JOINT LEGISLATIVE AUDIT AND REVIEW COMMISSION
OF THE VIRGINIA GENERAL ASSEMBLY

EVALUATION OF PROPOSED MANDATED HEALTH INSURANCE BENEFITS

Evaluation of SB 991 and HB 2426: Repeals of Mandated Offer for Autologous Bone Marrow Transplant or Stem Cell Transplant for Breast Cancer

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JLARC provides evaluations of proposed health insurance mandates in accordance with Sections 2.2-2503 and 30-58.1 of the *Code of Virginia*.

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Evaluation of SB 991 and HB 2426: Repeals of Mandated Offer for Autologous Bone Marrow Transplant or Stem Cell Transplant for Breast Cancer

JLARC SUMMARY

High dose chemotherapy (HDC) with an autologous bone marrow transplant (ABMT) or a stem cell transplant (SCT) is a procedure involving the administration of a toxic dose of chemotherapy to kill cancer cells, followed by ABMT or SCT to reduce the effects of the treatment on the patient's body. In the mid-1990s, oncologists believed this treatment would provide greater therapeutic benefit than conventional therapy to patients with the most serious forms of breast cancer. However, recent clinical research has determined that HDC-ABMT/SCT provides no additional benefit over conventional chemotherapy. SB 991 and HB 2426 would repeal provisions of Virginia's mandated offer of this procedure to reflect this research and eliminate a possibly obsolete statute.

MEDICAL EFFICACY AND EFFECTIVENESS

Clinical trials have found that high dose chemotherapy with autologous bone marrow transplant or stem cell transplant (HDC-ABMT/SCT) offers no additional benefit to breast cancer patients over conventional chemotherapy. Additionally, patients receiving HDC-ABMT/SCT are more likely to experience treatment-related complications than patients receiving conventional chemotherapy.

In This Evaluation

Appendixes

Today, most health care experts recommend that breast cancer patients only receive HDC-ABMT/SCT in the context of a well-designed clinical study. Although HDC-ABMT/SCT does not offer additional benefit to breast cancer patients, the treatment does offer additional benefit to people suffering from other diseases, such as Hodgkin's disease, multiple myeloma, neuroblastoma, or leukemia.

SOCIAL IMPACT

Since the release in 2000 of findings from clinical trials indicating that HDC-ABMT/SCT does not provide breast cancer patients additional benefits, the use and availability of the treatment have greatly decreased. Only three medical facilities in Virginia have dedicated bone marrow and stem cell transplant programs. JLARC staff did not find any evidence to indicate that physicians are currently using HDC-ABMT/SCT for breast cancer patients in Virginia. Further, JLARC staff did not find any evidence that insurance companies have paid claims for Virginia breast cancer patients to receive HDC-ABMT/SCT since 2003. If the mandate were repealed, it is likely that many insurance companies would drop coverage for this treatment. Patients who access the treatment through a clinical trial, as recommended by most medical experts, would still have coverage under the clinical trials mandate; however, patients accessing the treatment outside a clinical trial would be likely to face financial hardship since the treatment costs from 140 to 285 percent of Virginia's median household income.

FINANCIAL IMPACT

The proposed repeals would not have a significant financial impact. Physicians and patients have already stopped using the treatment, so demand is unlikely to decrease any further as a result of the proposed repeals. Due to the already diminished demand for the treatment, the mandate's premium impact is low. Therefore, repealing the mandate is likely to have a very small, if any, premium impact.

BALANCING MEDICAL, SOCIAL, AND FINANCIAL CONSIDERATIONS

Given the potentially catastrophic financial impact to an individual or family for obtaining HDC-ABMT/SCT, the current mandate is consistent with the role of insurance. Although this mandate is consistent with the role of insurance, the need for the mandate appears to be minimal. While the cost of the mandate appears to be relatively low and similar to other mandates, it is necessary to consider whether it is appropriate for the State to mandate a very

specific procedure that has a very low demand and utilization rate. Additionally, according to medical experts, most breast cancer patients receiving HDC-ABMT/SCT do not experience any superior results to breast cancer patients receiving conventional chemotherapy or newer types of treatment.

JLARC Evaluation of SB 991 and HB 2426: Repeals of Mandated Offer for Autologous Bone Marrow Transplant or Stem Cell Transplant for Breast Cancer

Senate Bill 991 of the 2007 General Assembly Session would repeal provisions in §38.2-3418.1:1 of the *Code of Virginia* that require health insurers, health care subscription plans, and health maintenance organizations to offer and make available coverage for the treatment of breast cancer by high dose chemotherapy (HDC) and autologous bone marrow transplant (ABMT). SB 991 would leave intact the provision of this section that requires health insurers to offer coverage for the treatment of breast cancer by stem cell transplants (SCT).

House Bill 2426 of the 2007 General Assembly Session would repeal §38.2-3418.1:1 of the *Code of Virginia* in its entirety. Passage of this bill would mean that health insurers, health care subscription plans, and health maintenance organizations would no longer be required to offer coverage of high dose chemotherapy with an autologous bone marrow transplant or stem cell transplant (HDC-ABMT/SCT) for the treatment of breast cancer.

BACKGROUND

When HDC-ABMT/SCT was introduced in the early to mid 1990s, it represented a potentially life-saving procedure for patients with the most serious forms of breast cancer. When insurers refused to pay for this treatment that they considered experimental, some patients sued their insurance companies. As a result, ten states, including Virginia, mandated that insurance companies provide or offer coverage of this treatment for breast cancer. By the early 2000s, five major clinical trials demonstrated that HDC-ABMT/SCT provided no additional benefit over conventional chemotherapy and it increased the risk of serious side effects. As a result, one of the ten states, Minnesota, which mandated that insurance companies provide or offer coverage for HDC-ABMT/SCT, repealed its mandate in 2004. HB 2426 and SB 991 seek to repeal the Virginia mandate because of this new evidence. These bills would not prevent insurers from continuing to offer coverage for the treatment, but they would not be required to do so.

a. Description of Medical Condition and Proposed Treatment

HDC-ABMT/SCT is a procedure for treating the most serious forms of breast cancer; however, today it has largely fallen out of use as a breast cancer treatment.

Breast Cancer. Cancer is a term for diseases in which abnormal cells in the body grow and divide without control. Thus, breast cancers are cancers that begin in the tissues of the breast, usually the ducts (tubes that carry milk to the nipple) or lobules (structures that make milk). Eventually, these cells form a mass or tumor. Tumors can be either benign (e.g., they continue to grow in size but do not affect adjoining tissue) or malignant (e.g., they can invade and destroy nearby tissue or spread to other parts of the body).

Malignant breast cancer can have four stages. The first and least severe stage, known as *in situ* or stage I breast cancer, is a malignant tumor that does not penetrate the surrounding tissue. The second stage, known as local or stage II breast cancer, is an invasive tumor that has not spread beyond the site of origin. Regional or stage III breast cancer is a tumor that has spread to immediately adjacent organs or tissues, or has metastasized (i.e., created secondary tumors), or spread to local lymph nodes. Stage IV, or metastatic breast cancer is a tumor that has spread by direct extension beyond the immediately adjacent organs or tissues, and/or has metastasized to distant lymph nodes or other distant organs.

Stage IV or metastatic breast cancer is generally considered incurable. According to the American Cancer Society, only 20 percent of patients diagnosed with metastatic breast cancer survive five or more years after their diagnosis. Metastatic tumors spread when cells break off and enter the blood stream. The cells then form a new tumor in a different organ, which is called a metastatic tumor. The cells of the metastatic tumor are the same as the cells of the primary tumor. For example, if breast cancer cells spread and formed a tumor on the brain, the tumor on the brain would be called a metastatic breast cancer tumor. Metastatic breast cancer most commonly spreads to the bones, liver, lungs, and brain. Certain treatments can, however, help increase chances of long-term survival, decrease morbidity, and increase quality of life for metastatic breast cancer patients.

The exact causes of breast cancer are unknown; however, middle-aged Caucasian women appear to be most at risk for developing the disease. Men rarely develop breast cancer. Many other factors also appear to be associated with developing breast cancer, including a family history of the disease, hormone therapy use, obesity,

alcohol use, early menarche, late menopause, oral contraceptive use, not having breastfed, and not having given birth.

The treatment regimen that a breast cancer patient receives depends on the stage and other characteristics of her cancer. Most patients will receive a combination of surgery, radiation therapy, chemotherapy, targeted therapy, and hormone therapy.

High Dose Chemotherapy (HDC) with Autologous Bone Marrow Transplant (ABMT) or Stem Cell Transplant (SCT). Chemotherapy is a drug regimen administered to kill cancer cells. To maximize the number of cancer cells killed by chemotherapy, patients are given the highest doses of chemotherapy they can tolerate, but in standard chemotherapy, the doses are limited to spare the toxic effects of these drugs on the bone marrow and stem cells (stem cells are bone marrow cells that mature into blood cells). Without healthy bone marrow and stem cells, new blood cells are not produced, and the patient's body is unable to fight infection, becomes anemic or has a high risk of bleeding. As a result, very high does of chemotherapy cannot be administered outside of special circumstances because it leaves the patient susceptible to infection.

