinical trials have demonstrated numerous clinical, biochemical, hemodynamic, and electrophysiologic variables that influence survival.[4] Strong independent predictors of mortality include older age, higher New York Heart Association (NYHA) functional class, and reduced left ventricular ejection fraction. The risk among patients with severe left ventricular dysfunction can be further stratified on the basis of right ventricular ejection fraction and oxygen consumption during peak exercise. In addition, the presence of arrhythmias, such as atrial fibrillation and nonsustained ventricular tachycardia, increases the risk of death.

The effect of the underlying cause of heart failure on survival is less clear. In general, patients with heart failure due to left ventricular dysfunction are classified broadly into two groups — those with cardiomyopathy due to ischemic heart disease and those with cardiomyopathy due to nonischemic causes. The presence of ischemic heart disease appears to influence prognosis adversely. In an analysis of 3787 patients with left ventricular dysfunction who underwent coronary angiography, an underlying cause of ischemia was a significant independent predictor of mortality.[5] Five-year survival among patients with cardiomyopathy due to ischemic heart disease was 59 percent, as compared with 69 percent among those with cardiomyopathy due to nonischemic causes. It is worth noting that one third of patients with cardiomyopathy due to nonischemic causes had typical angina and 48 percent had at least one risk factor for ischemic heart disease. Thus, bias due to misclassification may result when cardiomyopathy due to ischemic heart disease is diagnosed clinically, and such bias may explain why there was no significant difference in survival between patients with ischemic heart disease and those without it in the Studies of Left Ventricular Dysfunction.[6]

In this issue of the *Journal*, Felker et al.[7] examined the prognostic significance of the underlying cause of heart failure among patients with predominantly nonischemic causes of cardiomyopathy. Between 1982 and 1997, 1230 patients referred to Johns Hopkins University with unexplained cardiomyopathy underwent a rigorous diagnostic evaluation, including endomyocardial biopsy and, where appropriate, coronary angiography, and a single cause of cardiomyopathy was prospectively assigned. No cause was identified in 50 percent of patients, who were classified as having idiopathic cardiomyopathy. Using clinical records and the National Death Index, the authors determined long-term survival retrospectively. The five-year survival among patients with idiopathic cardiomyopathy was approximately 75 percent, similar to that found in population-based studies from the 1980s, but better than that in older, referral-based studies.[8] As compared with patients with idiopathic cardiomyopathy, patients with peripartum cardiomyopathy had a better prognosis, whereas patients with cardiomyopathy due to infection with the human immunodeficiency virus (HIV), amyloidosis, or doxorubicin therapy had a worse prognosis.

The population studied by Felker et al. was unique in that it was made up of younger patients who were

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CONVENTIONAL-DOSE CHEMOTHERAPY COMPARED WITH HIGH-DOSE CHEMOTHERAPY PLUS AUTOLOGOUS HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR METASTATIC BREAST CANCER

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ABSTRACT

Background We conducted a randomized trial in which we compared high-dose chemotherapy plus hematopoietic stem-cell rescue with a prolonged course of monthly conventional-dose chemotherapy in women with metastatic breast cancer.

Methods Women 18 to 60 years of age who had metastatic breast cancer received four to six cycles of standard combination chemotherapy. Patients who had a complete or partial response to induction chemotherapy were then randomly assigned to receive either a single course of high doses of carboplatin, thiotepa, and cyclophosphamide plus transplantation of autologous hematopoietic stem cells or up to 24 cycles of cyclophosphamide, methotrexate, and fluorouracil in conventional doses. The primary end point was survival.

Results The median follow-up was 37 months. Of 553 patients who enrolled in the study, 58 had a complete response to induction chemotherapy and 252 had a partial response. Of these, 110 patients were assigned to receive high-dose chemotherapy plus hematopoietic stem cells and 89 were assigned to receive conventional-dose chemotherapy. In an intention-to-treat analysis, we found no significant difference in survival overall at three years between the two treatment groups (32 percent in the transplantation group and 38 percent in the conventional-chemotherapy group). There was no significant difference between the two treatments in the median time to progression of the disease (9.6 months for high-dose chemotherapy plus hematopoietic stem cells and 9.0 months for conventional-dose chemotherapy).

Conclusions As compared with maintenance chemotherapy in conventional doses, high-dose chemotherapy plus autologous stem-cell transplantation soon after the induction of a complete or partial remission with conventional-dose chemotherapy does not improve survival in women with metastatic breast cancer. (N Engl J Med 2000;342:1069-76.)

