High-dose chemotherapy with bone marrow transplant for metastatic breast cancer
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Under its World Health Organization terms of reference, ECRI disseminates information on healthcare technology worldwide and accordingly has established a Committee on Women’s Health Technologies. The committee comprises representatives dedicated to helping discern and convey technical facts and conclusions about healthcare technology to the public. In addition, ECRI assembles a panel of outside experts on each topic to provide important consumer and patient perspectives. The guidance of the committee and panel was instrumental in producing this Patient Reference Guide.

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HDC with ABMT/BCT
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bout the information in this
Patient Reference Guide

This Patient Reference Guide is published as a public service by ECRI and is distributed to patients free of charge. It is offered to you and your family as you face difficult choices about your treatment for metastatic (stage IV) breast cancer. This Patient Reference Guide focuses on one of the treatments that may be offered to you: high-dose chemotherapy (HDC) with autologous bone marrow transplantation and/or blood cell transplantation (ABMT/BCT). This procedure is also commonly called bone marrow transplant or stem cell rescue. For accuracy and clarity, we'll use the term HDC WITH ABMT/BCT. Other medical terms that relate to this treatment are defined throughout, and words in bold small capitals are also in a glossary at the end of the text so that they'll be familiar to you, should your doctors or nurses use them.

ECRI cannot respond to calls from individual patients. Kindly refer to the listing of other information resources provided in this Guide. These national resources and agencies are especially prepared to respond to your inquiries.

You may have heard about HDC with ABMT/BCT for metastatic breast cancer from your doctor or other patients or from newspaper, magazine, or television coverage. These sources often provide conflicting information or present only one view about what is currently known about this technology and its effectiveness.

Many complicated issues surround the use of this therapy for patients with metastatic breast cancer. Doctors who treat cancer (oncologists) disagree about the effectiveness of the treatment. Some think it should be given only in the context of a research study; others believe that patients should be able to receive it outside of research studies.

The controversy on HDC versus standard-dose (also called conventional) chemotherapy has been fueled by divergent opinions and actions by all groups that have a stake in the matter. Unfortunately, patients are caught in the middle, facing critical, time-dependent decisions about their lives. The disagreements may make it difficult for patients and their families to know what to believe and to make the best possible decisions about their treatment options.

Ultimately, the controversy over the effectiveness of the treatment will be resolved by results provided by well-designed scientific studies, like randomized controlled clinical trials. Such studies compare how long and how well groups of patients with the same stage of the disease survive after HDC with ABMT/BCT versus standard-dose chemotherapy. Most cancer researchers agree that these studies are needed. For now, neither scientists nor doctors have the evidence to show that you are likely to live longer or have a better quality of life if you choose HDC with ABMT/BCT rather than standard-dose chemotherapy.

An analysis of all studies published through 1994 by an independent research agency, ECRI (please see page 3), shows that HDC with ABMT/BCT works no better than standard-dose chemotherapy. Some patients may do worse on HDC with ABMT/BCT than on standard-dose treatment. Since that analysis was completed in February 1995, ECRI has continued to analyze new studies. In October 1995, the first randomized controlled study ever completed on this treatment for metastatic breast cancer was published. It is a small study that reports some interesting results. However, researchers who have reviewed the study have raised many questions about the chemotherapy combination and regimens used and the results. These reviewers agree that the study does not put the controversy over this treatment to rest, although it may point to directions for future research. The study is discussed separately in this guide. This Patient Reference Guide is divided into several sections to help you and your family understand and consider your treatment options. Not all sections may interest you at once. They are provided because each
patient or family member reading this Guide is likely to be at a different point in the decision-making process. Many women and many families have shared their experiences with ECRI, including the enormous emotional impact of being given a diagnosis of metastatic breast cancer. Patients also spoke of the importance of having a friend or family member present during all physician consultations because hearing information about their medical condition and treatment options is often very stressful. These women and their families spoke of their desire for reliable, objective medical information about treatment options to help them make very personal and emotionally difficult decisions. This Guide is offered in a spirit of support for that process.
Summary of ECRI’s analysis of all studies on HDC with ABMT/BCT for metastatic breast cancer published through late 1994

Analysis of all studies published through 1994 show that there is an initially higher response rate to HDC with ABMT/BCT than to standard-dose chemotherapy. This means that, at first, the tumor shrinks. However, the response does not last and the cancer progresses. There is evidence that standard-dose chemotherapy offers patients with metastatic breast cancer a longer response time and an increased overall survival time, and more patients survive for one year compared to HDC with ABMT/BCT therapies. There is some evidence of shorter overall survival times after HDC with ABMT/BCT therapies than after standard-dose therapy. Results of a randomized controlled trial published in 1995 (the first such study completed on this procedure for metastatic breast cancer) have not altered these conclusions. The medical research on HDC with ABMT/BCT does not identify any subgroup of patients that is likely to have long-term disease-free survival after receiving the HDC.

Introduction

This section provides a background about breast cancer and its diagnosis and treatment. Then it describes the HDC with ABMT/BCT procedure and summarizes ECRI’s longer, in-depth analysis of all the published research on HDC with ABMT/BCT for metastatic breast cancer through September 1994. The studies were identified by searching through more than 1,500 articles about many aspects of breast cancer. The analysis represents a year-long effort by scientists to analyze all published data on the topic. It was undertaken by ECRI, a nonprofit research agency and Collaborating Center of the World Health Organization. (A 1995 update is provided on page 19 of this guide.)

Background

Nearly all cases of breast cancer first occur in one breast. When cancerous cells are found, they are examined by a pathologist in the laboratory to determine the characteristics of the specific cancer. Some of these characteristics have been studied to determine their relationship to the disease process and potential for response to various therapies. Some characteristics may be considered useful in forecasting the course of the disease in a patient. Some common forecasting, or prognostic, factors for breast cancer are as follows:

1. Estrogen RECEPTOR and/or progesterone receptor status; an estrogen-positive receptor status is desirable. For example, having an estrogen-positive receptor tumor has been statistically linked with a better response to hormonal therapy and a longer time cancer-free.

2. The tumor’s size and growth rate.

3. The extent to which the skin of the breast is affected (e.g., ulceration, inflammation).

4. The number of cancerous lymph nodes in the armpit area and/or above the collar bone.

5. The presence of the cancer in other organs or bones in the body. The more of each of the negative factors a patient has, the poorer her PROGNOSIS (likelihood of survival).

Patients who have developed cancer in one breast are two to five times more likely to develop another PRIMARY CANCER in the other breast than are those who have no history of the disease. A woman with a biologic mother, sister, or daughter who has breast cancer runs two to three times the risk of developing the disease.

Staging and survival rates

The American Joint Committee on Cancer has classified breast cancer into five stages: 0 through
Description of Stages of Breast Cancer and Treatment

Treatment options included here are only for stage II and the more advanced stages, as described by PDQ, a computer system operated as a service of the National Cancer Institute. Please see the information resources section on page 35 to learn how to contact PDQ.

Stage 0: A contained cancer with no evidence of invasion and therefore no spread to the lymph nodes, other organs, or tissue. Doctors call this carcinoma in situ.

Stage I: The primary cancer is 2 cm (about 3⁄4 inch) or less in diameter without any spread to the lymph nodes.

Stage IIA: The primary tumor is between 2 and 5 cm in diameter and has not spread to the lymph nodes.

Stage IIB: The primary tumor is between 2 and 5 cm in diameter and has spread to underarm lymph nodes, or the primary tumor is over 5 cm and has not spread to the lymph nodes.

Treatment: Surgery followed by radiation therapy. The surgical options are as follows: lumpectomy (removing the cancer and some surrounding tissue with axillary node dissection), partial or segmental mastectomy (removing part of the breast and armpit lymph nodes), total mastectomy (removing the entire breast and armpit area lymph nodes) or modified radical mastectomy (removing entire breast, the lining over the chest muscles, and armpit lymph nodes), and radical mastectomy (removing entire breast, chest muscles, and armpit lymph nodes). Radical mastectomy is rarely used now, except in situations in which the cancer has spread to the chest muscles. The specific surgical recommendation is based on tumor size and location and its appearance on the mammogram.

Adjuvant therapy: This follows the primary surgical treatment when all known tumor is removed. It includes chemotherapy with or without hormonal therapy, hormonal therapy or entry into one of several clinical trials that are evaluating chemotherapy before surgery and chemotherapy and/or hormone therapy after surgery, or no postsurgery adjuvant therapy for patients with a good chance of recovery. Patients with more than 10 cancerous lymph nodes may be candidates for a National Cancer Institute-approved CLINICAL TRIAL comparing HDC with ABMT/BCT to standard-dose chemotherapy. (Please see What kinds of studies are going on now?)

Stage IIIA: The differences between stages IIB and IIIA are subtle and related to the lymph nodes involved. Stage IIIA is a primary breast cancer of any size that has spread to underarm and other nearby lymph nodes and surrounding armpit tissues.

Treatment: Surgical options are modified radical mastectomy or radical mastectomy. Radiation therapy is given before or after surgery. Chemotherapy with or without hormone therapy is given with surgery and radiation therapy. Clinical trials are evaluating the following treatments: new standard-dose chemotherapy regimens with or without hormonal drugs, chemotherapy before surgery, and HDC with ABMT/BCT compared to conventional chemotherapy.

Stage IIB: Primary cancer of any size attached to the chest wall. It can involve the skin, ribs, and muscles in the chest. The cancer may have spread to the lymph nodes inside the chest near the breast bone.

Treatment: The patient undergoes a biopsy of the tumor, but in a majority of cases, the cancer found cannot be removed during the surgery. Some patients may undergo a mastectomy after radiation therapy if the cancer has markedly shrunk. Patients are offered:

1. chemotherapy;
2. hormonal therapy with or without surgery to remove ovaries; and/or
3. entry into a clinical trial that is testing new chemotherapy drugs, biological therapy, or new drug combinations. HDC with ABMT/BCT may be discussed.

Stage IV (metastatic): Primary cancer of any size that has spread to other sites of the body, most often the bone, lungs, liver, or brain, or the tumor has spread to the breast skin and other lymph nodes along the side of the neck or near the collarbone.

Treatment: Options at this stage are usually considered to be palliative — that is, they focus on relieving symptoms, extending the patient’s survival time, and improving the patient’s quality of life. Unfortunately, the medical and surgical treatments available at this time cannot offer a cure for this stage of cancer. However, the cancer in some patients does respond to therapy, and therapy may offer some time without progression of the cancer or some time with no detectable cancer. Treatment usually begins with a BIOPSY followed by one or more of these options: chemotherapy, radiation (and perhaps mastectomy to relieve symptoms), hormonal therapy with or without removal of the ovaries and/or entry into a clinical trial to test HDC with ABMT/BCT, hormonal drugs, or biological therapy.

Inflammatory breast cancer: This is a primary breast cancer in which the breast appears inflamed because it is red and warm. The breast is generally quite firm and may or may not be associated with a breast mass. The skin may appear dimpled or have ridges. This type of cancer tends to spread quickly unless treated appropriately.

Treatment: Similar to the options for patients with stage IIB or IV breast cancer. Patients are usually given neoadjuvant treatment, which is a combination of chemotherapy, hormonal therapy, and radiation therapy. Patients whose cancer shows a good partial or complete response undergo mastectomy.

Recurrent breast cancer: This is breast cancer (at any stage) that returns after a time during which no tumor was detectable. It can return in the original breast site or in another part of the body. A small number of patients with recurrent cancer can be cured, especially if it has returned in the breast in which lumpectomy and axillary lymph node dissection was done, and all can be treated. But, if the recurrent breast cancer appears in another part of the body, these patients usually cannot be cured.

Treatment: Options include one or more of the following:

1. hormonal therapy and possibly removal of ovaries;
2. surgery and/or radiation therapy if the recurrence is in one place only and is operable;
3. radiation to relieve pain if the recurrence is in the bones and other places; and/or
4. entry into a clinical trial testing new chemotherapy drugs, new hormonal drugs, biological therapy, or HDC with ABMT/BCT.

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3. radiation to relieve pain if the recurrence is in the bones and other places; and/or
4. entry into a clinical trial testing new chemotherapy drugs, new hormonal drugs, biological therapy, or HDC with ABMT/BCT.
IV. The stages are based on tumor size, the number of cancerous lymph nodes, and the number of places to which the cancer has spread (metastasized). The box on page 10 describes these stages. The life expectancy after diagnosis varies by the stage of cancer at the time of diagnosis. According to PDQ, the U.S. National Cancer Institute’s computer information system about cancer and treatment options, about 95% of stage 0, 85% of stage I, 66% of stage II, 41% of stage III, and 10% of stage IV patients survive at least five years after their initial diagnosis.