HDC-ABMT/SCT is based on the theory that more intensive dose chemotherapy will kill more cancer cells. HDC-ABMT/SCT is a way to overcome the problem of administering more effective cancer killing doses of chemotherapy without causing permanent or lethal damage to normal tissues, such as the bone marrow and stem cells. Before beginning HDC, adult bone marrow or peripheral stem cells are harvested from the patient in one of two ways. One method is through bone marrow transplant, which is a surgical procedure that is usually performed while the patient is under general anesthesia. The transplant physician inserts a needle into the patient's pelvic hip bone and extracts bone marrow. Once enough marrow has been collected, the marrow and stem cells are processed and frozen until they are needed.

The second method used to collect stem cells is called peripheral blood stem cell transplant. For this procedure, the patient receives daily injections of a drug to stimulate the stem cells to move or "mobilize" from the bone marrow into the blood stream. Once daily blood counts show that enough stem cells have mobilized from the marrow into the blood, the patient undergoes a procedure called apheresis. This involves taking blood from the patient, running it through a machine to separate blood cells from stem cells, and then returning the blood cells to the patient. Once the appropriate dose of stem cells has been collected, they are processed and frozen.

After the stem cells have been harvested or collected, the patient receives the HDC treatment. HDC more effectively destroys the cancer cells but also destroys the patient's bone marrow and stem cells as a side effect of the chemotherapy intensity, preventing the patient's body from producing new, healthy blood cells and thus compromising the patient's ability to fight infection. To restore the patient's bone marrow and stem cells, the stored stem cells are thawed and transfused into the patient, in the same way a patient would receive a blood transfusion. The idea is that the stem cells will migrate back into the marrow-bearing bones, replace the missing marrow and begin producing healthy new blood cells, restoring the patient's ability to fight infection.

b. History of Proposed Mandate

HDC-ABMT/SCT emerged in the early to mid 1990s as a promising treatment for patients suffering from the most severe forms of breast cancer. At that time, physicians had limited success treating metastatic breast cancer patients. Some physicians and researchers believed that if they could administer higher doses of chemotherapy to these patients, they would have much higher cancer cell kill rates; however, to do so would destroy the patients' bone marrow. By the late 1980s, some researchers and physicians began experimenting with administering high doses of chemotherapy and then "rescuing" the person's system by performing a bone marrow or stem cell transplant (as described in the previous section).

Clinical Trials

Clinical trials are categorized as Phase I through Phase IV, depending on how far the research has progressed. Phase I is the earliest phase. Phase II trials usually investigate the treatment's safety and effectiveness. Phase III trials compare the new treatment's effectiveness to no treatment or the standard treatment. Many treatments being researched never make it to Phase IV, which determine side effects, optimal uses, and risks.

Early reports indicated that the treatment could be successful for treating metastatic breast cancer, but since no randomized clinical studies (also known as Phase III studies) had been performed, it was unclear whether this treatment yielded significantly improved results over conventional chemotherapy. Although the treatment seemed successful, it had more severe side effects and cost three to five times as much as conventional chemotherapy. Due to its unproven superiority to conventional chemotherapy, its high cost, and its high toxicity, many insurance companies refused to cover the treatment for their members. Some of these patients sued their insurance companies. Other advocates lobbied state legislatures to pass legislation mandating that health insurance companies provide or offer coverage for HDC-ABMT/SCT.

Virginia's first proposed mandated offer for this treatment, HB 539, came before the House of Delegates in 1992 and was referred to the Special Advisory Commission on Mandated Health Insurance Benefits. The Commission received comments on the proposed mandate at two different meetings. In its December 1992 report on the mandate, the Commission recommended that the

mandated offer not be adopted due to the treatment's unproven medical efficacy. The Assembly did not adopt the mandate in 1993.

In 1994, a similar bill came before the Virginia House of Delegates and was referred to the Commission. The Commission held a public hearing on the bill at which 24 speakers provided oral comments. The Commission recommended that the Assembly adopt the proposed mandated offer because of additional evidence supporting the procedure's medical effectiveness, and the inability of many Virginians to access the treatment without coverage. The General Assembly passed the bill, and the Governor signed it into law (see Appendix B).

By 2000, results of Phase III clinical trials for HDC-ABMT/SCT began to be released. These trials indicated that while HDC-ABMT/SCT could be successful at treating metastatic and primary high risk breast cancer, it was no more effective than conventional chemotherapy. Other results released in subsequent years concurred with the initial Phase III results that HDC-ABMT/SCT did not yield significantly improved outcomes for advanced breast cancer patients. Some clinical trials are still being conducted to determine whether the treatment can be more effective than conventional chemotherapy for treating high risk primary breast cancer patients.

Difference Between HB 2426 and SB 991. Due to the procedure's decreased use for treating breast cancer, its high cost, and severe side effects, two bills have been introduced to the General Assembly which would repeal the mandated offer (see Appendix C). In the 2007 Session, SB 991 was introduced, which would repeal the portion of the mandate that requires insurers to offer coverage for high dose chemotherapy and autologous bone marrow transplant. SB 991 would leave intact provisions requiring insurers to offer coverage for stem cell transplants. During the same session, HB 2426 was introduced, which would repeal the mandate in its entirety. These bills would not prevent insurers from offering coverage of the treatment, but they would not be required to do so.

Both the medical literature and experts at Virginia Commonwealth University (VCU) Medical Center indicate that breast cancer patients would not receive any benefit from receiving only a stem cell transplant without high dose chemotherapy. HDC treats the cancer, while the SCT rescues the body from HDC's toxic effects. Additionally, ABMT achieves the same objective as SCT; in other words, ABMT and SCT are two different methods, surgical versus apheresis, of achieving the same goal of harvesting stem cells. Any future research or developments with the treatment will

almost certainly involve HDC with ABMT or SCT as interchangable rescue techniques.

c. Proponents and Opponents of Proposed Mandate

Proponents and opponents of SB 991 and HB 2426 had an opportunity to officially express their views at the public hearing on July 18, 2007, conducted by the Special Advisory Commission on Mandated Health Benefits. Proponents of the bills appear to be the Virginia Association of Health Plans (VAHP) and the insurance industry. Proponents support the legislation because they believe this mandate was prematurely enacted, before the medical community knew the efficacy of this treatment for breast cancer. Now that research indicates that the treatment is no more effective than conventional chemotherapy, proponents want the legislature to repeal what they see as an erroneously imposed mandate.

Opponents of the legislation appear to be primarily breast cancer survivors who have received the treatment. The opponents believe that the treatment should be available to patients with breast cancer, especially those who may have few treatment options available. Without the mandate, opponents believe that insurance companies will not cover the treatment, even in desperate situations.

MEDICAL EFFICACY AND EFFECTIVENESS

JLARC staff reviewed the medical literature regarding HDC-ABMT/SCT for breast cancer and found that a number of peer-reviewed Phase III study results indicate that HDC-ABMT/SCT does not provide any additional benefit to the overall population of breast cancer patients. (Specific research examined for this review is listed in Appendix E.) JLARC staff also contacted a medical expert at VCU Medical Center. This expert indicated that breast cancer patients should not be treated with HDC-ABMT/SCT unless it is in the context of a well-designed clinical study.

a. Medical Efficacy of Benefit

Medical Efficacy

Assessments of medical efficacy are typically based on clinical research, particularly randomized clinical trials, demonstrating the success of a particular treatment compared to alternative treatments or no treatment.

Medical research has mainly investigated using HDC-ABMT/SCT for two forms of breast cancer. The first form is metastatic breast cancer, where the cancer has spread to distant organs or tissues. Phase III clinical trials of HDC-AMBT/SCT with metastatic breast cancer patients indicate that the treatment may yield some marginally superior results in terms of disease-free survival (meaning patients alive without evidence of disease recurrence), but it does not yield statistically significant benefits in terms of overall survival. These trials also noted that this treatment tended to have more severe side effects than conventional therapies.

The second form of breast cancer for which medical research has investigated using HDC-ABMT/SCT is high risk primary breast cancer, where the cancer is still confined to the breast and surrounding tissues, but the cancer is likely to spread within a few months to years after removal of the primary breast tumor. The current research on the use of HDC-ABMT/SCT for high risk primary breast cancer also indicates that the treatment is no more effective than conventional chemotherapy approaches. A meta-analysis, including 13 Phase III studies and 5,064 patients, found that no statistically significant differences existed between groups receiving conventional chemotherapy and groups receiving HDC-ABMT/SCT in terms of overall survival. The study did find that HDC-ABMT/SCT yielded a statistically significant benefit in terms of event-free survival at three and four years after treatment. However, the study also found that patients receiving HDC-ABMT/SCT were more likely to suffer a treatment-related death than patients receiving conventional chemotherapy.