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MOST women with metastatic breast cancer have a response to various combinations of conventional-dose chemotherapy, but less than 5 percent of them are alive 10 years after the detection of metastatic spread.[1] Several phase 2 trials performed in the late 1980s reported promising results for high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation in patients with chemotherapy-responsive metastatic breast cancer.[2-6] These trials consistently reported high overall rates of response (combined complete and partial responses), ranging from 73 to 100 percent. Despite a median survival of only 10 to 24 months, 7 to 18 percent of patients in these studies remained free of progressive disease for up to 5 years after the treatment. This result was perceived to be an improvement as compared with that in historical controls. The incidence of severe adverse effects, however, was thought to be greater than that reported in historical controls; the transplantation-related mortality ranged from 0 to 22 percent, but improved supportive care and better patient selection promised reduced toxicity in the future.[7]

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By the late 1980s, interest in hematopoietic stem-cell transplantation increased quickly among patients and physicians. Demands on insurers for financial coverage increased, and breast cancer became the most common indication for such transplantations in North America,[8] despite the lack of studies comparing stem-cell transplantation with conventional-dose chemotherapy.

The unresolved question about what constituted optimal therapy for women with metastatic breast cancer led the Philadelphia Bone Marrow Transplant Group to design and conduct a study of postremission therapy. Later, to increase the accrual rate, the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group (SWOG), and the North Central Cancer Treatment Group (NCCTG) joined the study, which had been designated a high priority by the National Cancer Institute. Patients who had not received prior chemotherapy for metastatic disease were first given conventional-dose chemotherapy, and patients with an objective response were randomly assigned to receive a prolonged course of cyclophosphamide, methotrexate, and fluorouracil in conventional doses or high-dose chemotherapy with carboplatin, thiotepa, and cyclophosphamide plus autologous stem-cell transplantation. The primary objective of this study was to compare the overall survival, the time to progression, and the toxicity associated with these two treatment regimens.

METHODS

Patients

Enrollment began in Philadelphia in December 1990 and ended in December 1997. The NCCTG joined the study in 1990, and ECOG and SWOG joined in 1994. The coordination of the study was transferred to ECOG in 1995, the same year it was designated a high-priority study by the National Cancer Institute. To be eligible, women had to be 18 to 60 years old; to have adequate renal and hepatic function, a normal cardiac ejection fraction, and an ECOG performance status of 0 or 1; to have locally recurrent or distant metastatic breast cancer; and to have received no previous chemotherapy for metastatic disease. If a patient had received adjuvant chemotherapy after surgical treatment of the primary tumor, the adjuvant therapy had to have been concluded more than six months before enrollment in the study. Patients could be premenopausal or postmenopausal, and if they had a positive estrogen-receptor assay, they must have had at least one prior hormonal treatment unless life-threatening visceral disease was present. Patients were excluded if they had metastases to the central nervous system, an uncontrolled infection, or any illness that would preclude the possibility of subsequent stem-cell transplantation. All patients provided written informed consent.

Induction Chemotherapy

For patients who had previously received a total dose of less than 400 mg of doxorubicin per square meter of body-surface area, induction chemotherapy consisted of oral cyclophosphamide (100 mg per square meter per day for 14 days), intravenous doxorubicin (30 mg per square meter on day 1 and day 8), and intravenous fluorouracil (500 mg per square meter on day 1 and day 8) (Fig. 1). For patients who had previously received a total dose of 400 to 500 mg of doxorubicin per square meter, induction chemotherapy consisted of oral cyclophosphamide (100 mg per square meter per day for 14 days), intravenous methotrexate (40 mg per square meter on day 1 and day 8), and intravenous fluorouracil (600 mg per square meter on day 1 and day 8), with optional treatment with prednisone (40 mg per square meter orally for 14 days), given at the discretion of the treating physician. Four to six cycles of chemotherapy were given at intervals of 28 days.

Randomization

After receiving induction chemotherapy, patients were reevaluated. Patients were eligible to undergo randomization if they had had a complete remission (defined as no evidence of disease), a partial remission (defined as a reduction of at least 50 percent in the size of all measurable tumor areas in more than 50 percent of involved organ sites), or a partial remission restricted to bone (defined as bone lesions that remained stable on bone scans and x-ray films for a period of at least eight weeks in association with an improvement in the ECOG performance status, a decrease in the requirement for analgesia, or both). Patients were withdrawn if they had new lesions or progression (defined as an increase of more than 25 percent in the size of measurable lesions). Eligible patients had to have no detectable involvement of bone marrow by the tumor; adequate hematopoietic function; normal renal, cardiac, pulmonary, and hepatic function; and no severe medical or psychiatric problems.

All patients again provided written informed consent at the transplantation center. Randomization had to occur within eight weeks after the last dose of induction chemotherapy. Patients who did not have a complete or partial remission after six cycles of therapy were withdrawn from the study.