**Treatment**

Therapy options depend on the stage of the cancer, your overall health and other PATIENT CHARACTERISTICS, including estrogen receptor status (i.e., positive or negative), age, and menopausal status. Treatment may include surgery, radiation, chemotherapy, hormonal therapy, or a combination of these. The treatments typically offered for more advanced stages (stages III, IV, and recurrent breast cancer) are also described in the box on page 10.

Chemotherapeutic agents often used in standard-dose chemotherapy (and in combination) include cyclophosphamide (CYC), 5-fluorouracil (5-FU), methotrexate (MTX), etoposide (VP-16), doxorubicin (DOX) or Adriamycin (A), mitoxantrone (MXT), and vincristine (VCR). Some of these, as well as other drugs, are also used in high-dose regimens. Standard dosages have been increasing to achieve optimal effects, and sometimes the division between a standard and high dose is not clearly defined. Hormonal therapy often uses tamoxifen (TAM), although estrogens, androgens, progestins, and corticosteroids have been used obtaining RESPONSE RATES of about 40% or lower. This means that 40% of the patients receiving therapy have a PARTIAL RESPONSE (at least half the measurable tumor disappears for 30 days) or a COMPLETE RESPONSE (the entire measurable tumor disappears for at least 30 days) of their disease.

Ovaries may also be removed to completely stop hormonal function. (A discussion of the possible complications and consequences of ovary removal is not included here.) Many of the drugs used in HDC and their side effects are listed in Appendix B on page 42. Many of the combination regimens used in published studies are in Appendix C on page 44.

**HDC with ABMT/BCT for metastatic breast cancer**

HDC with ABMT/BCT is based on the concept that some of the chemotherapeutic drugs used in STANDARD-DOSE CHEMOTHERAPY might kill more cancer cells if given at much higher doses. High doses are toxic to the bone marrow, which produces the blood cells that fight infection. Thus, HDC makes patients very vulnerable to infection. Standard-dose chemotherapy also makes patients vulnerable to infection. HDC is even more toxic; it may permanently damage the patient’s ability to make blood cells and make the patient more susceptible to life-threatening infections. These infections are often caused by tiny organisms that ordinarily do not cause disease in healthy persons.

To restore a patient’s ability to make blood cells, a procedure known as AUTOLOGOUS STEM CELL RESCUE was developed. The patient’s cells that produce blood (STEM CELLS) are removed from the patient before HDC. They are preserved, stored, and then given back to the patient after she completes a course of HDC. The drugs used in HDC are chosen in part because they are most toxic to the bone marrow (which can be replaced) and less toxic to other organs (which cannot be replaced). The highest dosages that an individual patient can tolerate are determined by studies of large groups of patients to evaluate the drugs’ toxicity to the blood circulatory system, central nervous system (brain and spinal cord), heart, liver, lungs, and kidneys.

HDC with ABMT/BCT is given to selected patients with metastatic breast cancer in an effort to prolong their lives. It has also been proposed for some patients with stage II or stage III breast cancer to try to eradicate the cancer and to prevent its recurrence or metastasis after surgery, radiation, and/or standard-dose chemotherapy.

**The steps of the procedure**

1. **Mobilizing stem cells**
   
   Days, weeks, or months before undergoing autologous stem cell rescue, the patient may receive one or more courses of standard-dose chemotherapy with or without GROWTH FACTORS. Growth factors may help to increase, or mobilize, the number of stem cells that can be obtained from the bone marrow or from the
circulating blood. Growth factors are biologic agents that speed the growth of certain kinds of cells, including blood cells.

2. Possible induction chemotherapy

The patient may also receive "induction" chemotherapy. This involves giving higher doses than those given for standard-dose chemotherapy, but not as high as "high-dose" chemotherapy. The purpose of induction is to find out if the patient's cancer is likely to respond to the chemotherapy combinations that are to be given during high-dose regimens. Responding to induction therapy is also sometimes called "passing" induction. In many cases, only patients whose cancer responds to induction therapy are given HDC with ABMT/BCT. However, passing induction therapy does not mean that a patient will live longer if she undergoes HDC than if she undergoes standard-dose chemotherapy. Also, it does not mean that she will have a better quality of life than if she had received standard-dose chemotherapy.

3. Harvesting

Two methods for harvesting stem cells have been developed:

- Bone marrow method — This procedure generally requires a one-day hospital stay. The procedure is performed in the operating room with the patient under general anesthesia. Bone marrow, which contains stem cells, is surgically removed from the patient's hip bones by suction using a large needle. About 2 pints of bone marrow are removed, which is less than 10% of the total marrow cells in the body. This procedure has no apparent long-term harmful effects on the patient. In the short-term, most patients experience pain in the hip and buttocks areas for several days where the needle was inserted.

- Blood cell method — This is an outpatient procedure, called apheresis, and is similar to that of donating blood, except that it takes a few hours instead of several minutes. Stem cells are removed from the blood circulating throughout the patient's body. Typically, the only pain associated with this process occurs during the needle insertion into a vein and lasts for a few seconds. Blood flows from the vein through a closed tubing system into special bags used for blood collection. During the collection, stem cells are separated from the patient's other blood components by a machine connected to the tubing system. The other blood components return to the patient through her other arm using the closed tubing system of the machine. It takes a few hours so that as many stem cells as possible can be collected with little damage to other cellular components of the blood. The procedure is relatively safe. More than one collection session may be needed to obtain a sufficient quantity of stem cells. If this is the case, the collections are taken over several days or weeks.

Comparison of the methods

Bone marrow harvesting is done at one time, requires two or more hours of operating room time, and enables clinicians to process and freeze the entire stem cell collection at one time. Blood cell harvesting may require several collection sessions. Bone marrow harvesting subjects patients to the hazards of general anesthesia, whereas blood cell harvesting may increase the extremely small chance of infection around the site where needles are inserted to collect the blood. Patients undergoing the therapies (i.e., chemotherapy, growth factors) used before blood cell harvesting to increase stem cell collection may be subject to additional risks of toxicity. However, obtaining stem cells from the circulating blood avoids the hip and buttocks pain that patients experience after the bone marrow harvesting procedure. Also, the blood cell producing system recovers more quickly with blood cell harvesting than with bone marrow harvesting. Cancer centers that offer HDC are now doing blood cell harvesting more often than bone marrow harvesting.

Storage

After stem cell harvest, the cells are concentrated, preserved, frozen, and stored. However, stem cells may also contain cancer cells that could reintroduce cancer to the patient when the cells are returned. Therefore, techniques referred to as "purging" have been developed in an attempt to remove contaminating cancer cells from the stem cells in the laboratory before reinfusion into the patient. However, the effectiveness of these purging techniques is not known, and they are not offered at every center performing HDC with ABMT/BCT. Some researchers think BCT may decrease the likelihood that tumor cells will be
contained in a stem cell collection, compared to those in a bone marrow collection. There is little reliable information about how often this occurs, however.

4. High-dose chemotherapy

Days or weeks after stem cells have been obtained and stored, patients are given very high doses of chemotherapy — 2 to 10 times the dose given in standard-dose chemotherapy. Doctors may refer to this part of the procedure as HDC, “myeloablative” therapy, or “intensification” therapy. Currently, 2- and 3-drug combinations are used, not single drugs. (See Appendix C that lists HDC regimens that have been reported in published studies.) Radiation therapy may also be given.

The patient receiving HDC may be confined to an isolation room to minimize the risk of infection. These specially designed isolation units are equipped with air-filtering systems. Air pressure inside the room is generally higher than it is on the outside so that, when a door is opened, air travels out. This prevents unfiltered, possibly contaminated air from being sucked into the room. Floor tiles in these units are specially sealed to prevent dirt from accumulating between them, which could serve as a breeding ground for germs.

On the other hand, some centers are using outpatient protocols. For example, researchers at Duke University in North Carolina and Johns Hopkins University in Maryland have reported that cancer patients who undergo HDC with ABMT/BCT are isolated in hotel rooms near the clinic, rather than in hospital isolation rooms. The patients receive the HDC as an inpatient and, if there are no complications, are placed in the special hotel rooms. Each patient must have a friend or family caregiver who can stay with her during this time. The patient goes to the outpatient clinic daily for evaluation by her team of doctors and nurses. If there is any sign of complications, she is readmitted to the hospital.

5. Transplanting the stem cells and recovering the ability to produce blood cells

Within 24 to 72 hours after HDC, the stem cell concentrate is thawed and given back intravenously to the patient. This is the “transplantation.” The patient’s ability to begin producing blood cells again depends on both the HDC regimen and her health condition before the therapy. Until the bone marrow adequately recovers its function, patients produce few if any blood cells and are at serious risk of infection. Recovery of the system is defined as reaching a minimum target of the production of a type of white blood cell, PMNs (polymorphonuclear leukocytes). When the number of these white cells reaches 500 cells/mm³, usually about 25 days after infusion, the transplantation is considered to be successful. This level is a minimum target.

For five to six months after transplantation, the patient may remain very vulnerable to bacterial, viral, fungal, or parasitic infections. The patient may also develop conditions such as skin rash, inflammation of the urinary bladder, and bleeding and gastrointestinal disorders.

Studies show that up to 10% of transplantations do not restore the patient’s blood cell producing system to adequate levels. A stem cell rescue failure occurs if:

1. A patient’s production of PMNs does not reach at least 100 PMNs/mm³ 4 weeks after transplantation, or
2. The patient’s PMN count stays consistently low (500/mm³ or lower).

Of the 10% of transplantations that fail, some patients may be sustained for some time (several months or longer) by receiving blood transfusions or COLONY STIMULATING/GROWTH FACTORS as needed. However, some patients are unable to survive very long, even with transfusions and growth factors, and they die within several months of receiving HDC with ABMT/BCT.

History of the procedure

The concept of this procedure arose from animal research in the 1960s. By 1986, about 2,500 HDC with ABMT or BCT procedures had been performed in humans to treat various cancers (including breast cancer). Sixty percent of the procedures performed had been for cancers of the blood and lymph system. The rest were for solid tumors, including breast, lung, and ovarian cancers.

By 1992, about 19,000 procedures had been performed to treat several types of cancer. The Autologous Blood & Marrow Transplant Registry — North America
reports that it collects data from about half the U.S. centers that offer HDC with ABMT/BCT for breast cancer. Between 1989 and 1992 in the United States and Canada, HDC became used more often for metastatic breast cancer than for non-Hodgkin's lymphoma. The registry also reported that, as of 1992, its database had cataloged about 2,500 breast cancer patients who had received HDC with ABMT/BCT. However, to date, the registry has published little on the outcomes of these patients.

**How do researchers decide which patients are suitable for the procedure?**

According to published studies on breast cancer, researchers offered HDC with ABMT/BCT to patients who met the following criteria:

1. Metastatic or advanced breast cancer;
2. Younger than 65 years (60 years at many centers);
   and
3. No central nervous system, liver, kidney, or heart/lung impairment.

In many studies, researchers offered the treatment to the healthier of their patients with metastatic breast cancer. (Healthier patients were those who were not bedridden and were able to perform some of their usual daily activities and whose cancer had spread to fewer sites.)

Currently, the trend among researchers seeking patients with metastatic or advanced cancer to enroll in clinical trials is to offer the treatment to patients under age 65 who meet all of the following criteria:

1. The cancer has not responded to hormonal therapy;
2. The cancer is responsive to chemotherapy, and the patients have had little or no prior chemotherapy;
3. The total amount of the cancer size is small (for stage IV), and there are only a few tumors; and
4. The patient has normal organ function and/or no cancer in the bone marrow. These criteria mean that patients currently being given this therapy represent a healthier group of patients among those with stage IV breast cancer.

Patients age 65 years or younger who have locally advanced disease or inflammatory breast cancer are also considered candidates if they have no evidence of any cancer on examination or test procedures after systemic and/or local therapy, if they have partially responded to induction therapy, or if their cancer has been found in many (typically 10 or more) armpit lymph nodes. (Please see What kinds of studies are going on now? on page 23.)

**Recent developments in the procedure**

The focus of current clinical research is to find better combinations and/or dosage regimens of the existing chemotherapy and hormonal agents.

Investigations into finding ways to improve recovery after transplantation continue. Methods are also being refined to increase the quantity of stem cells obtained during harvesting.

The use of purging techniques to remove cancerous cells after collection remains controversial and unproven. At this time, there are no randomized controlled trials under way to compare the effectiveness of purged versus unpurged stem cell concentrates on treatment response or survival outcomes for patients with breast cancer.

