



PriorityHealth®

MEDICAL POLICY
No. 91066-R9

**BONE MARROW/PERIPHERAL STEM CELL/OR BLOOD CELL
TRANSPLANTATION**

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Summary of Changes

Clarifications:

- Page #1, under COVERAGE, language added to clarify the order in which transplant referrals will be directed and approved.

Deletions:

-

Additions:

-

COVERAGE

Allogenic or Autologous Bone Marrow, Peripheral Stem Cell, or other Blood Cell Transplants are a covered benefit for specific indications that are not experimental or investigational and for which the procedure has been proven to be effective. All bone marrow, peripheral stem cell, or other blood cell transplants must be pre-authorized by Priority Health and performed at a Priority Health approved facility. **Transplant referrals will be directed and approved in the following order:**

- 1. Priority Health network facilities. If not available in network, then**
- 2. LifeTrac Select facilities. If not available, then**
- 3. LifeTrac Supplemental facilities. If not available, then**
- 4. Out of network (OON) facilities.**

An approved Bone Marrow, Peripheral Stem Cell, or other Blood Cell Transplant includes coverage for the following:

1. Pre-transplant care
2. Transplant care, facility and professional fees
3. Harvesting of donor. Priority Health will cover donor fees for transplant recipients who are members, unless donor fees are covered by another Health Plan.
4. Post Transplant care, including immunosuppressant drug therapy if the group has outpatient prescription drug coverage.

General guidelines for consideration for bone marrow/stem cell transplantation must be met. These guidelines include, but are not limited to, the following:



The member must meet all of the criteria below:

1. Adequate major organ function and lack of major systemic complications to include adequate liver function, cardiac function, pulmonary function and renal function
2. Predicted ability to tolerate the surgical procedure as well as the post-transplant immunosuppression regimen and potential complications
3. Emotional and psychiatric stability, including a strong family or alternative support network (documented by formal social work evaluation)
4. Ability to understand the risks of the procedures

Priority Health does not cover bone marrow/stem cell transplantation when any of the following conditions are present:

1. Persistent or active substance or alcohol abuse
2. Presence of psychiatric disease that would interfere with the member's ability to comply with the pre or post transplant therapeutic regimen
3. Significant history of medical noncompliance
4. Unwillingness or inability to adhere to post transplant lifestyle restrictions and medical regimen

Transportation and lodging for the patient, donor or family are not a covered benefit.

Experimental, investigational or unproven bone marrow, peripheral stem cell, or other blood cell transplants are not a covered benefit unless coverage is determined to be appropriate under the Experimental/Investigational/Unproven Care/Benefit Exceptions medical policy or the Clinical Trials for Cancer Care medical policy.

LIMITS/INDICATIONS

Individual conditions and medical necessity criteria follow in this policy. Conditions not listed require medical director review.

Tandem bone marrow, peripheral stem cell, or other blood cell transplants are not a covered benefit unless approved under the Experimental/Investigational/Unproven Care/Benefit Exceptions medical policy or the Clinical Trials for Cancer Care medical policy. The following exception to non-coverage of tandem transplant applies: A tandem stem cell transplant may be covered for multiple myeloma as noted in that section of the policy.

Umbilical cord blood stem cell transplants (UCBSCT)

Priority Health covers UCBSCT in patients who meet all eligibility requirements for an allogeneic BMT but for whom a suitable bone marrow donor cannot be found and a suitable cord blood sample with a maximum of 3 HLA mismatches is available.

Priority Health does not cover UCBSCT in patients for whom a well-matched bone marrow donor is available. This coverage decision is based on unanswered questions regarding the relative efficacy of UCBSCT compared with BMT from a suitable donor.

Priority Health does not cover UCBSCT for patients not meeting patient selection criteria for AllBMT. This coverage decision is based on lack of evidence regarding safety and efficacy of



stem cell transplant in patients whose primary disease or overall physical condition do not warrant this procedure.

Special Notes:

See Experimental/Investigational/Unproven Care/Benefit Exceptions Medical Policy

See Clinical Trials for Cancer Care Medical Policy

MEDICAL NECESSITY REVIEW

Required

Not Required

Not Applicable

APPLICATION TO PRODUCTS

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

- ❖ **HMO/EPO:** *This policy applies to insured HMO/EPO plans.*
- ❖ **POS:** *This policy applies to insured POS plans.*
- ❖ **PPO:** *This policy applies to insured PPO plans.*
- ❖ **ASO:** *For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern.*
- ❖ **INDIVIDUAL:** *For individual policies, consult the individual insurance policy. If there is a conflict between this medical policy and the individual insurance policy document, the provisions of the individual insurance policy will govern.*
- ❖ **MEDICARE:** *Coverage is determined by the Centers for Medicare and Medicaid Services (CMS).*
- ❖ **MEDICAID:** *Coverage is determined by the Michigan Medicaid Provider Manual and the Michigan Medicaid Fee Schedule at: http://www.michigan.gov/mdch/0,1607,7-132-2945_42542_42543_42546_42551-159815--,00.html.*
- ❖ **MICHILD:** *For MICHILD members, this policy will apply unless MICHILD certificate of coverage limits or extends coverage.*

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Definitions

Tandem Transplantation is defined as two or more planned courses of high dose chemotherapy and stem cell support, either autologous or allogeneic. Tandem transplants are typically administered at intervals of two to six months, contingent on recovery from prior toxicity. Multiple cycles of high-dose chemotherapy with stem cell transplantation differs from tandem transplant in that more time is allowed between transplantation to permit hematopoietic recovery.

Responsive is defined as a tumor showing either a complete or partial remission. Partial remission is defined as at least a 50% reduction in tumor burden. For multiple myeloma, this is typically measured in terms of serum levels of beta-2 microglobulin or monoclonal immunoglobulins, both considered tumor markers for multiple myeloma.