High-Dose Chemotherapy and Stem-Cell Transplantation

Hematopoietic stem cells were harvested from the blood before the start of high-dose chemotherapy in all patients who were to undergo autologous stem-cell transplantation. In the initial stage of the protocol, granulocyte–macrophage colony-stimulating factor was administered to stimulate the mobilization of stem cells from the bone marrow. A minimum of 2×10^8 nucleated cells per kilogram of body weight was also harvested from the bone marrow and cryopreserved.[9] The bone marrow and blood stem cells were combined and infused after high-dose chemotherapy. Later in this investigation, the protocol was amended to allow stimulation with granulocyte colony-stimulating factor, with an optional bone marrow harvest. If only stem cells from the blood were used, a minimum of 6×10^8 nucleated cells per kilogram was harvested.

The preparative regimen for autologous stem-cell transplantation lasted four days and consisted of a continuous infusion of cyclophosphamide (1500 mg per square meter; total dose, 6000 mg per square meter), carboplatin (200 mg per square meter; total dose, 800 mg per square meter), and thiotepa (125 mg per square meter; total dose, 500 mg per square meter).[10] Stem cells were infused on day 0, approximately 48 hours after the completion of chemotherapy, and granulocyte–macrophage colony-stimulating factor (250 mg per square meter) was administered to stimulate hematopoietic recovery (i.e., until the absolute neutrophil count exceeded 1000 per cubic millimeter for a period of three days).

Conventional-Dose Chemotherapy

Patients who were randomly assigned to receive maintenance therapy received cycles of cyclophosphamide, methotrexate, and fluorouracil in the same doses as those used for induction chemotherapy and according to the same schedule. Treatment continued until treatment-limiting toxic effects or disease progression occurred or until 24 cycles had been administered (Fig. 1).

Statistical Analysis

The study was originally designed to have a power of 90 percent to detect a doubling of the median survival with high-dose chemotherapy and stem-cell transplantation within the complete-response subgroup and the partial-response subgroup. The original design required the randomization of 99 eligible patients with a complete response and 247 eligible patients with a partial re-