Since 1992, the use of BCT and colony-stimulating factors has decreased the amount of time patients must remain hospitalized after HDC and transplantation because the time it takes to recover bone marrow function is decreased. A 1994 survey of 48 centers performing HDC with ABMT/BCT reported that patients remained hospitalized an average of 29 days; some patients were hospitalized for as few as 10 days, and some for as many as 50 days. Another group of researchers found that about half the patients with breast cancer who underwent BCT spent about two weeks less time in the hospital than patients who underwent ABMT. A randomized controlled trial from South Africa published in October 1995 reported that patients without complications spent only an average of 9 days in the hospital after the procedure.

**How safe is the procedure?**

The safety of HDC with ABMT/BCT depends greatly on the health of the patient before therapy. It also depends on the toxicity of the chemotherapy, the time it takes for the patient to recover her ability to produce blood cells, and the quality of the monitoring and sur-
veillance of treatment regimens at the cancer center giving the care.

“Early Deaths”

Patients dying from treatment-related complications, such as chemotherapy toxicity or infections, within 30 days after stem cell reinfusion are sometimes referred to by researchers as “early deaths.” The early death rate for patients with metastatic breast cancer who received HDC with ABMT/BCT was reported in 31 studies published between 1984 and 1994. The average early death rate was about 10% in studies published between 1992 and 1994. The average early death rate in studies published only in 1994 was about 17%. However, some centers that have greater experience with the procedure may have consistently lower (5% or lower) early death rates.

Toxicities

The drugs used in HDC can produce severe TOXICITY. Appendix B on page 42 lists many of the chemotherapy drugs used and the type of immediate and longer-term complications that may occur. Side effects are listed in order of most to least common.

The analysis of the published studies

Background

The specific methods ECRI used to select the studies that could be used for comparing standard-dose chemotherapy and HDC with ABMT/BCT are in Appendix A. Additional background information is given here to help you understand what scientists and doctors can and cannot be certain about.

The 200-page, highly detailed ECRI report, from which this summary is derived, presents several types of analyses. The most important of these analyses is known as META-ANALYSIS: a systematic way of combining the results of many different CLINICAL TRIALS. It enables scientists to determine the overall effect of a treatment or given variables (such as estrogen RECEPTOR status) on different patient groups. In this way, effects can be discerned that might not be apparent when one looks only at individual studies because meta-analysis includes many more patients than any one study.

It is important to see the overall clinical picture of how well HDC with ABMT/BCT for metastatic breast cancer works because, at the time of our analysis, no study had ever directly compared various regimens of standard-dose chemotherapy to high-dose chemotherapy. In October 1995 (after the meta-analysis was completed), a study that directly compared a regimen of standard-dose chemotherapy and HDC with ABMT/BCT in patients with metastatic breast cancer was published. It is a small study that is discussed separately on page 19.

While analyzing studies published through September 1994, ECRI scientists identified some important gaps in scientific research. One of the first things they considered was that not all patients with metastatic breast cancer can be evaluated as though they are the same. Patient characteristics (such as the number and sites of cancer spread and menopause and estrogen receptor statuses) are important because they may have a greater effect on the prognosis than the treatment itself.

Some oncologists have asserted that certain patient characteristics (such as no spread of the cancer to the liver or to the soft tissue or fewer sites where the cancer has spread) are useful predictors of improved survival for patients who receive HDC with ABMT/BCT. But very few studies have looked at the relationship between patient characteristics and the effectiveness of HDC with ABMT/HDC. A list of patient characteristics that should be considered in studies to see if they make a difference in patient survival is listed on the checklist on page 32.

To see if there is, in fact, any particular group of patients that does well with this therapy, ECRI tried to analyze the medical literature in terms of these patient characteristics and patient response and survival. But, because some published studies did not report patient characteristics at all and because some studies reported them on only some patients, not all the important characteristics could be analyzed to answer questions about patient response and survival.

The lack of reporting such data in published studies points out one of many weaknesses in the published medical literature on HDC with ABMT/BCT for metastatic breast cancer. The failure to report characteristics also presents significant problems for any
Another problem in using the published medical literature to analyze how well HDC with ABMT/BCT works is related to how patients are chosen for studies. In studies of standard-dose chemotherapy, induction therapy is not used first to determine which patients might respond best to the therapy. All patients are given the chemotherapy. However, in many HDC studies, only the patients who first responded to induction chemotherapy were allowed to enter the study.

It is only ethical that, in practice, doctors choose patients they think are most likely to respond to the therapy. However, enrolling in a study only those patients who are most likely to respond creates “selection bias.” It makes it difficult to tell whether the new therapy is actually better than the standard therapy. The new therapy may appear to be better simply because the selection process for choosing patients has improved, not because HDC with ABMT/BCT really works better than standard chemotherapy for all patients.

How do researchers tell how well chemotherapy is working?

In clinical studies, researchers measure the effects of chemotherapy by:

1. The amount that the tumors shrink (RESPONSE),
2. How long that effect lasts (RESPONSE DURATION),
3. How many patients in the study respond out of all those receiving the treatment (RESPONSE RATE).

Researchers are mainly concerned with two kinds of response rates:

1. COMPLETE RESPONSE of the cancer, which means that no cancer can be found after testing, and
2. PARTIAL RESPONSE of the cancer, which means that 50% or more of the cancerous tissue appears to be gone.

(The glossary gives more detailed definitions of responses and survival measures.)

For patients, usually the most important issue is how long their disease partially or completely responds because that affects quality of life. In the published studies, the length of time a response lasts is called “disease-free” or “progression-free” survival. Disease-free means all the cancer appears to be gone. In other words, no cancer can be detected by the testing methods used. Progression-free means that the cancer is not growing or spreading. However, neither of these terms mean that a patient is cured. They mean that the cancer is not detectable, has shrunk, or at least has stayed the same for a period of time.

In the published studies, disease-free and progression-free times were not measured in the same way from study to study. Some researchers measured patient responses from the time of induction therapy to the time the disease was detected again. Other studies measured responses from the time of HDC with ABMT/BCT until the cancer was detected again. The first method of measuring could make survival times for patients who got HDC with ABMT/BCT appear weeks or months longer than they appear to be in other studies. When studies report SURVIVAL TIMES, it is important to know how the researchers defined their measuring points to understand what the survival times reported really mean.

Response durations are also looked upon as general indicators of patient quality of life. The length of time patients are able to enjoy life with little or no cancer after treatment suggests that their quality of life may be improved. However, there may be lingering side effects from HDC that affect quality of life. Unfortunately, virtually no published studies have examined quality of life during or after HDC. Therefore, patients must rely on anecdotal information from other patients, nurses, and doctors about quality of life.

Some studies report how long patients live after the treatment, which is called survival time. Survival time alone does not tell you whether the cancer completely responded. Some studies used statistical methods to translate survival time into one-, two-, and three-year survival rates — the percentage of patients who can be expected to survive one, two, or three years after receiving treatment. Again, the length of time that patients live after receiving treatment does not tell us anything about their quality of life. For example, a patient could survive for 15 months, but be too ill to resume any normal activities.
What studies were used in the ECRI meta-analysis?

A search of 12 medical databases identified about 1,500 studies published worldwide as of September 1994 that included data on breast cancer. A small number of these studies had data for HDC with ABMT/BCT for metastatic breast cancer; none were randomized controlled clinical trials, which means none of them compared the new treatment (HDC with ABMT/BCT) to standard chemotherapy. (The 1995 randomized controlled trial that compared HDC to standard-dose chemotherapy is separately discussed on page 19.)

The studies were reviewed for possible inclusion in the meta-analysis. Two ECRI analysts independently reviewed each of the studies and selected those that provided the data needed for a meta-analysis of the efficacy of HDC with ABMT/BCT for stage IV breast cancer. Forty studies with a total of 1,017 patients had data that could be used for meta-analysis. (More details of the selection criteria for studies included in the meta-analysis are given in Appendix A.)

Then, to find out how well HDC with ABMT/BCT works compared to standard-dose therapy for women with metastatic breast cancer, our analysts had to obtain data from published studies of standard-dose chemotherapy for comparison. The studies selected had to include groups of women whose medical characteristics were similar to the groups of women in the HDC with ABMT/BCT studies. Seventy-eight studies on standard-dose chemotherapy for metastatic breast cancer were identified among the initial set of 1,500 studies. Of these, 35 studies had data on a total of 4,889 patients that could be used to make comparisons with groups of patients from HDC with ABMT/BCT studies. Of the many comparisons made in the analysis of these data, three stand out as most important:

1. An overall comparison of response durations and survival between conventional and HDC studies.
2. A comparison of HDC and standard-dose studies in which at least 40% of each group of patients achieved a partial or complete response.
3. A comparison of HDC and standard-dose studies in which at least 50% of each group of patients achieved a partial or complete response.

What are the results of this analysis?

Based on all available data, ECRI found the following:

1. At first, there is a higher response rate to HDC with ABMT/BCT than to standard-dose chemotherapy. However, the response does not last long, and the cancer progresses. The higher response rate may reflect patient selection criteria for HDC with ABMT/BCT, not the effectiveness of the treatment. Often, only those patients whose cancer has first responded to induction therapy go on to receive HDC with ABMT/BCT.

2. In published studies, standard-dose chemotherapy yielded longer disease-free and overall survival times than HDC with ABMT/BCT. In particular, the one- and two-year disease-free survival rates were lower in studies of HDC when the standard-dose and HDC studies that had the highest (50% or greater) complete and partial response rates were compared.

3. There is some evidence of shorter overall survival times after HDC with ABMT/BCT therapies than after standard-dose therapy, as reported in published studies for all response and survival outcomes measured, except the response rate.

4. There is evidence that standard-dose chemotherapy offers patients with metastatic breast cancer a longer response time and an increased overall survival time and that more patients survive for one year compared to those receiving HDC with ABMT/BCT therapies. Remember: overall survival is not the same as disease-free survival. Overall survival means that life was prolonged. These studies did not evaluate quality of life.

5. The medical research on HDC with ABMT/BCT does not identify any subgroup of patients that is...
HDC with ABMT/BCT

likely to have long-term disease-free survival after receiving the HDC. (See What recommendations can be made based on the ECRI analysis? on page 33 for discussion of the implications of these results.)

Are there any other data besides the published studies?

There is a database of information on patients who have received HDC with ABMT/BCT — the Autologous Bone Marrow Transplant Registry-North America. Reporting to this registry is voluntary. Since 1989, this registry has maintained records of the tumor type, menopausal status, estrogen receptor status, previous therapies, HDC regimens, and response outcomes for each patient from participating centers. The registry has collected data on half or more of patients with breast cancer who have received HDC with ABMT/BCT. However, analyses of these data have not been published as of this writing.

ECRI contacted the registry and was able to obtain some data (but not patient characteristics). The data made available were used to make general comparisons for one- and two-year progression-free survival rates of patients with stage IV breast cancer between specific HDC with ABMT/BCT regimens in the registry and regimens in published studies. Comparisons were also made with the standard-dose chemotherapy studies used in ECRI’s analysis. No differences were found between the results of published studies and the data in the registry.

Are there studies of this therapy’s use in other stages of breast cancer?

No published studies of HDC with ABMT/BCT for earlier-stage breast cancers (stage II, stage III) and for inflammatory breast cancer included any comparison group of patients who received standard-dose treatment. There are insufficient data to determine how well HDC with ABMT/BCT works for these stages of breast cancer. Randomized controlled clinical trials are needed to evaluate this. (See What kinds of studies are going on now? on page 23.)
Update 1996: What does the only published study directly comparing a high-dose and standard-dose regimen in patients with metastatic breast cancer tell us?

The conclusions of any technology assessment are not permanent; they are based on what is known at the time of the assessment, and subsequent new evidence from published studies may alter conclusions. Since completing a meta-analysis in 1995, ECRI scientists have been examining the medical literature for important new studies published on high-dose chemotherapy with autologous bone marrow or blood cell transplantation (HDC with ABMT/BCT) for metastatic breast cancer.

In October 1995, The Journal of Clinical Oncology published the results from the first RANDOMIZED CONTROLLED TRIAL (RCT) ever completed on HDC with ABMT/BCT for metastatic breast cancer (“High-dose chemotherapy with hematopoietic rescue as a primary treatment for metastatic breast cancer: a randomized trial,” pages 2483-89). This study, by W.R. Bezwoda and colleagues from the University of Witwatersrand, South Africa, is described below.

In the RCT, 90 patients with metastatic breast cancer were assigned to receive either HDC with ABMT or BCT or a lower dose regimen of chemotherapy not requiring ABMT or BCT. The authors hypothesized that high (50% or better) COMPLETE RESPONSE RATES from HDC should have a substantial impact on survival. (However, based on ECRI’s review of the medical literature, high complete RESPONSE RATES have not been shown to correlate with longer survival for this patient population.)