HDC-ABMT/SCT is a well-tolerated standard treatment for many other cancers. This treatment can be used to treat lymphomas (including Hodgkin's disease, non-Hodgkin's, and children's non-Hodgkin's), leukemia (including acute lymphocytic, acute myeloid, children's, chronic lymphocytic, and chronic myeloid), multiple myeloma, testicular cancer, myelodysplastic syndrome, myelodysplastic/myeloproliferative diseases, and neuroblastoma. Research has shown that HDC-ABMT/SCT can yield significantly improved results over other therapies for patients with these diseases. However, even though most insurance companies cover HDC-ABMT/SCT for the treatment of these diseases, the Commonwealth does not mandate it.

b. Medical Effectiveness of Benefit

Medical Effectiveness

Medical effectiveness refers to the success of a particular treatment in a normal clinical setting as opposed to ideal or laboratory conditions.

As mentioned previously, HDC-ABMT/SCT has largely fallen out of use as a treatment for breast cancer. In the mid-1990s, HDC-ABMT/SCT was most commonly used to treat breast cancer patients, and some sources claim that by 1996, as many as 41,000 breast cancer patients nationally had received HDC-ABMT/SCT. Despite the treatment's widespread use in the mid-1990s, the National Comprehensive Cancer Network, which publishes treatment guidelines for cancer, did not include HDC-ABMT/SCT in its treatment guidelines for breast cancer because the medical community had not expressed agreement on whether the treatment yielded superior results over conventional chemotherapy. Today, most medical professionals, including those affiliated with the American Cancer Society, Susan G. Komen for the Cure, and the VCU Medical Center, indicate that breast cancer patients should only receive HDC-ABMT/SCT treatments in the context of a well-designed clinical study.

SOCIAL IMPACT

Few individuals, if any, would be impacted by repealing this mandate. Although the cost of this treatment is very high, HDC-ABMT/SCT is no longer considered a standard of care for breast cancer patients. The few breast cancer patients who do receive the treatment are likely doing so in the context of a clinical trial, and they could have coverage for this treatment under Virginia's clinical trials mandate.

a. Utilization of Treatment

Medical professionals no longer use HDC-ABMT/SCT as a standard treatment for breast cancer patients. From the mid-1990s to the early 2000s, practitioners used HDC-ABMT/SCT as a standard treatment for some breast cancer patients. However, when researchers began publishing results of clinical trials which indicated that HDC-ABMT/SCT did not have any significant benefits over conventional therapies, medical professionals stopped using the treatment.

JLARC staff did not find evidence of any utilization of HDC-ABMT/SCT for breast cancer in Virginia in the past five years. Neither VCU Medical Center nor University of Virginia (UVA) Medical Center has performed the procedure on a breast cancer patient in the past five years, according to staff from these facilities. Furthermore, neither the State employee health plan, which covers more than 94,000 employees, nor Medicaid, which covers approximately 355,000 Virginia adults, has paid a claim for HDC-ABMT/SCT for the treatment of breast cancer in the past five years, according to the Department of Human Resources Management (DHRM) and the Department of Medical Assistance Services (DMAS).

The Virginia State Corporation Commission Bureau of Insurance (BOI) surveys Virginia's top 50 insurers annually regarding proposed mandates. Forty companies returned the survey, but nine of these companies indicated that their business is not impacted by insurance mandates. Of the 31 companies providing responses to the survey, eight insurance companies reported paying a total of 45 claims for ABMT or SCT in the past five years.

JLARC and BOI staff followed up with two of these eight insurance companies reporting claims for HDC-ABMT/SCT for breast cancer. Based on their responses, it appears to be unlikely that the claims reported to BOI in the survey were for HDC-ABMT/SCT for the treatment breast cancer. In some cases, the claims appear to be coding errors. For example, one company reported that it paid claims performed at VCU Medical Center. When JLARC staff in-

quired with VCU Medical Center and the insurance company regarding these claims, officials at the insurance company and VCU researched the claims and discovered that they were coding errors. In these cases, the patients had received HDC-ABMT/SCT, but it was to treat lymphoma, leukemia, or myeloma. None of these patients had received the treatment for breast cancer, and none of them had breast cancer histories. A few of the claims also appear to be HDC-ABMT/SCT in the context of a clinical trial.

Although JLARC staff did not find any evidence that HDC-ABMT/SCT has been used for Virginia breast cancer patients in the past five years, the possibility cannot be completely ruled out that someone received the treatment for breast cancer in the State since not all medical providers and health insurance companies operating in the State were surveyed.

b. Availability of Coverage

Currently, the Commonwealth mandates that insurers offer this coverage to their members; therefore, all Virginians purchasing health care through fully insured plans should have the option to buy coverage. These proposed repeals would likely result in a reduction in the availability of coverage for HDC-ABMT/SCT for the treatment of breast cancer. Of those insurers responding to the BOI survey, 44 percent responded that they would not offer coverage for the bone marrow transplant if it was not mandated (27 responses), and 48 percent responded that they would not offer coverage for the stem cell transplant if it was not mandated (27 responses).

c. Availability of Treatment/ Benefit

Currently, bone marrow and stem cell transplants are most likely to be performed at one of three transplant centers in the State: VCU Medical Center in Richmond, Inova-Fairfax Hospital in Falls Church, or Cancer Specialists of Tidewater in Virginia Beach and Chesapeake.

At the height of the treatment's utilization, it was widely available throughout the State. The treatment was performed at local hospitals as well as outpatient centers specializing in ABMT and SCT for breast cancer patients. When the clinical studies results were released starting in 2000, most hospitals and treatment centers stopped offering HDC-ABMT/SCT.

d. Availability of Treatment Without Coverage

As discussed in the next section, the cost of HDC-ABMT/SCT is sufficiently high that most individuals could not afford the treatment without health insurance coverage. However, patients could receive treatment through a clinical trial, which medical experts indicate is the appropriate setting in which breast cancer patients should receive this treatment. Phase II through Phase IV clinical trials are covered by insurance, as required by Virginia's clinical trials mandate.

e. Financial Hardship

The repeal of this mandate would significantly impact patients who choose to undergo this treatment outside a clinical trial. The cost of any procedure depends on many factors, including the cancer's characteristics, the provider, and the treatment location. However, the Government Accountability Office (GAO) estimated that HDC-ABMT/SCT treatment would have cost between $80,000 and $150,000 in 1996. A physician at VCU estimates that the procedure would cost between $100,000 and $200,000 today.

Based on the median household income of $56,859 in Virginia in 2007, the cost would make this treatment inaccessible to most Virginians. The cost of HDC-ABMT/SCT could range from approximately 140 percent to 285 percent of median household income.

f. Prevalence/ Incidence of Condition

The American Cancer Society estimates that 6,080 new breast cancer cases were diagnosed and 1,170 people died of breast cancer in Virginia in 2006. Breast cancer is the most commonly diagnosed cancer in women, and it is the second most common cause of cancer deaths in women. According to Susan G. Komen for the Cure, in recent years, due to increased screening, the proportion of breast cancer cases diagnosed at an early stage has increased, while the proportion of cases diagnosed at later stages has decreased.

g. Demand for Proposed Coverage

Demand for HDC-ABMT/SCT from breast cancer patients appears to be low. This treatment is generally limited to the subset of breast cancer patients who have advanced breast cancer. Despite the frequent use of the treatment for advanced breast cancer patients in the past, JLARC staff did not find any evidence to indicate that Virginia breast cancer patients are currently receiving HDC-ABMT/SCT treatments.

h. Labor Union Coverage

Labor unions do not appear to have advocated specifically for the inclusion of this benefit in their health benefit packages. Typically, labor unions advocate for broader benefits, rather than an offer as specific as coverage of HDC-ABMT/SCT for the treatment of breast cancer.

i. State Agency Findings

In 1993, the Special Advisory Commission reviewed the then-proposed offer of coverage for treatment of cancer by autologous bone marrow transplant. This bill only required insurers to offer coverage for autologous bone marrow transplant, not high dose chemotherapy or stem cell transplants. This early proposal also mandated that insurers offer coverage for the treatment of any cancer with this procedure. The Commission did not recommend that the mandate be adopted because of the lack of evidence demonstrating the treatment's medical efficacy.

In 1995, the Commission reviewed a bill similar to the one reviewed in 1993; however, this bill mandated that insurers offer coverage for high dose chemotherapy, autologous bone marrow transplant, and stem cell transplant. The bill also limited the offer of coverage to breast cancer patients. The Commission's report summarized many of the arguments for and against the mandate, and recommended the adoption of the mandate. The Commission made this recommendation based on the treatment's efficacy in Phase II trials and the lack of coverage for the treatment that many Virginians experienced.

j. Public Payer Coverage

As public payers, Medicare and Medicaid are exempt from this mandate; however, both programs appear to cover the treatment. Medicaid covers HDC-ABMT/SCT for breast cancer patients, but no Virginia Medicaid recipient has utilized the benefit since 2001. Medicare does not have an explicit policy on covering HDC-ABMT/SCT for breast cancer patients. Rather, its policy states that the treatment should be non-experimental and medically necessary.

k. Public Health Impact

The proposed repeals of this mandate are not expected to impact public health because the benefits of the mandate are directly received by patients.