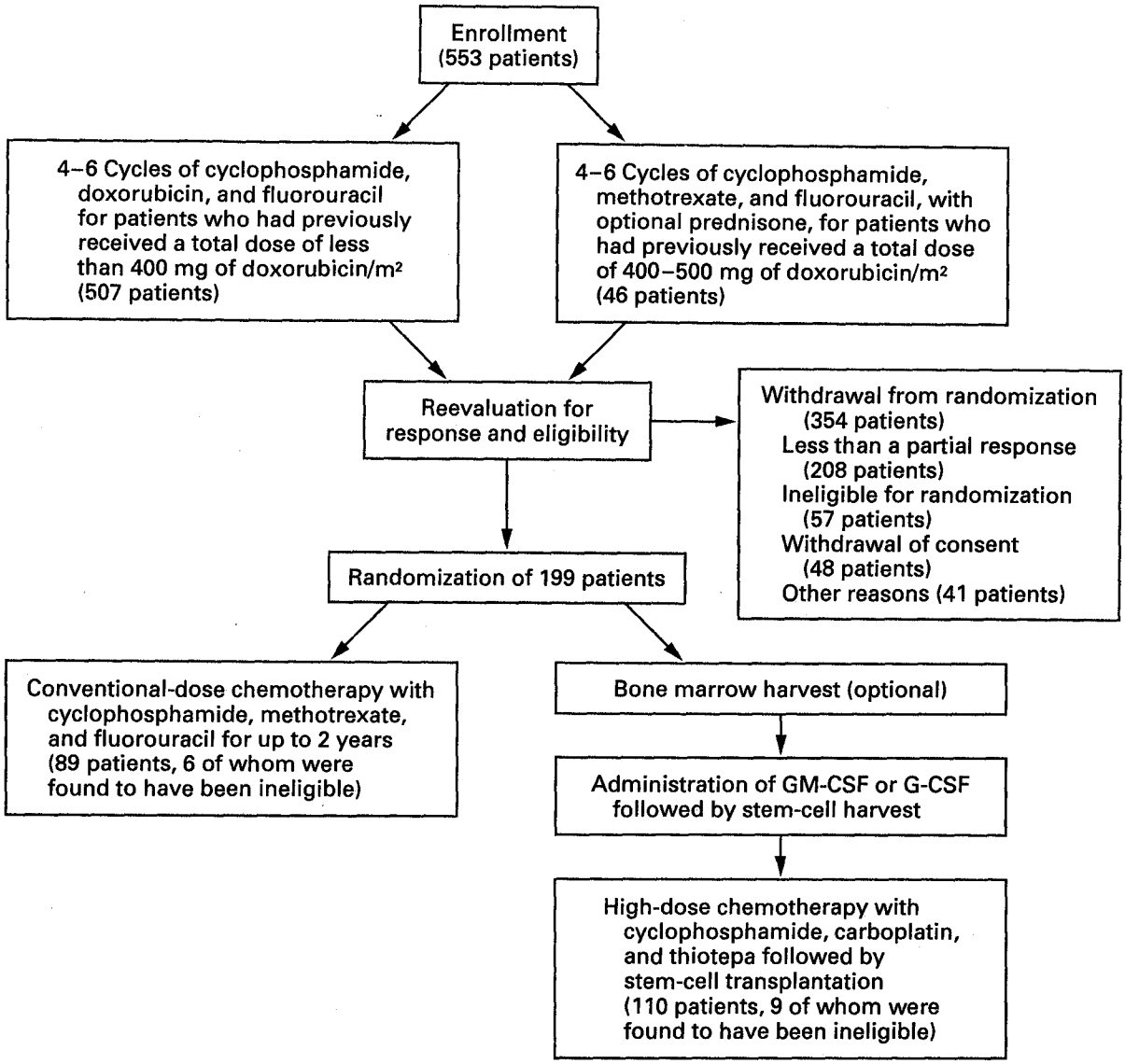

Figure 1. Enrollment of Patients, Induction Chemotherapy, and Randomization to High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation or Conventional-Dose Chemotherapy.

GM-CSF denotes granulocyte–macrophage colony-stimulating factor, and G-CSF granulocyte colony-stimulating factor.

sponse. In the fall of 1996, the design was modified due to low enrollment. In the revised design, there were no longer separate accrual goals or analyses planned on the basis of response status. Instead, the analysis was to be stratified according to the response to induction chemotherapy (complete response or partial response). The revised design required the randomization of 164 eligible patients. For design purposes, we assumed the following: one third of the randomized patients who had a response to induction chemotherapy would have a complete response, and two thirds of the randomized patients would have a partial response; for the patients who were randomly assigned to receive conventional-dose chemotherapy, median survival would be 2.5 years for those with a complete response and 1 year for those with a partial response; 10 percent of all patients would be found to be ineligible after randomization; and 10 percent of each group would be noncompliant with treatment. Two interim analyses were planned — the first after 66 randomized patients had died and the second after 96 patients had died — and a final analysis was scheduled after 120 patients had died. The stopping boundaries used at each interim analysis for decision making were calculated from the O'Brien–Fleming use function.[11] This design gave the study a power of 85 percent to detect a doubling of the median survival with a two-sided alpha level of 0.05, with use of a stratified log-rank test.

The primary analysis was conducted on an intention-to-treat basis and included eligible randomized patients. Randomization was stratified according to five factors: the type of response to induction chemotherapy (complete or partial), the predominant site of distant metastasis (visceral or other), age (≤42 years or >42 years), estrogen-receptor status (positive or negative), and cooperative group. Overall survival was measured from the time of randomization until death from any cause. Progression was measured from the time of randomization until progression of the disease. Data

on one patient who died without progression were censored when she was last known to be in remission.

The first interim analysis was conducted in November 1997 after 65 deaths had occurred, and the second was conducted in November 1998 after 93 deaths had occurred. At the time of the second interim analysis, the data-monitoring committee recommended that the study be unblinded because the likelihood that the study would show a significant difference in favor of stem-cell transplantation at the final analysis was very low (a conditional-power calculation showed that the likelihood was less than 1 percent). The unadjusted 95 percent confidence interval of the hazard ratio for the likelihood of survival with conventional-dose chemotherapy as compared with high-dose chemotherapy plus stem-cell transplantation was 0.52 to 1.22. On the basis of the method of Jennison and Turnbull,[12] the 95 percent repeated confidence interval for the hazard ratio with use of the O'Brien–Fleming use function was 0.48 to 1.32. Given the actual rate of noncompliance, a true hazard ratio of 2.0, the target alternative hypothesis, equates with an observed hazard ratio of approximately 1.72. Since 1.72 is outside the repeated confidence interval, the data at the second interim analysis were inconsistent with the alternative hypothesis.

At the time of the final analysis, after 114 deaths had occurred, the 95 percent repeated confidence interval for the hazard ratio for the likelihood of survival after conventional-dose chemotherapy, as compared with high-dose chemotherapy plus stem-cell transplantation, was 0.53 to 1.17. Given the actual rate of noncompliance, a true hazard ratio of 1.25, for example, would equate with an observed hazard ratio of 1.19. Since 1.19 is outside the repeated confidence interval, even a 25 percent improvement in survival as a result of transplantation is inconsistent with our data.