The women enrolled in the Bezwoda study were age 50 years or younger.* They had normal kidney, liver, and heart function; had no prior chemotherapy; and were able to undertake most of their normal activities. The chemotherapy agents used in the standard- and high-dose regimens used comparable drugs.

The high-dose regimen was cyclophosphamide, mitoxantrone, and etoposide (HD-CNV); the standard-dose control group regimen was cyclophosphamide, mitoxantrone, and vincristine (CNV). Patients in the HDC group received two courses of HDC; patients in the standard-dose group received 6 to 8 courses of therapy. Patients who had a PARTIAL or complete response to the chemotherapy were given tamoxifen maintenance therapy after the chemotherapy.

The researchers found a significantly higher overall response rate (the overall rate includes complete and partial responders) for patients who received HDC (95%) compared with standard-dose treatment (53%). This means that the tumors shrunk by 50% to 99% in more patients in the group receiving HDC; however, higher response rates do not necessarily mean there will be longer survival times. (The higher response rate for HDC was also found in ECRI’s meta-analysis.) About 20% of HDC patients’ responses lasted 2 years. The median durations of response and survival were significantly longer for HDC patients (80 weeks and 90 weeks, respectively) than for standard-dose patients (34 weeks and 45 weeks, respectively). (“Median” means that half the patients were above this point and half below.) There were no treatment-related deaths in the study and mostly moderate side effects. Hospital stays for HDC patients ranged from 2 to 9 days; about two-thirds of HDC patients required hospital admission for a median of 5 days for treatment with antibiotics.

The results seen in the HDC group of the Bezwoda study were achieved without induction therapy, suggesting that this may not always be necessary.

A well-designed RCT showing that a specific HDC with ABMT/BCT regimen is superior to the

*The “Update 1995,” as originally issued in February 1996, contained a printing error describing patients as “age 50 or older.”
most effective standard regimens could provide sufficient evidence to conclude the HDC regimen was the best option for patients. The results of the Bezwoda study, although intriguing, are insufficient to prove the superiority of HDC with ABMT/BCT for the following reasons:

1) The results of the HDC group in this trial are better than the results of standard-dose regimens in most published studies. However, the median survival times of groups of patients from several published studies of standard-dose regimens are about the same or better than the median survival times of HDC patients in the Bezwoda study. Published studies of standard-dose regimens that achieved similar or longer survival times are listed at the end of this section.

2) In the Bezwoda study, the standard-dose group used for comparison to HDC received a chemotherapy regimen that was less effective than the optimal standard-dose chemotherapies (of other drug combinations) available. The standard-dose CNV regimen used in this study is not commonly used. The 45-week median survival seen in patients in the standard-dose group was shorter than the 68-week median survival seen in standard-dose groups in ECRI’s meta-analysis. The length of time the response lasted in the Bezwoda study standard-dose group (34 weeks) was also shorter than that seen in standard-dose studies (41 weeks) in ECRI’s meta-analysis.

In addition, as pointed out in an editorial published with the Bezwoda study by Johns Hopkins University oncologist M.J. Kennedy, these researchers previously obtained better results giving the same CNV dosage — when it was given to patients for twice as long. Thus, the HDC group results in the new study appear better than they would if they were compared to a more effective standard-dose regimen.

3) The follow-up time in the Bezwoda study was short. Patients were entered in this study between 1991 and 1993, and results were analyzed in 1994. Half the number of patients were in the study less than 1½ years (72 weeks); the others were in the study for at most 2½ years. As the editorial stated, “more protracted analysis of larger ongoing studies will be necessary to quantitate precisely the effect that is suggested.”

4) The study size is small, 90 patients in total (45 in the HDC group and 45 in the standard). A maximum of 9 HDC patients responded for two years or longer. Smaller studies tend to have less generalizable results than larger studies.

Patients may wish to consult other references for additional critiques of the study, which can be found in the editorial published with the study and in letters published in the February 1996 Journal of Clinical Oncology.

In conclusion, the Bezwoda study reports better results with HDC than are seen with most other HDC regimens and with many standard-dose regimens. Still, some standard-dose regimens have achieved comparable or better results.

Published standard-dose regimens that achieved similar or better results than the HDC group in the Bezwoda study:


Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide v fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre
HDC with ABMT/BCT is used to treat several kinds of cancer, and it may be more effective for some cancers than others. The U.S. Health Care Financing Administration, which oversees Medicare, calls the procedure experimental for any indication other than acute leukemia in remission, resistant non-Hodgkin’s lymphoma, recurrent neuroblastoma, and advanced Hodgkin’s disease (for patients whose cancer has not responded to conventional therapy).

Among private health insurers and health maintenance organizations (HMOs), coverage varies from carrier to carrier and within each carrier, depending on the plan. Some private insurers and HMOs use the determinations of the Health Care Financing Administration with regard to the “experimental” status of specific procedures as a basis for their coverage policies. Some pay for the procedure only if the patient is enrolled in a CLINICAL TRIAL — any clinical trial (not just RANDOMIZED CONTROLLED TRIALS). Other insurers and HMOs pay for the procedure only if the patient is enrolled in a National Cancer Institute-approved randomized clinical trial. One large national HMO, U.S. Healthcare, and several regional plans of a large national fee-for-service insurer, Blue Cross/Blue Shield, are funding various portions of National Cancer Institute-approved randomized clinical trials for this procedure. These trials are comparing HDC with ABMT/BCT and standard-dose chemotherapy for stages II, III, and IV breast cancers.

Another example of the diversity among coverage policies is illustrated by insurers’ use of an outside consumer advocate service to make coverage decisions case by case for this therapy for breast cancer. At least two large national health insurers and HMOs (Aetna and Kaiser Permanente) use an independent patient advocate service to determine coverage on a case-by-case basis.

Cancer-specific agencies and advocacy groups sometimes issue statements on what they believe insurers/HMOs should cover. For example, the American Cancer Society Cancer Response System states, “Patient care costs should be reimbursed by third-party providers for those persons participating in treatment trials,” and that “includes cancer patients and others treated on National Cancer Institute-approved protocols for high-dose chemotherapy and autologous bone marrow transplantation and/or peripheral stem-cell support.” The National Breast Cancer Coalition and Y-ME Breast Cancer Organization also advocate that health plans support high-quality clinical trials of HDC with ABMT/BCT (such as those that follow National Cancer Institute protocols) by covering the treatment costs of patients who enter trials. These organizations do not advocate giving the treatment for breast cancer outside of clinical trials.

**Questions to ask your doctor and health plan about coverage**

1. Is the procedure covered outside of clinical trials?
2. If not, which trials are covered, and what center would I have to go to?
3. Are both inpatient and outpatient medical services included in coverage?
4. Are there any aspects of the procedure that are not covered?
5. Are travel and lodging costs covered if I have to go to another location to participate in the trial?
6. Are medical complications and side effects that may arise during or after the treatment covered? (For example, some insurers will cover the cost of a wig for patients who lose their hair during chemotherapy.)
7. If HDC with ABMT/BCT is not covered, what other options for me are covered?
States and organizations that have mandated coverage

At this writing, at least nine states (Florida, Massachusetts, Missouri, Minnesota, New Hampshire, New Jersey, Tennessee, Vermont, and Virginia) legally require third-party carriers to offer coverage for HDC with ABMT/BCT for patients with breast cancer. Others are considering it. The nature of the coverage requirement varies from state to state.

In September 1994, the United States Office of Personnel Management “mandated immediate coverage of HDC/ABMT for all diagnoses for which it is considered standard treatment and, in addition, specifically for breast cancer, multiple myeloma, and epithelial ovarian cancer.” The 200 health insurers and HMOs that participate in the Federal Employee Health Benefits Program, which covers 9 million federal employees and their families, had to comply. Some of the health plans already covered the procedure. For those that did not, the Office of Personnel Management stated that coverage of the procedure could be limited to patients entering clinical trials (both randomized controlled or nonrandomized) in their service area.

Since there is so much variation in health plan coverage with regard to this procedure, patients who may be considering it can obtain assistance in understanding their health plan policy about this procedure by contacting their health plan’s member services department. Some questions you may want to ask about your health plan coverage are listed in the box in this section. If a patient’s doctor has recommended the procedure, the doctor (or a member of the staff) will usually handle the necessary communication with the health plan and supply the necessary medical information required to back up the recommendation. The health plan should explain the process for making its coverage decision and the rationale behind the decision (whatever it may be) to the patient. Some patient-support groups also offer information about health insurance issues for patients with cancer. See Some other resources on page 35.
What kinds of studies are going on now?

This section describes the National Cancer Institute-approved randomized controlled clinical trials now going on that compare HDC with ABMT/BCT to standard-dose chemotherapy. A general discussion about randomized controlled clinical trials and some concerns that women with breast cancer have voiced about entering these trials follow the description. A CLINICAL TRIAL is a scientific study of a treatment given to humans. There are many ways to design a clinical trial. The design of the trial is important because it has an impact on how reliable or meaningful the results of the trial will be. In the research community, the “gold standard” clinical trial is considered to be a RANDOMIZED CONTROLLED TRIAL. This type of clinical trial directly compares two or more treatments on similar groups of patients to learn which treatment option works best; no other type of trial can provide this kind of information.

More than 20 clinical trials are currently investigating how well HDC with ABMT/BCT for the treatment of breast cancer works. Only three of these trials are randomized controlled trials (RCTs) that compare standard-dose and HDC regimens and are approved by the National Cancer Institute. They compare HDC with ABMT/BCT with STANDARD-DOSE CHEMOTHERAPY. Each trial has many medical centers throughout the country participating in it (i.e., a multicenter trial). The National Cancer Institute has a listing of all participating centers and detailed fact sheets describing each of the three trials, which are briefly described here. The first two trials listed are for selected patients with stage II or stage III breast cancer. The third is for selected patients with stage IV (METASTATIC) disease.

Currently, none of these trials has a sufficient number of patients enrolled to be able to adequately compare treatments. The National Cancer Institute recently stated that early “trials from single institutions have proven the feasibility of this high-dose approach, and survival results from these trials are encouraging. However, these results are subject to strong patient

### NCI-approved RCTs on ABMT for breast cancer

1. The Cancer and Leukemia Group B Group (CALGB) is comparing the following 2 therapies, randomly assigning patients with 10 or more positive axillary (armpit) lymph nodes to receive:
   - A. Induction therapy of cyclophosphamide + doxorubicin + 5-fluorouracil followed by high-dose cyclophosphamide + carmustine + cisplatin with stem cell rescue, or
   - B. Cyclophosphamide + doxorubicin + 5-fluorouracil and standard-dose cyclophosphamide + carmustine + cisplatin.

2. The Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG) are comparing the following 2 therapies, randomly assigning patients with 10 or more positive axillary lymph nodes to receive:
   - A. Induction therapy of cyclophosphamide + doxorubicin + 5-fluorouracil followed by high-dose cyclophosphamide + thiotepa and stem cell rescue, or
   - B. Standard-dose chemotherapy.

3. The Philadelphia Bone Marrow Transplant Group, Eastern Cooperative Oncology Group, Southwest Oncology Group, and North Central Cancer Group are comparing the following two therapies, randomly assigning patients with metastatic disease (estrogen receptor negative or hormonally unresponsive) to receive:
   - A. Induction therapy of cyclophosphamide + doxorubicin + 5-fluorouracil followed by high-dose cyclophosphamide + thiotepa + carboplatin, or
   - B. Standard-dose cyclophosphamide + methotrexate + 5-FU.
selection *BIASES* and need to be confirmed in larger populations. . . . To accomplish this, the NCI has sponsored three trials through its Cooperative Group mechanism.”

Patients in the third trial listed will have stem cells harvested by either ABMT or BCT with granulocyte-macrophage colony-stimulating factors given during recovery of the blood cell producing system. This trial will also try to determine the impact of long-term therapy on patient lifestyle and on psychological quality of life.

**Discussion**

It is important not to confuse the quality of a scientific study with the quality of medical treatment or care. Quality of care, from the patient’s viewpoint, varies a great deal from healthcare setting to healthcare setting. Sometimes a new treatment becomes widely available before its *EFFICACY* has been proven, and patients are steered toward the new technology by their doctors rather than to enrollment in randomized trials. Patients who enter clinical trials must be given a written INFORMED CONSENT that clearly explains the clinical trial treatment and related matters. The trial is also explained to the patient by the physician conducting the trial to make sure all the patient’s questions are answered. To enter a trial, the patient must review and sign an informed consent document. Patients who are in the standard-dose group of a randomized controlled trial at a tertiary care center (a teaching hospital) generally fare better than patients not in a trial who are receiving similar treatment outside this setting.