FINANCIAL IMPACT

The proposed repeals would not have a significant financial impact. Physicians and patients have already stopped using the treatment, so demand is unlikely to decrease any further as a result of the proposed repeals. Due to the already diminished demand for the treatment, the mandate's premium impact is low. Therefore, repealing the mandate is likely to have a very small, if any, premium impact.

a. Effect on Cost of Treatment

It is not expected that these proposed repeals would result in any further reduction in the number of people utilizing the treatment for breast cancer. Therefore, repealing the mandate should not impact the cost of HDC-ABMT/SCT.

b. Change in Utilization

Since HDC-ABMT/SCT has fallen out of use for treating breast cancer, little change in utilization should occur as a result of this repeal. Most patients currently receiving the treatment are likely doing so in the context of a clinical setting. As mentioned, Virginia has a health insurance mandate requiring companies to provide coverage for treatment in clinical trials (Phase II through Phase IV only). Repealing the HDC-ABMT/SCT mandate would not affect the coverage provided through the clinical trials mandate, so breast cancer patients accessing HDC-ABMT/SCT through a clinical mandate would still have coverage.

c. Serves as an Alternative

Many alternatives to HDC-ABMT/SCT exist for breast cancer patients. The most common alternative is conventional chemotherapy. Most of the clinical trials reviewed by JLARC staff compared the outcomes of patients who received HDC-ABMT/SCT to patients who received conventional chemotherapy, and most of these trials found that all the patients had similar outcomes. Conventional chemotherapy also has less severe side effects than HDC-ABMT/SCT and costs three to five times less.

In addition to chemotherapy, treatment options for breast cancer patients have expanded greatly since the mid-1990s when HDC-ABMT/SCT was commonly used. Today, many treatment regimens are designed to attack the way cancer cells operate, rather than to bombard the cancer cells with toxic chemotherapy. These new treatments are called biologic or targeted therapies. In addition to these new treatments and chemotherapy, patients may also undergo surgery, radiation, and hormone therapy.

d. Effect on Providers

Due to the very small number of patients (possibly none) seeking HDC-ABMT/SCT for breast cancer, the effect of these repeals on Virginia's medical providers and hospitals is expected to be minimal. Most patients currently receiving this treatment for breast cancer are doing so in the context of clinical trials, so these repeals would not affect their access to trials.

e. Administrative and Premium Costs

The administrative and premium costs for this mandate are likely similar to the costs of other mandates. Repealing the mandate will likely result in low administrative and premium cost changes.

Administrative Expenses of Insurance Companies. Data are not currently collected from insurance companies regarding the administrative expenses to implement health insurance mandates. While it is reasonable to assume that companies incur some amount of administrative costs from health insurance mandates, the extent of these costs cannot be determined using existing data sources.

Premium and Administrative Expenses of Policyholders. This mandate has some premium expense for policyholders, although in most cases, it appears to be minimal. Forty insurance companies responded to the BOI survey on the proposed repeal of this mandate, but very few of those companies provided an estimate of the monthly premium cost. In terms of individual policyholders, eight companies provided a monthly premium estimate for ABMT, and seven companies provided an estimate for SCT. In terms of group policyholders, nine companies provided an estimate for ABMT, and eight companies provided an estimate for SCT.

For individual plans, premium estimates ranged from $0.04 to $2.00 for ABMT, and from $0.04 to $2.00 for SCT. The median premium estimate was $0.09 for ABMT and $0.04 for SCT. For group plans, premium estimates ranged from $0.04 to $16.12 for ABMT and from $0.04 to $16.12 for SCT. The median premium estimate was $0.11 for ABMT and $0.08 for SCT.

Additionally, two companies, which are not included in the results, noted that the premium cost for offering ABMT and SCT for their group plans was $0.00. These plans, likely, did not have any members utilize the benefit. Therefore, offering the benefit does not result in any additional premium costs.

Table 1: Estimated Monthly Premium Cost of Mandated HDC-ABMT/SCT

	# of Responses	Median Estimate	Highest Estimate	Lowest Estimate
Individual (ABMT)	8	$0.09	$2.00	$0.04
Individual (SCT)	7	$0.04	$2.00	$0.04
Group (ABMT)	9	$0.11	$16.12	$0.04
Group (SCT)	8	$0.08	$16.12	$0.04

Source: Bureau of Insurance survey of insurance companies, 2007.

According to the 2005 BOI report on the financial impact of mandated health insurance benefits, the HDC-ABMT/SCT mandate makes up 0.34 percent of the average premium for single coverage in an individual plan and 0.47 percent of the average premium for family coverage in an individual plan. For group plans, the mandate makes up 1.87 percent of the average premium for single coverage and 1.76 percent of the average premium for family coverage.

These estimates are higher than the premium impacts reported in the BOI annual survey, and they place HDC-ABMT/SCT among the top mandates in terms of premium impact as a percent of overall premium. However, this level of impact seems unlikely given the low level of utilization of the treatment. As indicated previously, some claims may have been inaccurately coded by insurance companies as HDC-ABMT/SCT for breast cancer. The actual premium impacts of the mandate are likely less than those included in the BOI annual report, and therefore the premium impact of repealing the mandate would likely be small.

f. Total Cost of Health Care

The proposed repeal of this mandate would have a negligible impact on the total cost of health care. The number of individuals potentially affected by the proposed repeal (stage III and stage IV breast cancer patients) is small, and the subset of this group of individuals who decide to undergo this treatment is very small, approaching zero. For those that do undergo HDC-ABMT/SCT, the treatment is extremely costly; however, it is likely that the very few people receiving this treatment now are doing so in the context of a clinical trial, which would still be covered by Virginia's clinical trials mandate.

BALANCING MEDICAL, SOCIAL, AND FINANCIAL CONSIDERATIONS

Given the potentially catastrophic financial impact to an individual or family for obtaining HDC-ABMT/SCT, the current mandate is consistent with the role of insurance. Although this mandate is consistent with the role of insurance, a need for the mandate appears to be minimal. While the cost of the mandate appears to be relatively low, it is no longer the standard of care and has a very low demand and utilization rate. Further, HDC-ABMT/SCT would continue to be available to patients through clinical trials, which medical experts indicate is the most appropriate setting for this treatment.

a. Social Need/ Consistent With Role of Insurance

Assuming that the role of health insurance is to promote public health, encourage the use of preventive care, and provide financial protection from catastrophic financial expenses for unexpected illness, then the current mandate is consistent with this role. By mandating insurance companies to offer coverage for HDC-ABMT/SCT for the treatment of breast cancer, the mandate compels insurance companies to provide protection from the potentially catastrophic financial expenses associated with this treatment.

However, an additional consideration is whether a social need exists for this mandate, and today, it appears that that need is minimal. When the mandate was first enacted, it addressed a refusal on the part of insurance companies to cover a promising and expensive treatment for the most serious forms of breast cancer. In the 13 years since the mandate's passage, the treatment approach to breast cancer has dramatically changed, and HDC-ABMT/SCT has been found to provide no additional benefit over other treatment options. These two factors have nearly eliminated the social need for this treatment. Even without this mandate, insurers will still be required to cover this treatment if it is performed as part of a clinical trial, which according to medical experts is the most appropriate setting for this treatment. Virginia's clinical trial mandate would remain in place if either SB 991 or HB 2426 were enacted. Additionally, if adopted, neither SB 991 nor HB 2426 would prohibit insurers from offering this coverage.

b. Need Versus Cost

Little need appears to exist for this mandate, despite the low estimated premium costs. Even though the cost of the treatment is very high, very few patients receive it because medical professionals no longer recommend it as a standard of care. This keeps the

premium cost of the mandate relatively low for policyholders. When treatment is recommended for breast cancer patients, it is provided as part of a clinical trial, according to medical experts. Even without the mandate, these patients would still be able to access this treatment through a clinical trial, and insurance coverage would be provided due to the separate clinical trials mandate.

c. Mandated Offer

The law currently mandates that insurance companies offer coverage for HDC-ABMT/SCT. Unless health insurance companies offer the treatment as a standard benefit in all their plans, health care purchasers can choose whether or not to pay for this coverage. However, it is necessary to consider whether it is appropriate for the State to mandate a very specific procedure that has a very low demand and utilization rate.

ACKNOWLEDGMENTS

JLARC staff would like to acknowledge the expertise, assistance, and information provided by staff at Virginia Commonwealth University Medical Center. JLARC would also like to thank Dr. Robert Valdez, President of Valdez and Associates, for his suggestions and expertise as a public health consultant. In addition, JLARC would like to thank the Virginia State Corporation Commission Bureau of Insurance, the Virginia Association of Health Plans, the Department of Human Resources Management, Anthem Blue Cross Blue Shield, the Department of Health Virginia Cancer Registry, and the Department of Medical Assistance Services.

Appendix A

Statutory Authority for JLARC Evaluation of Proposed Mandated Health Insurance Benefits

§ 2.2-2503. Special Advisory Commission on Mandated Health Insurance Benefits; membership; terms; meetings; compensation and expenses; staff; chairman's executive summary.