RESULTS

Enrollment of Patients

A total of 553 patients were enrolled for induction chemotherapy. The accrual rate was 70 patients per year before June 1994, and it subsequently increased to 88 patients per year after ECOG and SWOG joined the study. Of the 553 patients, 58 had a complete response and 252 had a partial response. Of these, 110 were randomly assigned to receive high-dose chemotherapy and autologous stem-cell transplantation and 89 were assigned to receive conventional-dose chemotherapy. The skewed assignment resulted from an attempt to balance the randomization for numerous stratification factors.

The remaining 354 patients did not undergo randomization. A total of 208 patients had less than a partial response to induction chemotherapy: 105 had stable disease, 74 had disease progression, and in 29 the disease or its status could not be evaluated. Thirty-two patients were found to have been ineligible for induction therapy: in 11 the laboratory evaluation before enrollment was inadequate, 6 were estrogen-receptor–positive and had received no prior hormonal therapy or had no visceral disease, the disease could not be evaluated in 4, 3 had received prior chemotherapy for metastatic breast cancer, 2 had central nervous system involvement, 2 had an ECOG performance status of more than 1, 1 had undergone oophorectomy less than four weeks before entry into the study, 1 had received prior radiotherapy to the pelvis and lower spine, 1 had inadequate data, and 1 had no metastatic disease. Among the remaining 114 patients with a complete or partial response after induction chemotherapy, 48 declined to undergo randomization or withdrew from the study, 21 had breast-cancer cells in the bone marrow, 4 were not eligible for other reasons, 3 died or had disease progression in the interim before randomization, and 38 did not undergo randomization for unknown or other reasons. The group of eligible patients who did not undergo randomization was not significantly different from those who did undergo randomization (data not shown).

Characteristics of Patients

Of the 199 randomized patients, 15 were found to be ineligible and were not included in the primary analysis: 9 did not have a documented response to induction chemotherapy, 3 were estrogen-receptor–positive and had received no prior hormonal therapy or had no visceral disease, 2 had disease progression in the interval before randomization, and 1 had no data other than documentation of a response. Nine of the 15 ineligible patients were assigned to receive high-dose chemotherapy and to undergo stem-cell transplantation, and 6 to receive conventional-dose chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. Nine additional randomized patients were ineligible according to eligibility criteria specified in the protocol but were included in the primary analysis. In the case of these patients the reasons for ineligibility were minor: inadequate laboratory evaluation before registration in four; bone marrow cellularity of less than 30 percent but adequate stem-cell collection in two; receipt of a course of appropriate induction chemotherapy before registration, a practice that was allowed early in the course of the study, in one; prior radiotherapy to the pelvis or lower spine but subsequent adequate stem-cell collection in one; and prior chemotherapy for locally recurrent disease in one. Of these nine patients, five were assigned to the transplantation group and four to the conventional-chemotherapy group.

Therefore, of the 199 randomized patients, 184 were included in the primary analysis; 101 had been assigned to autologous stem-cell transplantation and 83 to conventional-dose chemotherapy (Table 1). After induction chemotherapy, 24 percent of these 184 patients were in complete remission. No significant differences between the two treatment groups were found with respect to demographic and stratification factors, including age, predominant site of metastasis, or estrogen-receptor status. In addition, the two groups were well balanced with respect to prior treatment with adjuvant chemotherapy, adjuvant hormonal therapy, and hormonal therapy for metastatic disease. The numbers of patients with complete or partial responses did not differ significantly between the treatment groups; however, the number of patients who underwent randomization while in complete remission was small.

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	HIGH-DOSE CHEMOTHERAPY PLUS STEM-CELL TRANSPLANTATION (N=101)	CONVENTIONAL-DOSE CHEMOTHERAPY (N=83)
Response to induction chemotherapy — no. (%)		
Complete	29 (29)	16 (19)
Partial	72 (71)	67 (81)
Age at randomization		
≤42 yr — no. (%)	36 (36)	25 (30)
>42 yr — no. (%)	65 (64)	58 (70)
Median — yr	46	47
Range — yr	30–60	32–61
25th percentile — yr	40	42
75th percentile — yr	52	53
Predominant site of metastatic disease — no. (%)		
Visceral	58 (57)	43 (52)
Other	43 (43)	40 (48)
Sites of metastatic disease — no. (%)		
Soft tissue and nodes	52 (51)	42 (51)
Bone	37 (37)	44 (53)*
Bone only	9 (9)	8 (10)
Lung and pleura	37 (37)	26 (31)
Liver	26 (26)	26 (31)
Estrogen-receptor status — no. (%)		
Negative	46 (46)	38 (46)
Positive	50 (50)	38 (46)
Unknown	5 (5)	7 (8)
Prior therapy — no. (%)		
Adjuvant chemotherapy	61 (60)	43 (52)
Doxorubicin	23 (23)	19 (23)
Adjuvant hormonal therapy	32 (32)	27 (33)
Hormonal therapy for metastatic disease	19 (19)	16 (19)

*There were no significant differences between the groups with respect to any characteristic except bone metastasis (P=0.04).