The 3 trials listed here currently need from 150 to 750 more enrollees for each trial (the number varies according to the trial). Unless more patients enroll, physicians will be unable to obtain enough information to learn if the new treatment is more or less effective than standard-dose chemotherapy.

If appropriate scientific studies have not been done, ultimately, the effects of a widely used but unproven treatment may become apparent only after many years pass. Scientists conduct “look back” studies by gathering available (and often incomplete) data from medical records of patients who had the new treatment to see what their long-term outcomes have been. Sometimes randomized trials are undertaken and eventually completed. Unfortunately, patients may have suffered unnecessarily or died prematurely from a new treatment that is finally proven to be less effective than the standard treatment it was measured against.

A case in point dates back 25 years when modified radical mastectomy was routinely recommended by doctors to most women with breast cancer (even those in early stages) before any evidence supported it as the most efficacious treatment. At the time, doctors believed they would be risking patients’ lives by offering more conservative surgery (lumpectomy) and that it would be unethical. The basis for this rationale was historical: mammography was unavailable (it had not been developed yet), breast self-exam was not widely used, and routine breast exams performed by physicians typically found breast cancer at later stages than cancer is found today. Many doctors did not want their patients to enter randomized trials because their training led them to believe that radical mastectomy was superior.

However, in the end, the trials were carried out comparing modified radical mastectomy and lumpectomy. By the late 1980s, the results proved that lumpectomy with radiation therapy is just as effective as modified radical mastectomy and far less traumatic for patients. Those results were reconfirmed in 1995 with the publication of more long-term data that show that “less treatment” is as effective as “more treatment.”

Nonetheless, patients sometimes do not want to enter randomized trials. The reasons given by women vary. Many women have said that the therapy must be better than the standard-dose therapy because it is new, or “state of the art.” Some doctors may believe this themselves or encourage this view by saying that a new therapy looks “promising,” without making it clear that there is little or no evidence that it is the best option. Certainly, if the therapy did not appear promising or encouraging, researchers and the National Cancer Institute would not want to carry out randomized trials on it. But promising does not mean proven or superior to standard-dose treatment. Promising means that there are some indicators that suggest that perhaps the therapy may work in an as yet unidentified subgroup of patients. To go beyond the tentativeness and uncertainty of “promising” requires conducting randomized controlled clinical trials.

Some women with metastatic breast cancer have also reasoned that, given the poor odds that standard-dose...
Chemotherapy will significantly prolong their survival, it makes sense to seek an alternative. On the other hand, some women may now fear HDC because of the highly publicized recent deaths of two patients with breast cancer who received accidental overdoses of chemotherapeutic agents in very prestigious institutions. Physicians will often discuss with patients how HDC with ABMT/BCT might lead to “disease-free” survival. They may even offer it as “the only chance for cure.” Often, the actual meaning of disease-free survival is not explained to patients. Some patients are left with the impression that disease-free survival means cure. Unfortunately, for almost all patients with metastatic breast cancer, a cure is elusive. The anticipated disease-free survival time is a very important piece of information for patients, but disease-free means that the cancer cannot be detected. It does not mean that the disease will necessarily remain in remission.

Other reasons some women with metastatic breast cancer choose HDC rather than enter a randomized clinical trial have centered around personal interpretations and misinterpretations about the meaning of the term “high-dose chemotherapy.” Some patients infer that the stronger the dose, the more effective it will be at “killing the cancer.” This logic makes standard-dose chemotherapy sound like the “weaker” weapon in the battle against the cancer. However, this logic is not supported by medical evidence. Just as modified radical mastectomy (i.e. the “stronger” treatment) was believed by many doctors in the 1960s and early 1970s to be the most effective treatment (and that it would be dangerous to offer patients a “weaker” therapy — lumpectomy with radiation therapy), many physicians today believe that HDC is more effective for patients with breast cancer than standard-dose treatment. Unfortunately, they really don’t know for certain and will not know until the randomized controlled clinical trials are completed.

Entering a randomized clinical trial is clearly in society’s best interest. But is it in the individual patient’s best interest? This is not so clear. Certainly, very high-quality care and long-term follow-up are given to patients in all groups of a randomized controlled clinical trial. Also, patients are likely to fare better at a center participating in a National Cancer Institute-approved trial than if treated elsewhere. However, since no one knows which of the treatments being compared is better, the patient is taking a risk. The patient will only know if she received the treatment that ultimately proves to be the most effective after the trial is completed. But the patient is also taking a risk, and one that may be greater, if she chooses to have a treatment outside a clinical trial because the evidence about which is the better option is not available yet. Also important to consider is that no one has ever claimed in print that HDC with ABMT/BCT cures anything.

The most important questions for you are how much the treatment you choose extends your life and what your quality of life will be during and after treatment. Many women, their families, and the media have also expressed views that the only reason that access to the procedure is being denied is because health insurers do not want to pay for new high technology that can cost from $50,000 to $200,000. Arguing that a therapy is good because it is new or involves high technology that a health plan does not want to pay for misses the most important issue for the patient: Is the therapy effective and will it maintain or improve the patient’s quality of life?

In fact, cost (which ranges from $50,000 to $200,000) may become less of an issue because the costs of HDC with ABMT/BCT have decreased somewhat as techniques have been refined, the length of hospital stays has decreased, and more aspects of the procedure are being performed on an outpatient basis. No matter what treatment is chosen, the cost of care for breast cancer is substantial because extensive, high-level care and follow-up are needed. It is not a case of providing HDC or no medical care. And it should also be recognized that improvements in chemotherapy regimens without ABMT/BCT are also the subject of research.
What should I ask my doctor before deciding on treatment?

Discussing the following issues may give you a sense of what the data mean for your situation. Each question is followed by a discussion, from a patient perspective, of why the answers — or lack of answers — might be important to your decision-making process. Many of the issues raised by these questions are likely to be included in INFORMED CONSENT discussions with your doctor about the treatment options.

Thinking of all the important questions you may want to discuss with your doctor about a therapy when facing a potentially life-threatening illness is difficult, especially if no one really knows how effective the proposed treatment is. Recognizing that each patient’s circumstances are unique, the following questions are suggested to help you obtain the information you need to make the best possible decision for you. This list of questions can be used to discuss treatment options with your physician.

Some patients have mentioned that it is very stressful to pose some of the questions themselves. They have emphasized that it is very helpful and quite normal to bring a friend or family member to physician consultations. This person can take notes, tape record your discussions, and ask questions that you may find difficult to ask. Patients have also pointed out that physician consultations can be extremely stressful because of the nature of the information being given. Relying on your memory alone to recall all of the discussion points and options at a later time may be difficult. The presence of a friend or family member to take notes or tape record discussions frees you to focus on listening and facilitates reflection, discussion, and decision making after the consultation is over.

Your physician may be unable to respond to all the questions at one visit because he or she may need to obtain more information for you. Leave a copy of any unanswered questions with your doctor (and keep one for your records). Ask when he or she can provide answers. You may find that, for some of these questions, the answers are unknown because results of “apples-to-apples” comparisons of HDC with ABMT/BCT and standard-dose chemotherapy are not available yet. But having the discussion with your doctor about what is and what isn’t known is still worthwhile because it will probably help your decision making.

If you ask questions that are not answered, we encourage you (or a family member or PATIENT ADVOCATE*) to ask your doctor if he or she can suggest where to go for more information. If definitive answers cannot be given, this may indicate that there is less certainty about the treatment than you or your doctor would like. It may help to clarify in your mind the kind of research that is still needed to show whether or not HDC with ABMT/BCT is as good as or any better than standard chemotherapy.

* While some hospitals provide their own “patient advocates,” these advocates may or may not be trained in breast cancer specific issues. Local chapters of support groups for patients with cancer may offer advocateservices that represent the patient perspective. See Some other resources on page 35.

1. What is my medical status now?

Your medical status (also referred to earlier as patient characteristics) at the time of therapy can have a bigger impact on your outcome than the treatment itself. Patient characteristics that are important to consider are in the box on page 32. Complete your medical status profile by asking about each one; note the items that pertain to you. The checklist will help you ask further questions about patients who are like you, based on your patient characteristics.

2. Is there any way to determine whether I will respond better to standard-dose chemotherapy or to high-dose chemotherapy and bone marrow or blood cell transplantation?

You and your loved ones want the therapy that offers you the best chance of survival and the best quality of life. At this time, there is no way to tell whether you will respond better to one approach or the other. Patients should understand that “induction chemotherapy,” which is given to patients who are being
considered for HDC with ABMT/BCT, is intended to determine whether your cancer is likely to respond to the drugs used in high-dose chemotherapy. Induction chemotherapy may achieve some response, but it is usually not a therapy in itself. Some patients and their families have expressed that, before undergoing induction, they were unaware of being on a “track for HDC with ABMT” when given induction chemotherapy. If induction chemotherapy is proposed to you, and you feel that you don’t yet fully understand HDC with ABMT/BCT, be sure to ask about it.

If your cancer does respond to induction chemotherapy (i.e., the tumor shrinks), it is more likely that it will respond to HDC than to cancer that does not respond to induction. However, responding to (also called “passing”) induction therapy does not mean that HDC with ABMT/BCT will be as effective or more effective than standard-dose chemotherapy. Responding to induction means that the cancer is sensitive to chemotherapy. It does not mean that you will live longer or have an equivalent or better quality of life if you undergo HDC than if you have standard-dose chemotherapy.

3. Why are you recommending this therapy to me?

This is another way of expanding your discussion about the evidence that exists about the therapy and its effectiveness. Your doctor’s response will tell you if he or she has evidence backing up the recommendation for you, in particular, based on your patient characteristics.

The answer can also give you a sense of your physician’s reasons for recommending it to you, in particular. It may be that a doctor feels a need to offer you something, even if he or she is uncertain how much the therapy may benefit you. Your doctor may be uncomfortable telling you that your chance of long-term survival is limited. Your doctor also may want to give you hopeful advice and support a positive attitude. These are important emotional aspects of dealing with your illness. However, patients also should be given evidence. Knowing whether your doctor is recommending the therapy solely to give you hope, rather than because there is evidence to suggest that it will benefit you, may be important to your considerations, since the therapy presents significant risks.

Another possible reason that a doctor may recommend a therapy of unproven effectiveness is that he or she may believe that you want “high technology” or more treatment, even if there is no evidence and little chance of benefit from the treatment. Thus, the recommendation may be your doctor’s effort to respond to what he or she assumes are your wishes and hopes.

It is important for patients to know that the selection criteria of patients recommended for HDC with ABMT/BCT may differ somewhat among cancer centers. Also, the experience of each center and the total number of patients each center has treated with this procedure vary widely. Some centers only offer the therapy as part of a randomized controlled clinical trial approved by the National Cancer Institute. Generally, all patients in clinical trials, including those not receiving the experimental treatment, receive very high-quality care and long-term follow-up, which may or may not be the case outside of a clinical trial. Regardless of the center you go to, it is important to learn, very specifically, whether that center’s doctors have gathered data about patients who have your same characteristics (age, stage of cancer, estrogen receptor status, etc.). Ask about the response rate and duration of response for patients with your characteristics at that center. Ask whether any of the center’s data show that patients like you are more likely to respond better and survive longer if they have standard-dose chemotherapy or HDC with ABMT/HDC. Ask to speak to one or more patients like you who have completed the treatment to get an idea of what it is like from their view.

Since there is only one study reporting results from a randomized controlled trial at this time, you will have to decide how satisfied you are with the data that you are being given by the center. If, for example, the center has treated very few patients with characteristics like yours, you may wish to seek information from other transplant centers.

Based on ECRI’s experience in obtaining published and unpublished data, it is unlikely that you will be able to get the ideal “apples-to-apples” comparisons that you request. This is one of the compelling arguments for patients to enter randomized controlled clinical trials because these trials are designed to make “apples-to-apples” comparisons. If the doctors proposing to treat you have not treated patients with
your characteristics or have not gathered complete data on the patients they have given HDC with ABMT/BCT, then you should consider finding another center that does, if at all possible.

4. Should I enroll in a randomized clinical trial (RCT) or not? Why?

Randomization in a clinical trial means that a patient does not choose which chemotherapy protocol to undergo, but is assigned to receive either standard-dose treatment or high-dose chemotherapy and a transplant (if it is one of the three trials previously described; some trials are comparing different HDC regimens and different ABMT/BCT methods). From a research point of view, such trials are important to everyone concerned about which therapy is better for all patients or a particular group of patients with breast cancer. Although HDC with ABMT/BCT has been used for over 15 years, only 1 randomized controlled clinical trial has ever been completed on 1 chemotherapy combination. This is why there is so much controversy about this technology. From a patient point of view, the benefits of enrollment in a clinical trial are that your quality of care will likely be very high, your care and response to treatment will be very closely monitored, and you will be followed up during your lifetime.