A. The Special Advisory Commission on Mandated Health Insurance Benefits (the Commission) is established as an advisory commission within the meaning of § 2.2-2100, in the executive branch of state government. The purpose of the Commission shall be to advise the Governor and the General Assembly on the social and financial impact of current and proposed mandated benefits and providers, in the manner set forth in this article.

B. The Commission shall consist of 18 members that include six legislative members, 10 nonlegislative citizen members, and two ex officio members as follows: one member of the Senate Committee on Education and Health and one member of the Senate Committee on Commerce and Labor appointed by the Senate Committee on Rules; two members of the House Committee on Health, Welfare and Institutions and two members of the House Committee on Commerce and Labor appointed by the Speaker of the House of Delegates in accordance with the principles of proportional representation contained in the Rules of the House of Delegates; 10 nonlegislative citizen members appointed by the Governor that include one physician, one chief executive officer of a general acute care hospital, one allied health professional, one representative of small business, one representative of a major industry, one expert in the field of medical ethics, two representatives of the accident and health insurance industry, and two nonlegislative citizen members; and the State Commissioner of Health and the State Commissioner of Insurance, or their designees, who shall serve as ex officio nonvoting members.

C. All nonlegislative citizen members shall be appointed for terms of four years. Legislative and ex officio members shall serve terms coincident with their terms of office. All members may be reappointed. However, no House member shall serve more than four consecutive two-year terms, no Senate member shall serve more than two consecutive four-year terms, and no nonlegislative citizen member shall serve more than two consecutive four-year terms. Vacancies occurring other than by expiration of a term shall be filled for the unexpired term. Vacancies shall be filled in the manner as the original appointments. The remainder of any term to which a member is appointed to fill a vacancy shall not constitute a term in determining the member's eligibility for reappointment.

D. The Commission shall meet at the request of the chairman, the majority of the voting members or the Governor. The Commission shall elect a chairman and a vice-chairman, as determined by the membership. A majority of the members of the Commission shall constitute a quorum.

E. Legislative members of the Commission shall receive such compensation as provided in § 30-19.12, and nonlegislative citizen members shall receive such compensation for the performance of their duties as provided in § 2.2-2813. All members shall be reimbursed for all reasonable and

necessary expenses incurred in the performance of their duties as provided in §§ 2.2-2813 and 2.2-2825. Funding for the compensation and costs of expenses of the members shall be provided by the State Corporation Commission.

F. The Bureau of Insurance, the State Health Department, and the Joint Legislative Audit and Review Commission and such other state agencies as may be considered appropriate by the Commission shall provide staff assistance to the Commission. The Joint Legislative Audit and Review Commission shall conduct assessments, analyses, and evaluations of proposed mandated health insurance benefits and mandated providers as provided in subsection D of § 30-58.1, and report its findings with respect to the proposed mandates to the Commission.

G. The chairman of the Commission shall submit to the Governor and the General Assembly an annual executive summary of the interim activity and work of the Commission no later than the first day of each regular session of the General Assembly. The executive summary shall be submitted as provided in the procedures of the Division of Legislative Automated Systems for the processing of legislative documents and reports and shall be posted on the General Assembly's website.

§ 30-58.1. Powers and duties of Commission.

The Commission shall have the following powers and duties:

A. Make performance reviews of operations of state agencies to ascertain that sums appropriated have been, or are being expended for the purposes for which such appropriations were made and to evaluate the effectiveness of programs in accomplishing legislative intent;

B. Study on a continuing basis the operations, practices and duties of state agencies, as they relate to efficiency in the utilization of space, personnel, equipment and facilities;

C. Make such special studies and reports of the operations and functions of state agencies as it deems appropriate and as may be requested by the General Assembly;

D. Assess, analyze, and evaluate the social and economic costs and benefits of any proposed mandated health insurance benefit or mandated provider, including, but not limited to, the mandate's predicted effect on health care coverage premiums and related costs, net costs or savings to the health care system, and other relevant issues, and report its findings with respect to the proposed mandate to the Special Advisory Commission on Mandated Health Insurance Benefits; and

E. Make such reports on its findings and recommendations at such time and in such manner as the Commission deems proper submitting same to the agencies concerned, to the Governor and to the General Assembly. Such reports as are submitted shall relate to the following matters:

1. Ways in which the agencies may operate more economically and efficiently;

2. Ways in which agencies can provide better services to the Commonwealth and to the people; and

3. Areas in which functions of state agencies are duplicative, overlapping, or failing to accomplish legislative objectives or for any other reason should be redefined or redistributed.

Appendix B

Mandated Offer for Autologous Bone Marrow Transplant or Stem Cell Transplant for Breast Cancer

The *Code of Virginia*, § 38.2-34.18.1:1, Coverage for bone marrow transplants.

A. Each insurer proposing to issue individual or group accident and sickness insurance policies providing hospital, medical and surgical, or major medical coverage on an expense-incurred basis, each corporation providing individual or group accident and sickness subscription contracts, and each health maintenance organization providing a health care plan for health care services shall offer and make available coverage under such policy, contract or plan delivered, issued for delivery or renewed in this Commonwealth on and after January 1, 1995, for the treatment of breast cancer by dose-intensive chemotherapy/autologous bone marrow transplants or stem cell transplants when performed pursuant to protocols approved by the institutional review board of any United States medical teaching college including, but not limited to, National Cancer Institute protocols that have been favorably reviewed and utilized by hematologists or oncologists experienced in dose-intensive chemotherapy/autologous bone marrow transplants or stem cell transplants.

B. Such coverage shall not be subject to any greater copayment than that applicable to any other coverage provided by such policies, contracts or plans, and such coverage shall be subject to the same deductible as that applicable to any other coverage; however, a deductible for such coverage in an amount different than that applicable to any other coverage may also be offered and made available.

C. The provisions of this section shall not apply to short-term travel, accident-only, limited or specified disease policies, or to short-term nonrenewable policies of not more than six months' duration.

(1994, c. 699.)

Appendix C

Repeals of Mandated Offer of Bone Marrow or Stem Cell Transplants for Breast Cancer

SENATE BILL NO. 991
Offered January 10, 2007
Prefiled January 9, 2007
A BILL to amend and reenact § 38.2-3418.1:1 of the Code of Virginia, relating to coverage for autologous bone marrow transplants.

Patron—Blevins

Referred to Committee on Commerce and Labor

Be it enacted by the General Assembly of Virginia:
That § 38.2-3418.1:1 of the Code of Virginia is amended and reenacted as follows:

§ 38.2-3418.1:1. Coverage for stem cell transplants.

A. Each insurer proposing to issue individual or group accident and sickness insurance policies providing hospital, medical and surgical, or major medical coverage on an expense-incurred basis, each corporation providing individual or group accident and sickness subscription contracts, and each health maintenance organization providing a health care plan for health care services shall offer and make available coverage under such policy, contract or plan delivered, issued for delivery or renewed in this
Commonwealth on and after January 1, 1995, for the treatment of breast cancer by ~~dose-intensive chemotherapy/autologous bone marrow transplants or~~ stem cell transplants when performed pursuant to protocols approved by the institutional review board of any United States medical teaching college including, but not limited to, National Cancer Institute protocols that have been favorably reviewed and utilized by hematologists or oncologists experienced in ~~dose-intensive chemotherapy/autologous bone marrow transplants or~~ stem cell transplants.

B. Such coverage shall not be subject to any greater copayment than that applicable to any other coverage provided by such policies, contracts or plans, and such coverage shall be subject to the same deductible as that applicable to any other coverage; however, a deductible for such coverage in an amount different than that applicable to any other coverage may also be offered and made available.

C. The provisions of this section shall not apply to short-term travel, accident-only, limited or specified disease policies, or to short-term nonrenewable policies of not more than six months' duration

HOUSE BILL NO. 2426

Offered January 10, 2007

Prefiled January 9, 2007

A BILL to repeal § 38.2-3418.1:1 of the Code of Virginia, relating to mandated coverage for bone marrow transplants.

———————

Patron—Byron

———————

Referred to Committee on Commerce and Labor

———————

Be it enacted by the General Assembly of Virginia:

That § 38.2-3418.1:1 of the Code of Virginia is repealed.