Twenty of the 184 eligible randomized patients (11 percent) refused their treatment assignment. Of the 101 patients assigned to undergo autologous stem-cell transplantation, 6 (6 percent) refused the therapy; 5 received either no therapy or conventional-dose chemotherapy, and 1 patient underwent autologous stem-cell transplantation with an alternative regimen. In comparison, of the 83 patients assigned to receive conventional-dose chemotherapy, 14 patients (17 percent) refused the therapy. Ten underwent autologous stem-cell transplantation (all of whom relapsed and eight of whom died), three patients received no therapy, and in the case of one patient the data were insufficient to determine the result of off-protocol therapy. In addition, three patients who received conventional-dose chemotherapy subsequently received high-dose chemotherapy and underwent autologous stem-cell transplantation after relapse.

Outcome

By April 1999, 114 deaths had occurred among the 184 eligible randomized patients. The median follow-up was 37 months (minimum, 4; maximum, 96). The median follow-up for the 70 patients who were alive at that time was 25 months. The median number of cycles of cyclophosphamide, methotrexate, and fluorouracil received by the group assigned to conventional-dose chemotherapy was 8 (range, 1 to 24).

The 3-year survival rate, calculated from the date of randomization, among all 184 eligible patients was 33 percent, and the median survival was 25 months. As Figure 2 shows, there was no significant difference in survival between the two treatment groups (P=0.23, with stratification according to response to induction chemotherapy). The median survival in the group treated with high-dose chemotherapy and stem cells was 24 months, with a 3-year survival rate of 32 percent. The median survival in the conventional-chemotherapy group was 26 months, with a 3-year survival rate of 38 percent. The results were similar when the analysis included all 199 patients who underwent randomization (P=0.14, with stratification according to the response to induction chemotherapy).

Similarly, there were no significant differences in survival between the two treatment groups when the groups were analyzed according to the extent of the response to induction chemotherapy (complete or partial), age (≤42 years or >42 years), estrogen-receptor status (negative or positive), or predominant site of metastatic disease (visceral or other). Among patients who were older than 42 years, those who received conventional-dose chemotherapy appeared to have a survival advantage over those who received high-dose chemotherapy and underwent stem-cell transplantation. Since this analysis was within a subgroup, the results must be interpreted with caution. Patients consistently had a higher rate of survival if they were in complete remission at the time of randomization, but there was no significant difference in the rates between the two treatment groups (Table 2).

As Figure 3 shows, there was no significant difference in the time to progression in the two treatment groups (P=0.31, with stratification according to response to induction chemotherapy). The median time to progression for patients who received high-dose chemotherapy and autologous stem cells was 9.6 months, and the 3-year rate of progression-free survival was 6 percent. The median time to progression for the group given conventional chemotherapy was 9.0 months, and the 3-year rate of progression-free survival was 12 percent. Similarly, there were no significant differences in the time to progression within the various subgroups. Again, the patients who were in complete remission before randomization fared better than those who were in partial remission (Table 2). The results were similar when the analysis included all 199 randomized patients (P=0.30, with stratification according to response to induction chemotherapy).

One hundred thirty-nine patients were in partial

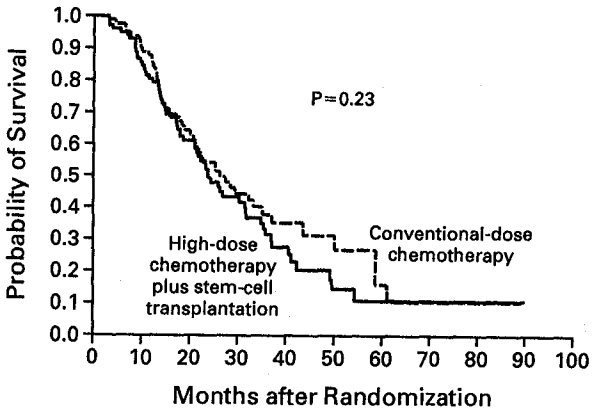

Figure 2. Kaplan–Meier Estimates of Overall Survival of Patients with Metastatic Breast Cancer Who Were Randomly Assigned to Treatment with Conventional-Dose Chemotherapy Alone or High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation.

The median survival was 26 months in the group assigned to receive conventional-dose chemotherapy and 24 months in the group assigned to receive high-dose chemotherapy plus stem-cell transplantation. The survival rates at three years were 38 percent and 32 percent, respectively (P=0.23).