If your physician does not, in general, support randomized controlled clinical trials for this treatment, ask why. Your doctor could be unaware of the overall lack of scientific evidence proving the therapy to be the best option available or may have formed an impression based on his or her experience. Of course, even if your doctor supports randomized trials, he or she might not recommend that you enter a trial anyway, for a number of valid reasons. For example, you may be ineligible for enrollment in a study because of a particular patient characteristic or your medical history. If you are interested in more information about enrolling in an RCT, discuss this with your physician. He or she can help connect you with the physicians conducting the studies, or you can telephone the National Cancer Institute’s Cancer Information Service at 1-800-4-CANCER. (See What kinds of studies are going on now? on page 23 for more discussion about RCTs for HDC with ABMT/BCT.)

5. How reliable are the statistics that appear in studies or that are given to me by cancer centers?

Statistics can be presented in many ways. In the medical literature on HDC with ABMT/BCT for metastatic breast cancer, statistics have often made patient outcomes appear better than they really are. One of the most important things that was found during ECRI’s analysis of studies on HDC with ABMT/BCT for metastatic breast cancer was that most published studies reported survival rates that did not include patients who died from treatment-related complications within 30 days after transplantation (also called “early deaths” by researchers).

Excluding the deaths of these patients from calculations of survival rates makes the rates look better than they really are. If you are given statistics on survival times from a particular center, ask if early deaths are included. In contrast, survival times for patients receiving standard-dose chemotherapy typically do include the patients who die within 30 days of starting treatment.

Also, you may be given statistics that have little value to patients. For example, if a center gives you a statistic about a high response rate of all patients treated there, it does not mean that patients’ lives have been extended, that the cancer has completely responded to treatment, or that patients’ quality of life has been maintained or improved. Remember that response really means the tumor has shrunk, not that the patient is cured.

The combined response rate and response duration (also called disease-free or progression-free survival time) are useful for you to know.

6. What are the disease-free survival rates (at six months and one, two, and three years) of patients like me who have had the treatment at this center? How many patients like me are your survival rates based on?

Another way that survival rates can be misleading is when rates are calculated based on very few patients. For example, if a study reports that there was a 50% survival rate at 1 year, but only 6 patients were in the study (3 lived, 3 died), it doesn’t give you much helpful information. A 50% survival rate in a study of 200 patients would carry more weight (i.e., 100 patients survived). Survival rates calculated from small studies are of little value to you in making a decision. That’s why combining and analyzing the results of many studies (META-ANALYSIS) can give a more accurate picture of the real value of a therapy.

If you’re considering undergoing HDC with ABMT/BCT, ask about the total number of patients
like you who have received the treatment at the center and the total number who were alive six months and one, two, and three years after treatment.

7. Of the patients who did not survive at the center you are in contact with, how many died of the cancer and how many from treatment-related causes?

This gives you another way to view and weigh the results at a specific cancer center.

8. Describe the entire procedure proposed for me and the timing of each step, including whether it involves the ABMT or BCT method, the HDC regimen and dosage, the toxicities, the side effects, and the length of time they last.

Much of this information may be covered during INFORMED CONSENT discussions. During these discussions, the treatment is explained to the patient, and the patient signs a document stating that she understands the treatment, its possible side effects, and risks and that she agrees to receive the treatment. Getting as much detail as possible about the procedure proposed for you will help you determine how it will affect the lives of you and your family. Some centers are performing the procedure almost entirely on an outpatient basis; others still do it as an inpatient procedure at this time. However, there is variation from center to center and among patients with regard to the timing and techniques used.

High-dose chemotherapy regimens and dosages vary widely. Sometimes physicians may tell patients only about the major side effects. Others may run through a long list of side effects, but might not say how common each is. Appendix B lists the drugs often used in HDC regimens and their short- and long-term side effects in order of most common to least common. Ask your doctor which drugs will be used and what medications will be offered to offset any side effects. It is also important to ask how long these effects typically last and how they could affect your daily living activities (ability to get up and walk around and to eat, drink, sleep, drive, talk, etc.).

9. How long am I at risk of serious infection after HDC? How will this affect my quality of life?

There is no question that HDC with ABMT/BCT is risky and even life-threatening. It disarms an important part of the body’s defenses against infection. Getting the patient's blood cell producing system up and running is imperative to recovery. However, no one can absolutely guarantee that a patient’s blood cell producing system will return to normal after stem cell transplantation. If it doesn’t, the patient may die within weeks. However, periodic blood transfusions and other measures may sustain a patient whose blood cell producing system has not returned to normal for several months or more.

Ask your doctor about your risk of infection. What specific measures will be taken to protect you? Will you be given colony-stimulating factors? Are there additional medications you will be given to speed recovery? Will you be isolated? Many centers isolate patients to reduce the potential for infection. If isolated, where will you be, and for how long? What limitations would this place on visits and personal contact with family and friends?

10. How do I make an appointment with a nurse to discuss my concerns about quality-of-life issues before I decide on treatment? How can I get in touch with other patients like me who have already completed the treatment to talk?

Patients who have completed therapy have told us that some of the most valuable information they had to consider regarding quality-of-life issues came from other patients and the nurses who care for patients who receive HDC with ABMT/BCT. Patients who completed therapy several months or a year ago can tell you not only about side effects during treatment, but also quality-of-life issues and treatment side effects that may occur or linger months after treatment. Some doctors may place less importance on side effects than you do to focus mostly on the effectiveness of the therapy. Let your doctor and the nurses who will be caring for you know how important the issue of short-and longer-term side effects is to you.
11. If I choose not to undergo HDC with ABMT/BCT, what is my prognosis, and what are your recommendations for my care?

The answer may be one that is difficult for your doctor to deliver and devastating for you to hear. Some physicians are puzzled by a patient’s refusal to undergo a procedure that is offered, especially if it seems to be the only thing left that hasn’t been tried. Some doctors may even be offended, perceiving a refusal as questioning their knowledge and experience. It may be that this therapy is offered as a last hope. Some doctors have difficulty accepting that they can offer no other treatment. If you have advanced-stage breast cancer and refuse this therapy, your doctor may have no other option to offer to try to treat the cancer.

Nonetheless, many doctors honor the patient’s decision and offer support to make the patient’s quality of life as high as possible through adequate pain management and other measures. If you decide to try the therapy, and the cancer does not partially or completely respond, medical support should likewise include adequate management of pain and other measures that provide comfort. Remember, too, that at this time, there is evidence that you may survive longer by undergoing standard-dose chemotherapy with less risk and better quality of life than you would by undergoing HDC with ABMT/BCT.
 Patient Characteristics Checklist

These are the main characteristics that relate to your prognosis and treatment options. If you’d like a profile of your medical status, discuss this checklist with your doctor, and fill in the information that applies to you.

In clinical trials, it is important for researchers to note these characteristics about each patient when entering the trial so that the results can be analyzed to see if any group of characteristics is associated with a better response to treatment. Many of the published HDC studies have not included complete data on characteristics. From those that have included such data, no particular group of characteristics has been identified that indicates improved survival time or disease-free survival time for patients receiving HDC with ABMT/BCT.

1. Your age at diagnosis and menopause status:

2. Cancer stage:

3. Estrogen receptor status:  □ Positive or □ Negative

4. Progesterone receptor status: □ Positive or □ Negative

Women with a positive hormone receptor status often have a better response to hormonal therapy than those without receptors. Hormonal therapy may be recommended to patients with positive receptors before HDC is ever considered.

5. Places that the cancer has spread (metastasized):
   - □ Other breast (from the primary tumor, not a second breast cancer)
   - □ Liver
   - □ Lung
   - □ Bones
   - □ Skin
   - □ Lymph nodes
   - □ Brain

   The more places the cancer has spread, the less likely it is your doctor will recommend HDC with ABMT/BCT because your chance of withstanding this rigorous therapy is likely to be lower than for other patients who have advanced-stage breast cancer, but are “healthier.”

6. Prior chemotherapy:

   Patients who have had prior chemotherapy (not including induction therapy) are usually not selected to receive HDC with ABMT/BCT. If you have had prior chemotherapy, but have not responded to it, it is less likely that more chemotherapy (whether standard or high dose) will provide additional benefit to you.

7. Prior hormonal therapy:

   Patients who do not respond to hormonal therapy may be offered HDC with ABMT/BCT. In published studies, this is one of the selection criteria for patients being considered for HDC.
What recommendations can be made based on the ECRI analysis?

Since its founding as a nonprofit, independent, health technology research agency almost 30 years ago, ECRI’s mission has been to improve patient care. The following recommendations are intended to protect you and other patients facing similar circumstances, while enabling the scientific community to pursue the research needed to obtain answers about this therapy’s efficacy.

- Patients should be fully informed of the risks of HDC with ABMT/BCT and the uncertainties surrounding their prognoses, based on the complete body of clinical evidence to date and not on limited views. This Patient Reference Guide, produced in collaboration with the nationally recognized women’s health and patient advocacy groups listed on the cover, was published and made available to patients and their families free of charge for this purpose.

- The medical community and the public should be informed that the treatment’s effectiveness is unproven as yet and that there are potentially significant risks related to HDC with ABMT/BCT therapies reported in published studies. The 200-page report from which this Patient Reference Guide is derived is available for purchase by hospitals, medical centers, and other institutional organizations on a sliding-scale fee. Funds from the report are used by ECRI to support the cost of the research and to make the Patient Reference Guide available free of charge to patients and their families. The report has also been shared with public policy makers and has been given to editors at one of the world’s leading medical journals, The Lancet, for additional scientific review and comment.

- ECRI believes that science and individual patients would be best served if HDC with ABMT/BCT therapies for patients with stage IV breast cancer were limited to active randomized controlled clinical trials so that patients and the healthcare community can learn if it offers a benefit over standard-dose therapy. Informed consent for patients should include results of comprehensive analyses for overall survival and disease-free survival times; these analyses should include so-called “early deaths.”

- Published results of randomized controlled clinical trials comparing HDC with ABMT/BCT and standard-dose chemotherapy regimens must include appropriate statistical analyses to determine whether differences in outcomes are due to patient selection rather than differences in therapy.

- A comprehensive analysis of all breast cancer data in the Autologous Blood & Marrow Transplant Registry — North America should be performed and published. This analysis should compare outcomes of patients given HDC with ABMT/BCT to a similar group of patients who have received standard-dose chemotherapy.

- The quality of the medical literature on HDC with ABMT/BCT for metastatic and all other stages of breast cancer should be improved. Editors of research journals should ensure that studies adequately report details of patient characteristics and outcome measurements. Studies that are published only as “meeting abstracts” should not be considered “valid scientific evidence.” Abstracts are one- or two-paragraph summaries of a clinical study and have not been peer reviewed by appropriate experts in the medical community as to their quality and credibility.

- In view of the results thus far for patients with stage IV breast cancer, results for patients in earlier stages may also be poor. It is therefore recommended that patients in earlier stages of breast cancer enroll only in well-designed clinical trials.
Some other resources for information and support for patients and their families

ECRI is pleased to provide this guide as a public service to patients and their families; however, the research agency does not have the resources to respond to calls from individual patients. This resource list is provided to guide you to agencies that can respond to patient inquiries.

This list is a very brief and general listing of some national resources for cancer information and support. Hundreds of organizations nationwide provide information, and the organizations and sources listed below can refer patients to additional and local resources.

American Cancer Society Response Line
(800) 227-2345
(301) 929-8243
Provides publications and information about cancer and coping with cancer. Refers callers to local chapters for support services. 8:30 a.m. to 5:00 p.m. (East Coast time).

National Cancer Institute Cancer Information Service
Office of Cancer Communications
Building 31, Room 10A16
9000 Rockville Pike
Bethesda, MD 20892
1-800-4-CANCER
CancerFax 1-301-402-5874
Provides accurate, up-to-date information about cancer, treatment, ongoing clinical trials, and cancer-related resources by phone and CancerFax to patients, the public, and health professionals. CancerFax can be accessed 24 hours a day, 7 days a week, for only the cost of the telephone call. An online database, PDQ, is also part of the system. It includes information about clinical trial protocols, a directory of physicians and organizations that offer cancer care, and brief summaries from the medical literature. Cancer information specialists staff the Cancer Information Service and distribute free publications from the National Cancer Institute. 9:00 a.m. to 7:00 p.m. (East Coast time).