Appendix D

Evaluation Topic Areas and Criteria for Assessing Proposed Mandated Health Insurance Benefits

Topic Area	Criteria
1. Medical Efficacy	
a. Medical Efficacy of Benefit	The contribution of the benefit to the quality of patient care and the health status of the population, including the results of any clinical research, especially randomized clinical trials, demonstrating the medical efficacy of the treatment or service compared to alternatives or not providing the treatment or service.
b. Medical Effectiveness of Benefit *JLARC Criteria**	The contribution of the benefit to patient health based on how well the intervention works under the usual conditions of clinical practice. Medical effectiveness is not based on testing in a rigid, optimal protocol, but rather a more flexible intervention that is often used in broader populations.
c. Medical Efficacy of Provider	If the legislation seeks to mandate coverage of an additional class of practitioners: 1) The results of any professionally acceptable research, especially randomized clinical trials, demonstrating the medical results achieved by the additional class of practitioners relative to those already covered. 2) The methods of the appropriate professional organization to assure clinical proficiency.
d. Medical Effectiveness of Provider *JLARC Criteria**	The contribution of the practitioner to patient health based on how well the practitioner's interventions work under the usual conditions of clinical practice. Medical effectiveness is not based on testing in a rigid, optimal protocol, but rather more flexible interventions that are often used in broader populations.
2. Social Impact	
a. Utilization of Treatment	The extent to which the treatment or service is generally utilized by a significant portion of the population.
b. Availability of Coverage	The extent to which insurance coverage for the treatment or service is already generally available.
c. Availability of Treatment *JLARC Criteria**	The extent to which the treatment or service is generally available to residents throughout the state.
d. Availability of Treatment Without Coverage	If coverage is not generally available, the extent to which the lack of coverage results in persons being unable to obtain necessary health care treatments.
e. Financial Hardship	If the coverage is not generally available, the extent to which the lack of coverage result in unreasonable financial hardship on those persons needing treatment.
f. Prevalence/Incidence of Condition	The level of public demand for the treatment or service.
g. Demand for Coverage	The level of public demand and the level of demand from providers for individual or group insurance coverage of the treatment or service.

h. Labor Union Coverage	The level of interest of collective bargaining organizations in negotiating privately for inclusion of this coverage in group contracts.
i. State Agency Findings	Any relevant findings of the state health planning agency or the appropriate health system agency relating to the social impact of the mandated benefit.
j. Public Payer Coverage *JLARC Criteria**	The extent to which the benefit is covered by public payers, in particular Medicaid and Medicare.
k. Public Health Impact *JLARC Criteria**	Potential public health impacts of mandating the benefit.
3. Financial Impact	
a. Effect on Cost of Treatment	The extent to which the proposed insurance coverage would increase or decrease the cost or treatment of service over the next five years.
b. Change in Utilization	The extent to which the proposed insurance coverage might increase the appropriate or inappropriate use of the treatment or service.
c. Serves as an Alternative	The extent to which the mandated treatment or service might serve as an alternative for more expensive or less expensive treatment or service.
d. Impact on Providers	The extent to which the insurance coverage may affect the number and types of providers of the mandated treatment or service over the next five years.
e. Administrative and Premium Costs	The extent to which insurance coverage might be expected to increase or decrease the administrative expenses of insurance companies and the premium and administrative expenses of policyholders.
f. Total Cost of Health Care	The impact of coverage on the total cost of health care.
4. Effects of Balancing Medical, Social, and Financial Considerations	
a. Social Need/Consistent with Role of Insurance	The extent to which the benefit addresses a medical or a broader social need and whether it is consistent with the role of health insurance.
b. Need Versus Cost	The extent to which the need for coverage outweighs the costs of mandating the benefit for all policyholders.
c. Mandated Option	The extent to which the need for coverage may be solved by mandating the availability of the coverage as an option for policy holders.

*Denotes additional criteria added by JLARC staff to criteria adopted by the Special Advisory Commission on Mandated Health Insurance Benefits.

Source: Special Advisory Commission on Mandated Health Insurance Benefits and JLARC staff analysis.

Appendix E

Annotated Bibliography

PEER-REVIEWED RESEARCH

Breast Cancer, in general

Phase I or II Studies/Reviews

Antman, KH (1999). Critique of the high-dose chemotherapy studies in breast cancer: a positive look at the data. Journal of Clinical Oncology, 17: 30-35.

Data published to this date (1999) indicated that chemotherapy dose can make the treatment more effective. However, the studies that were available at this point did not follow patients for long periods of time. Additionally, these studies did not address the magnitude of the benefits of using HDC-ABMT over other treatments.

McCarthy, P, et al (1999). Autotransplants in men with breast cancer. Bone Marrow Transplantation, 24: 365-368. [Abstract].

Methodology: The researchers followed 13 men who received autologous bone marrow or stem cell transplants for breast cancer. The men had stage II, III, and IV breast cancer.

Results/conclusions: Three of the men relapsed and died after their transplants, seven of the men remained disease free after 23 months, and three men had progressive or recurrent disease. The authors conclude that high dose chemotherapy with a bone or stem cell transplant has similar results in men with breast cancer as in women.

Damon, LE, et al (2000). High-dose chemotherapy and hematopoietic stem cell rescue for breast cancer: experience in California. Biology of Blood and Marrow Transplantation: Journal for the American Society of Blood and Marrow Transplantation, 6: 496-505. [Abstract].

Methodology: The researchers retrospectively observed 1,111 breast cancer patients who received HDC-ABMT/SCT at five major California medical centers.

Results/conclusions: The researchers found that overall treatment related mortality was 2.3%, and it was not related to disease stage or the

specific HDC regimen received. It was correlated with whether a person received a bone marrow or a stem cell transplant, with patients who received just a stem cell transplant having a significantly lower treatment related mortality rate. The authors conclude that HDC-SCT is safe, and it can be beneficial for patients with high risk primary breast cancer and patients with metastatic breast cancer with no evidence of disease.

Gerrero, RM, Stein, S, Stadmauer, EA (2002). High dose chemotherapy and stem cell support for breast cancer, where are we now?. Drugs and Aging, 19: 475-485.

Reviews studies published until 2002 that evaluated the effectiveness of HDC with stem cell transplant for treating patients with breast cancer. The studies of metastatic breast cancer patients found no significant differences in outcomes between patients treated with conventional therapies and patients treated with HDC with stem cell transplants. The studies of high risk breast cancer patients are inconclusive because they are still following up with patients and they do not compare treatment outcomes of HDC-SCT to treatment outcomes of conventional chemotherapies.

Ueno, NT, et al (2006). High-dose chemotherapy and autologous peripheral blood stem cell transplantation for primary breast cancer refractory to neoadjuvant chemotherapy. Bone Marrow Transplantation, 37: 929-935. [Abstract].

Methodology: The researchers administered HDC followed by SCT to 42 patients with refractory breast cancer (cancer that is resistant to neo-adjuvant chemotherapy).

Results/conclusions: Thirty patients had a complete response to HDC, and five year overall survival was 57 percent. The researchers conclude that randomized clinical trials of this treatment on patients with refractory breast cancer are necessary.

Phase III Studies/Reviews

Weiss, RB (1999). The randomized trials of dose-intensive therapy for breast cancer: what do they mean for patient care and where do we go from here? Oncologist, 4: 450-458.

Reviews the results of clinical trials on the effects of HDC and stem cell transplants for metastatic breast cancer patients and high risk early disease breast cancer patients. With the exception of two studies, all of the studies demonstrated that HDC with stem cell transplant does not yield significantly improved results over conventional therapies.

Vij, R, et al (2000). Outcomes of high-dose chemotherapy and autologous stem cell transplant in isolated locally recurrent breast cancer: a multicenter evaluation. Bone Marrow Transplantation, 26: 947-953.

Methodology: The patients in this retrospective study had locally recurrent breast cancer with no evidence of distant metastases. These patients received conventional dose chemotherapy before HDC-SCT, and they received local radiation treatment before or after HDC-SCT. All patients received HDC, followed by SCT. The researchers collected data on these patients retrospectively, and performed univariate and multivariate regression analyses to examine factors related to survival.

Results/conclusions: The researchers found no significant differences in outcomes for the HDC-SCT treated group versus conventional therapy groups.

Mello, MM, Brennan, TA (2001). The controversy over high-dose chemotherapy with autologous bone marrow transplant for breast cancer. Health Affairs, 20: 101-117.

Summarizes and analyzes the history of HDC-ABMT. In the 1980s, reports indicated that HDC-ABMT resulted in tumor shrinkage; however, these studies suffered from selection bias, small sample size, and short follow-up time. In the 1990s, randomized trials were initiated. Four major randomized studies concluded that HDC-ABMT did not produce superior results to standard therapies.

Welch, HG, Mogielnicki, J (2002). Presumed benefit: lessons from the American experience with marrow transplantation for breast cancer. BMJ (British Medical Journal), 324:1088-1092.

Reviews the history of ABMT for the treatment of breast cancer. While the procedure was still in the investigational stages, the media reported that the procedure could be effective in treating breast cancer; however, most insurance providers did not cover the procedure for breast cancer. Little evidence existed to indicate the procedure's effectiveness in the long-term. Breast cancer patients sued their insurance companies to cover the cost of the procedure. The media only reported stories on how to pay for the costly procedure, but did not report on the procedure's unknown effectiveness. Seven states, including Virginia, mandated that insurance companies at least offer the procedure as a benefit. By 1999, several studies concluded that ABMT provided no benefit for metastatic breast cancer patients.

Williams, SF (2002). Is there a role for dose-intensive chemotherapy with stem cell rescue in breast cancer?. Oncology, 16: 1643-1646, 1649.