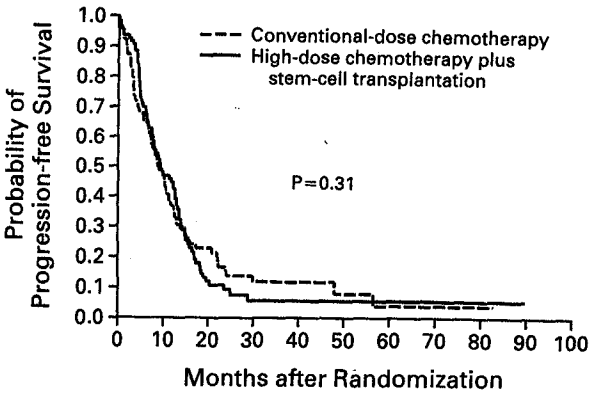

Figure 3. Kaplan–Meier Estimates of Progression-free Survival of Patients with Metastatic Breast Cancer Who Were Randomly Assigned to Treatment with Conventional-Dose Chemotherapy Alone or High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation.

The median time to progression was 9.0 months in the group assigned to receive conventional-dose chemotherapy and 9.6 months in the group assigned to receive high-dose chemotherapy plus stem-cell transplantation. The rates of progression-free survival at three years were 12 percent and 6 percent, respectively (P=0.31).

TABLE 2. RATES OF OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL AT THREE YEARS.*

GROUP	NO. OF PATIENTS	OVERALL SURVIVAL	PROGRESSION-FREE SURVIVAL
		percent (95% CI)	
High-dose chemotherapy plus transplantation			
All patients	101	32 (21–42)	6 (0.1–11)
Patients with complete response to induction chemotherapy	29	42 (22–62)	16 (0.7–32)
Patients with partial response to induction chemotherapy	72	27 (14–40)	0
Conventional chemotherapy			
All patients	83	38 (26–50)	12 (4–19)
Patients with complete response to induction chemotherapy	16	49 (21–77)	25 (2–48)
Patients with partial response to induction chemotherapy	67	36 (22–49)	8 (0.7–16)

*There were no significant differences between groups. Survival was measured from the time of randomization. CI denotes confidence interval.

remission at the time of randomization, 72 of whom were assigned to high-dose chemotherapy plus stem-cell transplantation and 67 of whom were assigned to conventional-dose chemotherapy. Of these 139, 12 subsequently had a complete remission: 5 after receiving high-dose chemotherapy and autologous stem cells (7 percent of the 72 patients in this group who were in partial remission at randomization) and 7 after treatment with conventional-dose chemotherapy (10 percent of the 67 patients in this group who were in partial remission at randomization). There was no significant difference in the rate of conversion to complete remission with these two treatments.

Table 3 shows the incidence of moderate and severe, but nonfatal, adverse effects in the two groups. Patients who underwent autologous stem-cell transplantation had a higher rate of severe leukopenia, thrombocytopenia, and anemia as well as infection, diarrhea, and vomiting than those who received conventional-dose chemotherapy. The incidence of severe mucositis was similar in the two groups. No lethal adverse effects were reported in the conventional-chemotherapy group. One patient died from venoocclusive disease of the liver 49 days after autologous stem-cell transplantation.

DISCUSSION

Our findings demonstrate that women with metastatic breast cancer who have a complete or partial response to standard chemotherapy and then receive high-dose chemotherapy and undergo autologous stem-cell transplantation do not survive longer or have a longer time to progression of disease than women who receive maintenance therapy with conventional doses of cyclophosphamide, methotrexate, and fluorouracil. The incidence of nonfatal but serious adverse effects was greater in the group assigned to high-

TABLE 3. INCIDENCE OF MODERATE AND SEVERE ADVERSE EFFECTS AFTER RANDOMIZATION.*

ADVERSE EFFECT	HIGH-DOSE CHEMOTHERAPY PLUS STEM-CELL TRANSPLANTATION	CONVENTIONAL-DOSE CHEMOTHERAPY
	percent	
Leukopenia	96	52
Thrombocytopenia	95	5
Anemia	69	6
Infection	31	3
Diarrhea	25	1
Hepatic complications	9	1
Vomiting	8	1
Cardiac complications	8	0
Pulmonary complications	7	1
Neurologic complications	6	0
Mucositis	5	2

*The Common Toxicity Criteria of the National Cancer Institute were used to define moderate adverse effects (grade 3) and severe adverse effects (grade 4).

dose chemotherapy plus transplantation, in which myelosuppression, infection, diarrhea, and vomiting were common. Even so, the treatment-related mortality (i.e., deaths occurring within 100 days after the initiation of therapy) was virtually the same in the two groups.