Y-ME National Breast Cancer Organization
Chicago, IL
(800)221-2141
(312)986-8228
Y-ME provides patients with presurgery counseling, treatment information, peer support, self-help counseling, and patient literature. The organization also offers information to any and all women concerned about breast health and breast cancer. Y-ME is one of the 300 national organizations that are part of the National Breast Cancer Coalition (see below). Toll-free 9:00 a.m. to 5:00 p.m. (Central time); local number operates 24 hours a day.

National Women’s Health Network (NWHN)
1325 G Street, N.W.
Washington, DC 20005
(202) 347-1140
NWHN offers many publications for healthcare consumers on many aspects of women's health, including breast cancer.

National Alliance of Breast Cancer Organizations (NABCO)
9 East 37th Street, 10th Floor
New York, NY 10016
(212) 719-0154
NABCO publishes a comprehensive Breast Cancer Resource List, fact sheets, and a quarterly newsletter. The $40 annual membership dues are tax-deductible and include a resource guide and newsletter.

National Breast Cancer Coalition
P.O. Box 66373
Washington, DC 20035
(202) 296-7477
This national coalition of more than 300 groups (including NABCO) was founded in 1991.
to coordinate a national grassroots political action plan to bring about change in public policy. Goals include increasing breast cancer research funding for well-designed clinical trials, educating advocates about how to read and understand statistics and the medical literature, improving access to breast cancer screening, and expanding the role of well-informed healthcare consumer advocates in formulating national research agendas and policy. If you are interested in engaging in political activities, the organization welcomes individual members as well as organization members.

National Coalition for Cancer Survivorship
1010 Wayne Avenue, 7th Floor
Silver Spring, MD 20910
(301) 650-8868

This is a national network of independent groups and individuals concerned about life after cancer diagnosis and treatment and quality of life after cancer. It offers support to patients and families.

Dr. Susan Love's Breast Book
Second Edition
Susan M. Love, M.D., with Karen Lindsey


This best-selling patient information book about breast cancer was revised, expanded, and updated in 1995. Written by a practicing breast surgeon, it contains information on healthy breasts, benign breast conditions, and the diagnosis, treatment options, and prognosis for every stage of breast cancer. Patient experiences with the various treatment options are interspersed throughout the book. Dr. Love also discusses the emotional issues of patients, as witnessed by her experience as a doctor treating breast cancer. She also discusses research issues, clinical trials, alternative therapies, and the politics of breast cancer. Appendixes include an extensive resource list for patients and their families.

Some online support services

Patient information about breast cancer therapies is posted and discussed on many electronic bulletin boards. Places to find information include the National Cancer Institute's PDQ, CancerNet, and CancerFax; Oncolink; and the Breast Cancer mail list (BREAST-CANCER@MORGAN.UCS.MUN.CA) accessed through the Internet and on the CompuServe Cancer Forum Section 3.
These terms are related to HDC with ABMT/BCT. Vague or inadequate definitions of some terms have contributed to misunderstanding about the procedure, remission rates of the cancer, and patient survival rates. This glossary is intended to clarify meanings of important terms for patients.

ABSTRACTS: As used in this Guide, an abstract is a summary of a clinical trial presented at a scientific meeting. Usually abstracts have not undergone review by other scientists for accuracy or reliability of the trials’ methods and results.

ADJUVANT THERAPY: Pharmacologic or radiation therapy that is given to a patient with cancer after all the detected tumor has been surgically removed. The intent of adjuvant therapy is to try to kill cancer cells that may be left, but undetected.

AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT): One of two basic methods of stem cell rescue performed on patients undergoing high-dose chemotherapy. Under general anesthesia, bone marrow is removed from the patient’s hip, processed, frozen, and stored. The transplantation occurs within 72 hours after high-dose chemotherapy when the bone marrow is thawed and returned to the patient intravenously. The purpose is to regenerate the blood cell-producing system that has been wiped out by very high doses of chemotherapy. (See also: BLOOD CELL TRANSPLANTATION, AUTOLOGOUS STEM CELL RESCUE, STEM CELLS.)

AUTOLOGOUS STEM CELL RESCUE: A procedure to harvest a quantity of blood cell producing cells from a patient who is to undergo high-dose chemotherapy. Cells may be obtained from the patient’s bone marrow or circulating blood. The procedure is considered a support technique that enables high doses of chemotherapy to be given to a patient. (See also: AUTOLOGOUS BONE MARROW TRANSPLANTATION, BLOOD CELL TRANSPLANTATION, STEM CELLS.)

BIAS: In a scientific study, any factor or conscious or unconscious predisposition of the researcher(s) that distorts events or findings and conclusions and thus jeopardizes the study’s validity.

BIOPSY: A sample of tissue that is removed from the patient’s tumor for examination to determine if it is cancerous and what type of cancer it is.

BLOOD CELL TRANSPLANTATION (BCT): One of two basic methods of stem cell rescue performed on patients undergoing high-dose chemotherapy. Stem cells are removed from the patient’s circulating blood through an intravenous needle and tubing that is connected to a collection bag. Several collection sessions are usually needed to obtain a sufficient quantity of stem cells. No anesthesia is required. The collected cells are processed, frozen, and stored. Transplantation occurs within 72 hours after high-dose chemotherapy. The stem cells are thawed and returned to the patient intravenously to restore the blood cell producing system that has been wiped out by high-dose chemotherapy. (See also: AUTOLOGOUS BONE MARROW TRANSPLANTATION, AUTOLOGOUS STEM CELL RESCUE, STEM CELLS.)

BONE MARROW: The soft organic material that fills the inside of the bones. The various types of blood cells (e.g., red and white cells) are produced in the bone marrow.

CLINICAL TRIAL: A planned scientific effort to study the effects of a drug, procedure, or device on selected patients, usually with respect to safety and efficacy. The design, purpose, length, patient selection, methods, intervention, endpoints, and the conditions under which the trial will be stopped are defined in a protocol.

• CONTROLLED TRIAL is a study designed to compare the outcomes or results of two different treatments. In the context of HDC with ABMT/BCT, it typically takes the form of a group that receives a standard-dose treatment and a group that receives the experimental treatment, or two groups that receive different HDC regimens.
PHASE I, II, III clinical trials are conducted on investigational new drugs to meet safety and efficacy requirements established by the Food and Drug Administration (FDA) before the drug can be used outside a clinical trial research setting. Clinical trials are also conducted to determine if a new procedure (that may include using FDA-approved drugs) is more efficacious than an existing procedure. Phase I establishes the safety and dosage in a small number of healthy volunteer subjects (or, in the case of cancer drugs, consenting patients with cancer that has failed to respond to all other treatment may be included); Phase II establishes safety and efficacy in a limited number of patients with the condition that the drug or procedure is intended to treat; and Phase III evaluates longer-term safety and efficacy of the drug or procedure and looks for uncommon adverse reactions.

FDA does not regulate medical or surgical procedures. After a drug has received FDA approval, physicians can exercise clinical discretion in how they use the drug. In the case of high-dose chemotherapy for breast cancer, the drugs used are FDA approved for the treatment of cancer. However, the high-dose regimens that have evolved are not subject to FDA regulation (i.e., clinical trials for safety and efficacy). Therefore, physicians can use the procedure without having evidence to prove that it works. Some physicians are investigating the efficacy of high-dose chemotherapy for breast cancer treatment in the context of clinical trials; many others are not.

RANDOMIZED CONTROLLED TRIALS involve assigning patients to different treatment groups with no predetermination as to which group they will be in. The goal is to eliminate possible bias in a study. Results from a well-designed and conducted randomized controlled trial are generally considered to be more credible than those of other types of clinical trials.

COLONY-STIMULATING FACTORS (CSF): Natural compounds made by the body that regulate the development of certain blood cells into mature white blood cells. There are various types of colony-stimulating factors to stimulate development of particular types of white blood cells. CSFs are commercially manufactured by means of recombinant biotechnology.

DISEASE-FREE SURVIVAL: The period of time during which a patient is completely free of detectable tumor after therapy. This may also be called the response duration. Disease-free does not mean a cure has been achieved.

EARLY DEATHS: A term used in published studies to describe patients who have died within 30 days after receiving HDC. In many published studies of HDC with ABMT/BCT, researchers excluded “early deaths” from results on survival.

EFFECTIVENESS: Effectiveness describes how well a test or treatment works when doctors use it on their patients in routine daily practice, outside a research setting. Effectiveness tells us how well a therapy works on a broader range of patients in everyday practice.

EVALUABLE PATIENTS: This refers to those patients who were enrolled in a study, received the therapy, and were available for follow-up. (Usually, studies on HDC with ABMT/BCT for metastatic breast cancer did not consider evaluable those patients who died within 30 days of treatment. Some of these patients may die from multiple causes.)

GROWTH FACTORS: This is a general term to describe naturally occurring compounds in the body that promote the growth of different kinds of cells, including colony-stimulating factors, as well as other biologic agents (such as interleukin).

HDC WITH ABMT/BCT: The abbreviation often used to denote “high-dose chemotherapy with autologous bone marrow transplantation and/or blood cell transplantation.” The therapy is also often referred to simply as “ABMT,” which omits an important part of the treatment, the chemotherapy.

HEMATOPOIETIC SYSTEM: The system in the body that forms and develops blood cells.

HIGH-DOSE CHEMOTHERAPY: A regimen of anticancer chemicals that is given at 2 to 10 times the standard dosage recommended on the product labeling (see: STANDARD-DOSE CHEMOTHERAPY).
INDUCTION THERAPY: A course of chemotherapy (at a lower dosage than high dose) given to patients to try to determine how likely their cancer is to respond to high-dose chemotherapy with stem cell transplantation. This is often a critical step in patient selection for the high-dose procedure.

INFORMED CONSENT: A written description of the protocol of a clinical trial that the researchers must give and fully explain to any patient who is entering their clinical trial. The consent describes the purpose of the study, details of the treatment, the length of treatment, how often patients will be monitored, what types of monitoring will be done (such as blood tests or electrocardiograms), what the patient's responsibilities are during the trial, and what if any care or referral for further care will be given after the trial. The consent form must also describe potential risks and adverse effects of the treatment. If, after reading and discussing the consent form, the patient decides to enter the trial, the patient signs the consent form and is given a copy for her (or his) records.

MEDIAN: The point that divides the distribution into two parts such that an equal number of values falls above and below the point. For example, if the median survival time for patients in a study is six months — half of the patients had survival times of six months or longer and half had survival times of less than six months.

MEDICAL LITERATURE: This generally refers to articles published in peer-reviewed medical journals. Peer-reviewed journals use panels of experts in medicine and science to review studies submitted for publication to determine the quality of the study and its results and conclusions. Studies are accepted or rejected for publication on the basis of peer review.

META-ANALYSIS: A systematic way of statistically pooling the results from many clinical studies to obtain an estimate of the overall effect of a particular therapy or variable on a specific outcome.

METASTASIS: The spread of cancer cells from one organ or part to another not directly connected to it. Cancer cells may spread by traveling through the lymph or blood system. Local metastasis means the spread to tissue or organs next to the primary cancer; regional metastasis involves nearby lymph nodes in addition to adjacent tissue or organs, and distant metastasis involves transfer of cancer cells to tissue or organs not adjacent to the point of origin of the disease. Metastatic describes cancer that has spread.

PATIENT ADVOCATE: A person trained in helping patients to obtain the information they need and want to make decisions about their healthcare. The advocate discusses with the patient (and possibly her family) her preferences and represents the patient's view to members of the healthcare team, as requested by the patient (e.g., when the patient is unable to do so) or her family.

PATIENT CHARACTERISTICS: Important medical characteristics that affect a patient's prognosis and treatment. In breast cancer, important patient characteristics include the stage of cancer, the number and sites of metastases, estrogen receptor status, age, and menopausal status.

PHASE I, II, III CLINICAL TRIAL: (See: CLINICAL TRIAL.)

PRIMARY CANCER: The site in the body where the cancer first developed.

PROGNOSIS: A forecast of the most likely outcome of a disease based on statistical analysis of groups of similar patients.

PROGRESSION-FREE DURATION: The period of time during which the patient's disease remains stable (i.e., the tumor does not grow or spread). A progression-free duration may occur with a complete or partial response. (See also: DISEASE-FREE SURVIVAL, RESPONSE.)

PROTOCOL: A description of the details of the design, methods, treatment course (dosage, timing of dosage, etc.), and follow-up care to be given to patients in a clinical trial by the researchers conducting the study.

PURGING: In the context of HDC with ABMT/BCT, this is the attempt to remove all cancer cells from the stem cells that have been collected from the patient before the stem cells are given back to the patient. There are many methods currently being used for purging, but no randomized controlled trials have compared the outcomes of patients receiving purged versus unpurged stem cells or of the purging method that works best.