This article reviews the clinical studies of HDC-SCT done as of the date of this article (2002). Most of the studies concluded that HDC-SCT does not yield significantly improved outcomes over conventional chemotherapies. The author concludes that further study and refinement of the method is necessary to make it yield superior results over conventional therapies.

High Risk Primary Breast Cancer

Phase I or II Studies/Reviews

Moore, HCF, et al (1999). Autologous stem-cell transplant after conventional dose adjuvant chemotherapy for high-risk breast cancer: impact on the delivery of local-regional radiation therapy. Annals of Oncology, 10: 929-936.

Methodology: This study followed 107 women with high-risk breast cancer (stage II or IIIa with four or more involved lymph nodes). Patients with any evidence of metastatic disease were excluded from this study. First, patients received conventional dose adjuvant chemotherapy, and then they underwent peripheral stem cell harvest. The stem cells were cryo-preserved. The women were then treated with high-dose chemotherapy. The stem cells were thawed and infused at least 48 hours after the conclusion of the chemotherapy. Patients who did not receive chemotherapy before treatment received radiation treatment after hematopoetic recovery.

Results/conclusions: The researchers conclude that HDC-SCT treatment does not significantly impact the delivery or outcome of radiation therapy.

Nieto, Y et al (1999). A predictive model for relapse in high-risk primary breast cancer patients treated with high-dose chemotherapy and autologous stem-cell transplant. Clinical Cancer Research, 5: 3425-3431.

Methodology: The researchers reviewed the records of 176 high risk primary breast cancer patients treated with HDC and SCT between 1993 and 1996. They conducted statistical analyses to test 23 different variables' association with relapse. The researchers verified the model's predictive power by applying it to a patient group at another site.

Results/conclusions: The researchers conclude that three variables (axillary nodal ratio, estrogen receptor/progesterone receptor status, and tumor size) have independent predictive value. These three variables can help health care professionals predict the effectiveness of HDC-SCT for high risk primary breast cancer patients.

Phase III Studies/Reviews

Tallman, MS, et al (2003). Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. New England Journal of Medicine, 349: 17-26.

Methodology: Patients in this study had stage II or III breast cancer with a high risk of recurrence. Patients first received adjuvant conventional dose chemotherapy, then they were randomized to a treatment or control group. The treatment group received high dose chemotherapy followed by an autologous hematopoietic stem cell transplant.

Results/conclusions: The researchers found that HDC-SCT treatment did not yield significantly improved results over conventional chemotherapy for these patients. The researchers found no significant differences between the treatment and control groups in terms of disease-free survival and overall survival. Furthermore, this study raises concerns about patients developing myelodysplastic syndrome or acute myelogenous leukemia as a complication from HDC-SCT treatment.

Zander, AR et al (2004). High-dose chemotherapy with autologous hematopoietic stem-cell support compared with standard-dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: first results of a randomized trial. Journal of Clinical Oncology, 22: 2273-2283. [Abstract].

Methodology: The researchers followed 307 high risk primary breast cancer patients who were randomized to receive either HDC-ABMT/SCT or conventional chemotherapy.

Results/conclusions: The researchers did not observe any significant differences between the two groups in terms of overall survival or event-free survival. A trend in favor of HDC treatment existed for event-free survival, but it was not statistically significant. HDC did carry more risk than the standard chemotherapy of treatment related complications. The authors conclude that more follow-up and a meta-analysis of all randomized studies are necessary.

Farquhar, C, Marjoribanks, J, Basser, R, Lethaby, A (2005). High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. Cochrane Database of Systematic Reviews, Issue 3, Art. No.: DC003139. DOI: 10.1002/14651858.CD003139.pub2. [Abstract].

Methodology: The researchers reviewed the results of 13 randomized clinical trials of HDC-ABMT for high risk breast cancer patients. They performed their own meta-analysis of the results that included 2,535 women randomized to HDC-ABMT treatment and 2,529 women randomized to conventional chemotherapy.

Results/conclusions: The HDC-ABMT treatment yielded a statistically significant benefit in event free survival at three years and four years after treatment. HDC-ABMT did not yield a statistically significant benefit in overall survival. The high dose group experienced more frequent and severe morbidity than the conventional therapy group. The authors conclude that the evidence available is not sufficient to recommend HDC-ABMT as routine treatment for high risk breast cancer patients.

Metastatic Breast Cancer

Phase I or II Studies/Reviews

Ayash, LJ, et al (1995). Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem-cell support for advanced breast cancer. Journal of Clinical Oncology, 13: 2043-2049. [Abstract].

Methodology: The researchers administered high dose chemotherapy followed by an autologous stem cell transplant to patients who had metastatic breast cancer. The researchers followed the patients for approximately 50 months.

Results/conclusions: Approximately 10 to 25 percent of the patients receiving the treatment remained progression-free at the end of the 50 months of observation. The authors found that tumor bulk, length of disease-free interval, and chemo-sensitive disease were correlated with disease-free survival.

Nieto, Y, et al (1999). Phase II trial of high-dose chemotherapy with autologous stem cell transplant for stage IV breast cancer with minimal metastatic disease. Clinical Cancer Research, 5: 1731-1737.

Methodology: The patients in this study had stage IV breast cancer with minimal metastases. First, patients received induction chemo-

therapy. Then they received high dose chemotherapy followed by an autologous stem cell transplant. Patients were then discharged, and cared for as outpatients.

Conclusions/results: The researchers find that the therapy is effective at rendering patients free of disease. As a phase II study, though, the researchers do not provide a control group or randomization. It is unclear whether this treatment renders superior results to conventional therapies in this group of patients.

Rowlings, PA, et al (1999). Factors correlated with progression-free survival after high-dose chemotherapy and hematopoietic stem cell transplantation for metastatic breast cancer. JAMA, 282: 1335-1343.

Methodology: Collected retrospective and prospective data on metastatic or locally recurrent breast cancer patients who had received autotransplants between January 1989 and January 1995. The researchers used univariate and multivariate regression analyses to test variables' association with treatment failure.

Findings/conclusions: In the univariate analysis, significant variable associated with treatment failure included: breast cancer stage at diagnosis, hormone receptor status, use of adjuvant chemotherapy, initial DF1, response to pretransplantation chemotherapy, pretransplantation Karnofsky performance score, and number of sites and metastases. The multivariate analysis had the following significant variables: age, pretransplantation Karnofsky score, hormone receptore status, adjuvant chemotherapy and DFI, pretransplantation sites of metastatic disease, and pretransplantation chemotherapy sensitivity. The authors conclude that more study of this treatment is necessary.

Rizzo, JD, et al (2003). Syngeneic hematopoietic stem cell transplantation for women with metastatic breast cancer. Bone Marrow Transplantation, 32: 151-155.

Methodology: The authors retrospectively reviewed the treatment of metastatic breast cancer patients who received high dose chemotherapy and syngeneic hematopoietic stem cell transplants (stem cells that came from an identical twin). The aim of the study was to determine whether the primary source of relapse in patients receiving HDC with stem cell support is the stem cell infusion or residual disease in the patient following HDC.

Results/conclusions: Eight of the 14 subjects died, one from treatment related causes and seven from progressive disease. Although this was a very small sample, the results of this study indicate that residual dis-

ease following HDC is the primary cause of relapse or progression of the disease after transplantation.

Stemmer, SM, Hardan, I, Brenner, HJ, Rizel, S (2004). High-dose chemotherapy and autologous stem cell transplant in women with de novo chemosensitive metastatic breast cancer. American Journal of Clinical Oncology, 27: 250-255. [Abstract].

Methodology: The researchers administered HDC with SCT to patients with de novo stage IV breast cancer. Patients received radiation to the sites of the metastases.

Results/conclusions: The median progression free survival for the group was 60 months from diagnosis. The researchers conclude that the treatment is safe, and appears to be beneficial for the patients; however, they believe that some selection bias may have skewed their results.

Kurian, S, et al (2006). Complete response after high-dose chemotherapy and autologous hemopoietic stem cell transplantation in metatstatic breast cancer results in survival benefit. Breast Journal, 12: 531-535. [Abstract].

Methodology: The researchers followed 198 metastatic breast cancer patients treated with HDC-SCT, excluding patients with central nervous system or bone marrow involvement.

Results/conclusions: At the time of HDC-SCT, 80 patients had no evidence of disease, and after HDC-SCT, 57 patients had complete responses. The authors concluded that a subset of metastatic patients may benefits from HDC-SCT.

Phase III Studies/Reviews

Antman, KH, Heitjan DF, Hortobagyi, GN (1999). High-dose chemotherapy for breast cancer. JAMA, 282: 1701-1703.

Reviews several randomized clinical trials of HDC-ABMT treatments for metastatic breast cancer patients. Few of the studies found any statistically significant differences in the outcomes for patients treated with conventional therapies versus HDC-ABMT. In most of the studies, patients receiving HDC-ABMT treatment had similar results to patients receiving conventional therapies.

Stadtmauer, EA, et al (2000). Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. New England Journal of Medicine, 342: 1069-1076.