The study was designed to have a high power to detect a doubling in median survival with high-dose chemotherapy plus stem-cell transplantation. Nonetheless, our data show that this treatment was unlikely to be associated with even a moderate improvement (e.g., a 6-month increase in median survival, from 24 months to 30 months), even when the possible effect of noncompliance was taken into consideration. The number of patients who survived for three years without signs of disease progression was so low that it is unlikely that the results will change significantly with continued follow-up. In addition, the treatment-related mortality rate of less than 1 percent after high-dose chemotherapy plus stem-cell transplantation could not have influenced the survival results. And since the methods we used for high-dose chemotherapy and hematopoietic stem-cell rescue are the current standard approach, our results should reflect outcomes being obtained currently.

The fact that a substantial proportion of enrolled patients withdrew from the study and thus did not receive the assigned treatment is potentially problematic. In published studies of patients with acute myeloid leukemia who received stem-cell transplantation, 33 to 50 percent of the patients who were initially in complete remission declined to undergo randomization and were withdrawn.[13] The rate was similar in our study: approximately 28 percent declined to undergo randomization. No substantial difference in the distribution of known prognostic factors was found between the patients who remained in the study and those with a complete response or a partial response who declined to undergo randomization.

Though there was no discernible difference in outcome with the two treatments for patients who had a complete response to induction chemotherapy, the number of such patients was admittedly small — 45 patients in all, 29 in the group treated with high-dose chemotherapy and stem-cell transplantation and 16 in the group treated with conventional-dose chemotherapy. A number of ongoing studies may be able to provide more information on this subgroup of patients with complete responses. Nevertheless, the likelihood that a significant difference in outcome will be found is low. Moreover, the difficulty of enrolling patients in a randomized trial of this sort is so great that any conclusions that are drawn may ultimately require extrapolation of the results of completed or ongoing trials involving high-risk patients with primary breast cancer.

It is possible that the promising results of pilot studies of high-dose chemotherapy and autologous stem-cell rescue were due in part to selection bias.[14-16] Patients undergoing this treatment for metastatic breast cancer are generally younger and healthier, and have had better responses to induction chemotherapy, than those who are treated with conventional therapies. To account for selection bias, we analyzed our results on an intention-to-treat basis. Even so, the outcomes were no different for the 106 patients who actually received high-dose chemotherapy and underwent autologous stem-cell transplantation than for the 101 patients who were randomly assigned to the treatment.

A French multicenter, randomized trial, which compared a single course of high-dose chemotherapy plus stem-cell rescue with conventional-dose chemotherapy for patients with chemotherapy-responsive metastatic breast cancer, was stopped prematurely after the enrollment of 61 patients because of a low rate of enrollment.[17] After five years of follow-up, there was no significant difference between the groups in progression-free survival (9 percent in each group) or overall survival (29.8 percent in the group treated with high-dose chemotherapy and autologous stem-cell rescue and 18.5 percent in the conventional-chemotherapy group, $P=0.12$). This small trial had a low statistical power to detect large differences, but the design was similar to ours. Our results contradict those of an earlier, single-center trial that purported to find an advantage of tandem cycles of high-dose chemotherapy.[18] This study is now under review as part of a misconduct investigation.[19]

A number of other randomized studies of patients with metastatic breast cancer are ongoing, and the results of several studies of patients with locally ad-

vanced but not metastatic breast cancer have yet to be reported. Our results should be interpreted in the context of those trials and cannot and should not be extrapolated to patients with nonmetastatic cancer who have multiple positive axillary nodes.

Our results lead us to conclude that the routine practice of administering several cycles of conventional induction chemotherapy followed by a single course of high-dose chemotherapy and stem-cell rescue cannot be recommended for women with metastatic breast cancer. Alternative strategies to improve the results of this therapy are being evaluated and include efforts to minimize the development of resistance to chemotherapy during induction chemotherapy; attempts to improve the processing and purging of stem cells; post-transplantation chemotherapy, hormonal therapy, and immune modulation to eliminate minimal residual disease; and the use of multiple cycles of dose-intensive therapy. These and other approaches should be investigated in well-designed trials to improve the treatment options and outlook for patients with metastatic breast cancer.

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APPENDIX

The following members of the Philadelphia Bone Marrow Transplant Group also participated in the study: University of Pennsylvania Cancer Center: J. Bird, D.L. Porter, P.A. Mangan, and P.A. Cassileth; Fox Chase Cancer Center: M. Daly, R. Krigel (deceased), and R. Schilder; Hahnemann University Hospital: M. Styler, and D. Marks; Temple University Hospital: S. Goldberg and L. Glenn; and Christiana Cancer Center: D. Biggs.

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