RANDOMIZED CONTROLLED TRIAL: (See: CLINICAL TRIAL.)

RECEPTOR: A molecule on the surface or within a cell that recognizes and binds with specific molecules and then has a certain effect on the cell. Estrogen- or progesterone-positive receptors are cells to which
HDC with ABMT/BCT

these hormones bind. Being estrogen receptor negative means that estrogen does not bind to your cells.

RESPONSE: This is the degree to which a cancerous tumor shrinks after anticancer therapy (see: RESPONSE RATES). Researchers categorize responses as follows:

- COMPLETE RESPONSE (CR): The disappearance of all measurable or assessable cancer for at least 30 days.
- PARTIAL RESPONSE (PR): A 50% or greater reduction in the size of measurable cancer or markers for the tumor for at least 30 days.

RESPONSE DURATION: The period of time during which patients completely or partially respond to a therapy. It is important to note whether a study defines this period from the time of induction to the progression of disease or the time of HDC to the time of relapse.

RESPONSE RATES: The number of patients whose tumors are reduced or eradicated divided by the total number of evaluable patients. Response rates do not address quality of life or duration of survival time. A cancer may initially respond to chemotherapy, but the response may not last. Researchers categorize response rates as follows:

- COMPLETE RESPONSE RATE: The number of patients whose cancer completely responded divided by the total number of evaluable patients.
- OBJECTIVE RESPONSE RATE: The number of patients whose cancer completely responded plus the number of patients whose cancer partially responded divided by the total number of evaluable patients.
- PARTIAL RESPONSE RATE: The number of partial-response patients divided by the total number of evaluable patients.

STANDARD-DOSE CHEMOTHERAPY: Anticancer chemicals that are given in the dosage recommended on the product labeling, based on data from clinical trials conducted to establish the safety and efficacy of the drugs. However, clinicians may increase dosages at their discretion, based on the individual patient's characteristics. Generally, standard dosages given currently are higher than those given a few years ago. The Food and Drug Administration requires data from clinical trials on new drugs to consider them for approval for commercial marketing.

STAGING: The assessment and definition of cancerous tumor size and involvement in organs and tissue, represented by the assignation of numbers “0” (earliest) through “IV” (most advanced). Further subclassifications are denoted by letters descriptive of the location and extent of the cancer in lymph nodes and other organs.

STATISTICALLY SIGNIFICANT: An index of how likely it is that a particular result in a clinical study is due to chance, rather than being caused by the effects of the treatment under study. A result is statistically significant if there is a 95% or greater likelihood that the observed results were caused by the treatment and not by chance.

STEM CELLS: Cells that have the potential to develop into one of the body's three basic types of blood cells — red cells, white cells, or platelets.

SURVIVAL RATE: Of all those given a treatment, the percentage of patients who survived the treatment. One-, two-, and three-year survival rates for HDC with ABMT/BCT are calculated using the number of treated patients who are alive at a given point in time divided by the total number of patients who were given the treatment. Survival rates beyond three years have not been calculated because no published studies have followed up on patients long enough to perform these calculations.

SURVIVAL TIME: The length of time a patient lives after induction or HDC with stem cell transplantation. (For patients, it is important to know whether survival is being measured from the time of induction or HDC.) Survival times are sometimes projected based on data from studies. In published studies on HDC for breast cancer, patients who died within 30 days of treatment were usually excluded from the calculations. This could create a misleading impression that HDC with ABMT/BCT improves survival time.

TOXICITY: The degree to which a drug or treatment is toxic or causes side effects.

TRANSPLANTATION: In the HDC with ABMT/BCT procedure, transplantation involves reinfusing the bone marrow/stem cells, which were preserved in a special type of plastic bag, through an intravenous line into the patient.
How ECRI selected studies for this analysis

Studies of HDC with ABMT/BCT for stage IV breast cancer were selected if they met the following basic criteria:

1. The study was a PHASE II OR III TRIAL (or not explicitly defined by its authors as a PHASE I TRIAL (see glossary: CLINICAL TRIALS); phase I trials determine the basic safety of a drug, not whether or how well it works).

2. The study used more than one HDC agent (this criterion was used because studies using only one agent tended to be phase I studies).

3. The study included five or more patients.

Forty studies (1,017 patients) met these criteria. Eighteen of the 40 studies were published only as ABSTRACTS from scientific meetings and lacked complete data or study descriptions. Unfortunately, studies published in peer-reviewed medical journals were also frequently missing important data on patient characteristics and outcomes.

To select studies of standard-dose chemotherapy for comparison, ECRI examined all published randomized controlled trials from 1976 to 1994 that compared different standard-dose therapies for metastatic (stage IV) breast cancer. Only randomized controlled trials were chosen because they usually reported patient-entry characteristics more thoroughly than uncontrolled trials. Initially, 78 standard-dose chemotherapy studies were identified. From these, 35 studies with patients similar to those in the HDC with ABMT/BCT studies were selected. The standard-dose studies used met the following additional criteria:

1. Each had 2 or more treatment groups receiving different conventional regimens; 61 treatment groups within the 35 studies were used, and they included 4,889 patients.

2. Studies of patients receiving hormonal treatments were excluded because the patients were not similar to patients who are given HDC with ABMT/BCT (i.e., HDC patients typically haven’t ever been given hormonal therapy).

3. Treatment groups in studies were not used if they excluded premenopausal patients.

4. Studies were not selected in which 20% or fewer of the patients achieved a partial or complete remission.

5. Studies were excluded that had fewer than 20 patients.

ECRI also excluded studies that were apparent duplications (reporting of the same patients by the same authors in different publications); that did not specify any response rates, durations, or survival outcomes; and that combined the results of patients whose cancer had spread with patients whose cancer had not spread.
## APPENDIX B

### Anticancer Drugs Used in High-dose Chemotherapy for Breast Cancer and Side Effects*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan</td>
<td>Nausea and vomiting; rare diarrhea</td>
<td>Bone marrow depression; pulmonary infiltrates and fibrosis (lung damage); hair loss; ovarian failure; hyperpigmentation; leukemia; chromosome aberrations; cataracts; hepatitis; seizures and veno-occlusive disease</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Nausea and vomiting</td>
<td>Bone marrow depression; hearing loss; transient cortical blindness; hemolytic anemia; rarely peripheral neuropathy (nerve damage and altered sensation)</td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>Nausea and vomiting; phlebitis in veins around intravenous site</td>
<td>Delayed (and possibly prolonged) leukopenia and thrombocytopenia (blood disorders); pulmonary fibrosis that may not be reversible; temporary liver damage; leukemia; decreased blood flow through the heart</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Nausea and vomiting; anaphylaxis; facial burning with intravenous administration; blurring of vision</td>
<td>Bone marrow depression; hair loss; bone marrow depression; hearing loss; transient cortical blindness; hemolytic anemia; rarely peripheral neuropathy (nerve damage and altered sensation)</td>
</tr>
<tr>
<td>Doxorubicin HCl</td>
<td>Nausea and vomiting; urine turns red (but not from blood); severe local tissue damage and decay; diarrhea; fever; transient changes in the ECG, irregular heart beat; anaphylaxis</td>
<td>Bone marrow depression; heart toxicity (may not show up for several years); hair loss; inflammation of tissues inside the mouth; loss of appetite; conjunctivitis (inflammation of eyelid tissue)</td>
</tr>
<tr>
<td>Etoposide (VP16)</td>
<td>Nausea and vomiting; diarrhea; fever; very low blood pressure; allergic reaction; phlebitis at infusion site</td>
<td>Bone marrow depression; rashes, hair loss; peripheral neuropathy; liver damage</td>
</tr>
<tr>
<td>Fluorouracil (5-FU)</td>
<td>Nausea and vomiting; confusion; kidney toxicity; heart toxicity</td>
<td>Bone marrow depression; diarrhea; brain defects; irregular heart beat; angina pectoris; hair loss; skin discoloration; inflammation of eyelid tissue; heart failure; seizures</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Mild nausea; hypersensitivity</td>
<td>Bone marrow depression (especially platelets); pulmonary infiltrates and fibrosis; cessation of menstruation; sterility; leukemia</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Nausea and vomiting; diarrhea; fever; anaphylaxis; death of liver tissue; Severe ulcers in the mouth and intestines</td>
<td>Bone marrow depression; liver toxicity, including cirrhosis; kidney toxicity; pulmonary infiltrates and fibrosis; osteoporosis; hair loss; skin discoloration; irregular menstrual function; infertility; lymphoma</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Nausea and vomiting; tissue death; fever</td>
<td>Bone marrow depression; inflamed mouth tissues; hair loss; lung, liver, and kidney toxicities; cessation of menstruation; hemolytic-uremic syndrome (a condition related to kidney failure); deposit of calcium salts in the bladder</td>
</tr>
</tbody>
</table>
## Anticancer Drugs Used in High-dose Chemotherapy for Breast Cancer and Side Effects*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone HCl</td>
<td>Blue-green color to urine and the white part of the eyeballs; nausea and vomiting; inflamed mouth tissues; phlebitis</td>
<td>Bone marrow depression; heart toxicity; hair loss; white hair; skin damage; liver damage; kidney failure</td>
</tr>
<tr>
<td>Paclitaxel (Taxol)</td>
<td>Anaphylaxis; breathing difficulty; very low blood pressure; large wheals from inflamed tissues deep beneath the skin; hives</td>
<td>Bone marrow depression; peripheral neuropathy; hair loss; muscle pain, heart toxicity; upset stomach</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Hot flashes; nausea and vomiting; transient increased bone or tumor pain; excess calcium in the blood</td>
<td>Vaginal bleeding and discharge; rash; thrombocytopenia (a bleeding disorder); fluid retention; depression; dizziness; headache, decreased visual acuity; diseases of the eye; blood clots; endometrial cancer</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Nausea and vomiting; rarely, hypersensitivity</td>
<td>Bone marrow depression; irregular menstruation; leukemia; excess production of mucous</td>
</tr>
<tr>
<td>Vinblastine sulfate</td>
<td>Nausea and vomiting; tissue damage and discharge</td>
<td>Peripheral neuropathy; hair loss; mild bone marrow depression; constipation; jaw pain; wasting away of eye tissue</td>
</tr>
</tbody>
</table>

*Side-effects are in order of most commonly occurring. Not all patients experience all side effects.

## APPENDIX C

### High-dose Chemotherapy Combinations for Treating Metastatic Breast Cancer Reported in Published Studies

<table>
<thead>
<tr>
<th>Chemotherapy Combination</th>
<th>High-dose Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYC + DOX</td>
<td>Cyclophosphamide 750 mg/m^2 + Doxorubicin 70 mg/m^2</td>
</tr>
<tr>
<td>CYC + TTP</td>
<td>Cyclophosphamide 2.5 g/m^2 (over 3 days) + Thiotepa 225 mg/m^2 (over 3 days)</td>
</tr>
<tr>
<td>CYC + HDB</td>
<td>Busulfan (16 mg/kg) + Cyclophosphamide (6 gm/m^2)</td>
</tr>
<tr>
<td>CYC + BCNU</td>
<td>Cyclophosphamide 160 mg/kg + Carmustine 600 to 900 mg/m^2</td>
</tr>
<tr>
<td>CYC + VP-16</td>
<td>Cyclophosphamide 7 g/m^2 + Etoposide 1.5 g/m^2</td>
</tr>
<tr>
<td>CYC + MXT</td>
<td>Cyclophosphamide 1.55 g/m^2/day for 2 days + Mitoxantrone 8 to 12 mg/m^2/d for 4 days</td>
</tr>
<tr>
<td>DOX + 5-FU</td>
<td>Adriamycin 150 mg over 2 days + 5-fluorouracil 1,500 mg over 2 days</td>
</tr>
</tbody>
</table>

HDC with ABMT/BCT
## APPENDIX D

### Comparison of Standard and High-dose Chemotherapy by Dosage

<table>
<thead>
<tr>
<th>Chemotherapy Drug</th>
<th>Standard Dose (mg/m$^2$)</th>
<th>High Dose with ABMT/BCT (mg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>400</td>
<td>2,000 to 2,400</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>60-100</td>
<td>200</td>
</tr>
<tr>
<td>Carmustine</td>
<td>200</td>
<td>1,200</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500 to 1,000</td>
<td>7,500</td>
</tr>
<tr>
<td>Etoposide</td>
<td>300 to 600</td>
<td>2,400 to 2,700</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>5,000</td>
<td>18,000</td>
</tr>
<tr>
<td>Melphalan</td>
<td>40</td>
<td>225</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>15 to 50</td>
<td>1,125 to 1,575</td>
</tr>
</tbody>
</table>