Methodology: This study's patients had either locally recurrent or distant metastatic breast cancer. First, patients received induction chemotherapy. Then, if they experienced a complete or partial remission within eight weeks after induction therapy, they were randomized. The control group received conventional-dose chemotherapy. The other group underwent stem cell harvest, followed by high dose chemotherapy. Approximately 48 hours after the completion of the high dose chemotherapy, patients received the stem cell transplant.

Results/conclusions: The results for patients receiving HDC-SCT were not significantly different from patients receiving conventional therapies. The authors tested many of their assumptions, and the results were still not significantly different. As a result, the authors state that they cannot recommend HDC-SCT treatment for metastatic breast cancer patients.

Tartarone, A, et al (2003). Should we continue to study high-dose chemotherapy in metastatic breast cancer patients? A critical review of the published data. Bone Marrow Transplantation, 31: 525-530.

This article reviews the randomized trials of HDC with stem cell support that had been performed by 2003. The authors note that these studies have little statistical power because of their relatively small sample sizes. They write that HDC with stem cell support remains an important avenue of research for patients suffering from metastatic breast cancer.

Farquhar, C, Marjoribanks, J, Basser, R, Hetrick, S, Lethaby, A (2005). High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database of Systematic Reviews, Issue 3, Art. No.: CD003142. DOI: 10.1002/14651858.CD003142.pub2. [Abstract].

Methodology: The researchers reviewed six randomized clinical studies HDC-ABMT/SCT for metastatic breast cancer. The researchers performed their own meta-analysis of the results that included 438 patients randomized to receive HDC-ABMT/SCT and 413 patients randomized to receive conventional treatment.

Results/conclusions: The meta-analysis revealed that no significant differences existed between the groups in their overall survival at three and five years. They did find that the high dose group had significantly improved

event-free survival rates at one and five years. However, the toxicity and treatment related deaths rate was higher in the high dose group. The authors conclude that HDC-ABMT/SCT should not be administered to metastatic breast cancer patients outside of clinical trials.

HDC-ABMT/SCT for the Treatment of Indices Other than Breast Cancer

Attal, M, et al (1996). A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. New England Journal of Medicine, 335: 91-97.

Methodology: The patients in this study were under 65 years old and suffered from Durie-Salmon stage II or III myeloma. Each patient was assigned to either a conventional-dose chemotherapy group or a high dose group. Patients in the high dose group received high dose chemotherapy, followed by an autologous bone marrow transplant.

Results/conclusions: The researchers find that HDC-ABMT treatment significantly improves these patients' event-free survival, response rate, and overall survival over similar patients receiving conventional chemotherapy.

Ravindranath, Y, et al (1996). Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute myeloid leukemia in childhood. New England Journal of Medicine, 334: 1428-1434.

Methodology: The patients in this study were individuals under 21 years old who were diagnosed with acute myeloid leukemia. All subjects first received induction chemotherapy. Then patients were randomly assigned to a group to receive intensive consolidation chemotherapy or autologous bone marrow transplant.

Results/conclusions: The researchers did not find any significantly improved results in patients receiving ABMT over intensive consolidation chemotherapy.

Burnett, AK, et al (1998). Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. Lancet, 351: 700-708.

Methodology: The patients in this study had acute myeloid leukemia. First, patients received three cycles of intensive chemotherapy. Next, bone marrow was harvested from the patients. Then, patients were randomized to receive ABMT or to receive no further treatment.

Results/conclusions: The researchers found that ABMT significantly improves these patients' chances of long-term survival.

Matthay, KK, et al (1999). Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-*cis*-retinoic acid. New England Journal of Medicine, 341: 1165-1173.

Methodology: Patients in this study were between 1 and 18 years old, and had been recently diagnosed with high risk neuroblastoma (an extracranial solid tumor). Patients receive 2 cycles of initial chemotherapy, then they were randomized to receive myeloablative therapy plus ABMT or continuation chemotherapy. The group receiving ABMT underwent bone marrow transplant between initial chemotherapy cycles three and four or between cycles four and five. After initial chemotherapy cycle five, the treatment group received myeloablative therapy plus ABMT, while the control group receive three more cycles of chemotherapy.

Results/conclusions: The researchers found that the patients receiving intensive chemotherapy, radiotherapy, and ABMT experienced significantly improved results to those patients who received only chemotherapy.

Other Research

Winer, EP, et al (1999). Quality of life in patients surviving at least 12 months following high dose chemotherapy with autologous bone marrow support. Psycho-Oncology, 8: 167-176.

Methodology: Patients in this study included three groups of patients treated in clinical studies at Duke University. These patients had either metastatic breast cancer or high risk stage II/III breast cancer with more than ten positive lymph nodes. These women received identical high dose chemotherapy regiments, followed by autologous bone marrow transplants. Winer et al contacted patients 12 months after the conclusion of treatment to request their participation in this quality of life study. If the patient agreed to participate, the researchers sent the patients a questionnaire packet to complete. Later the researchers contacted each patient to conduct a telephone interview to collect data.

Results/conclusions: The researchers find that women who were disease-free reported higher quality of life than patients who had evidence of recurrent disease. However, this study does not have a con-

trol group, and does not provide any comparisons to quality of life for breast cancer patients who received conventional therapies.

Feigin, R, et al (2000). The psychosocial experience of women treated for breast cancer by high-dose chemotherapy supported by autologous stem cell transplant: a qualitative analysis of support groups. Psycho-Oncology, 9: 57-68.

Methodology: The subjects for this study were women who had undergone HDC-SCT. The researchers invited them to participate in small support groups. At the support groups, members discussed and processed their experiences with breast cancer and HDC-SCT in a structured atmosphere. A researcher transcribed the meetings. The researchers then used qualitative methods to explore the post-transplant psychosocial experience and how group support can help patients recover from the procedure.

Results/conclusions: First, the researchers found that psychosocial factors influence the treatment and recovery process. Second, the researchers noted that all participants described a complex care giving and receiving relationship that merits more research. Third, researchers found that the impact of the disease and treatment forced most of the patients into creating a new orientation to life. Fourth, the group offered psychological and emotional support that allowed the patients to cope with their experiences.

Frey, P, et al (2002). Outpatient transplantation, lack of caregivers limits use of outpatient hematopoietic stem cell transplant program. Bone Marrow Transplantation, 30: 741-748.

Methodology: This study included both breast cancer and hematologic malignancy patients. Each patient had to have a 24 hour caregiver to participate in the study. Patients and their caregivers were educated about the role or the caregiver. Then the patients and caregivers were housed in an outpatient facility, where they received daily monitoring by a home healthcare nurse. Patients who were ineligible for the outpatient group (usually because they did not have a caregiver) were accrued to an inpatient control group. In other words, assignment to groups was not a randomized procedure. Patients completed a weekly quality of life questionnaire, and caregivers kept a daily diary.

Results/conclusions: The study finds that delivering the treatment on an outpatient basis yields statistically significant cost savings, and no statistically significant differences in quality of life measures over delivering the treatment on an inpatient basis. Despite these findings, the

authors note that they had difficulty finding caretakers for patients, and most of the caretakers in their study were college-educated from families with incomes over $80,000 per year. This may indicate that the study's results are partly attributable to selection bias.

Atkins, D, Siegel, J, Slutsky, J (2005). Making policy when the evidence is in dispute. Health Affairs, 24: 102-113.

Presents a guide for making health care policy decisions when evidence is in question. The article points to using ABMT for breast cancer treatment as an instance of "acting on premature evidence."

Jantunen, E, et al. (2006). Early treatment-related mortality in adult autologous stem cell transplant recipients: a nation-wide survey of 1482 transplanted patients. European Journal of Haematology, 76: 245-250. [Abstract].

Methodology: The researchers retrospectively followed 1,482 Finish patients who received a stem cell transplant. 132 of those patients received the transplant for the treatment of breast cancer.

Results/conclusions: The researchers found that the risk of early treatment related death varied by diagnosis, but no early treatment related death was observed in patients receiving SCT for breast cancer. The highest risk of treatment related death from SCT was observed in patients being treated for amyloidosis and non-Hodgkin's lymphoma.

OTHER RESEARCH

American Cancer Society (2007). Cancer facts & figures 2007. http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf

Bunce, VC, Wieske, JP (2004). Health insurance mandates in the states, 2004. Council for Affordable Health Insurance. http://www.cahi.org/cahi_contents/resources/pdf/Mandatepub2004Electronic.pdf.

Government Accountability Office (1996). Coverage of ABMT for breast cancer. GAO/HEHS-96-83: 1-25.

Investigates the influences that caused insurers to cover ABMT while its effectiveness was still being studied, and the consequences of its increased use and coverage while it was still being studied. HDC-ABMT has a higher treatment morbidity and mortality rate than conventional treatments, and it has a higher cost than conventional treatments. In addition to the higher costs to the patient, the rapid proliferation of

HDC-ABMT had a high societal cost. Since patients could obtain HDC-ABMT treatments at many facilities nationwide, randomized clinical trials had difficulty accruing patients because patients did not want to run the risk of assignment to the conventional therapy group.

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