Partial response is defined as at least a 50% reduction in tumor burden.

Refractory is generally defined as a less than 50% reduction in tumor burden, unless defined elsewhere in this policy. Therefore, even those tumors that exhibited a 30% reduction in tumor burden, for example, would be considered refractory. Tumor response can be measured using serial CT scans, or levels of circulating tumor markers, such as alpha-fetoprotein.

Sources of Stem Cells

Autologous: Stem cells may be harvested from the patient's bone marrow or more commonly, peripheral blood. Peripheral stem cells are harvested via one or more pheresis procedures. A prior course of chemotherapy (typically cyclophosphamide) or growth factors or both can increase the number of circulating stem cells.

Syngenic: Syngenic stem cells refer to genetically identical bone marrow or peripheral stem cells harvested from an identical twin.

Allogeneic: Allogeneic stem cell support (alloSCS) provides two theoretical advantages; the lack of tumor contamination of autologous stem cells and the possibility of a beneficial graft vs. tumor effect. Allogeneic stem cells can be harvested from either the bone marrow or peripheral blood. See policy on Non-Myeloablative Allogeneic Stem Cell Transplant.

Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft vs. host disease.

Stem Cell Transplants for Treatment of Non-Malignant Conditions

Allogeneic bone marrow transplants may be considered medically necessary for selected patients with the following disorders:

- Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage, and with an HLA-identical donor. Factors associated with a high risk of stroke or end-organ damage include: recurrent chest pain syndrome, recurrent vaso-occlusive crises, red blood cell alloimmunization or chronic transfusion therapy
- Severe or very severe aplastic anemia, including congenital (e.g., Fanconi's anemia or Diamond-Blackfan syndrome) or acquired (e.g., secondary to drug or toxin exposure) forms. Appropriate patients include those with platelets less than $20 \times 10^9/L$, granulocytes less than $0.5 \times 10^9/L$, and reticulocytes less than 1% (corrected for hematocrit) and who have failed antithymocyte globulin therapy.
- Homozygous beta-thalassemia (i.e., thalassemia major)
- Wiskott-Aldrich syndrome
- Severe combined immunodeficiencies



- Infantile malignant osteopetrosis (Albers-Schönberg disease or marble bone disease)
- Mucopolysaccharidoses (e.g., Hunter's, Hurler's Sanfilippo, Maroteaux-Lamy variants) in patients who are neurologically intact);
- Mucopolidoses (e.g., Gaucher's disease, metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy) for patients who have failed conventional therapy (e.g., diet, enzyme replacement) and who are neurologically intact.
- Kostmann's syndrome
- Leukocyte adhesion deficiencies
- X-linked lymphoproliferative syndrome

High Dose Chemotherapy and Autologous Stem Cell Support for Autoimmune Diseases, Including Multiple Sclerosis

Autoimmune Diseases

There are over 40 disorders that are recognized as having an autoimmune pathogenesis, ranging from some cases of insulin dependent diabetes mellitus to rheumatoid arthritis and other connective tissue diseases to multiple sclerosis (MS). Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (i.e., rheumatoid arthritis, systemic lupus erythematosus [SLE], and scleroderma). However, a subset of patients does not respond to or cannot tolerate long-term immunosuppression. In this select group of patients, high dose chemotherapy with autologous stem cell support has been investigated as a curative technique. The rationale is based on the premise that autoimmune diseases are the manifestation of a clonal proliferation of pathogenic lymphocytes, which can be eliminated through marrow ablation. The premise depends on the hypothesis that the pathogenic clone of lymphocytes is not related to an abnormal clone of stem cells; otherwise, one would expect disease recurrence after the autologous stem cells are reinfused.

The autoimmune diseases that have been most commonly treated with high dose chemotherapy and autologous stem cell support include rheumatoid arthritis, scleroderma, SLE, and multiple sclerosis.

Policy/Criteria

High dose chemotherapy and autologous or allogeneic stem cell support is considered investigational as a treatment of autoimmune diseases, including, but not limited to: multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and systemic sclerosis (i.e., scleroderma).

High Dose Chemotherapy and Autologous Stem Cell Support for Malignant Astrocytomas and Gliomas.

Astrocytomas and Gliomas

Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into three grades of malignancy, grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme. Oligodendrogliomas are diffuse neoplasms that are clinically and biologically most closely related to the diffuse fibrillary astrocytomas. However, these tumors have generally better prognoses than diffuse astrocytomas with mean survival times of 10 years. In addition, oligodendrogliomas appear to be more chemosensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than 2 years for most patients.

Treatment of primary brain tumors focuses on surgery, either with curative intent or optimal tumor debulking. Surgery may be followed by radiation therapy and/or chemotherapy. Survival after chemoradiotherapy is largely dependent on the extent of residual tumor after surgical debulking. Therefore tumors arising in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex, which typically cannot be extensively resected, have a particularly poor outcome. Treatment of children less than 3 years old is complicated by the long-term effects of radiation therapy on physical and intellectual function. Therefore, in young children, CNS radiation is avoided whenever possible.



Astrocytomas and gliomas arise from the glial cells. Tumors arising from the neuroepithelium constitute a separate category of malignancies that include CNS neuroblastoma, medulloblastoma, ependymoblastomas, and pineal blastomas. Collectively these tumors may be referred to as primitive neuroectodermal tumors (PNETs).

Policy/Criteria

High dose chemotherapy with autologous or allogeneic stem cell support is considered investigational as a treatment of malignant astrocytomas and gliomas. (The latter diagnosis includes both glioblastoma multiforme and oligodendroglioma).

Background

Although there has been much research interest in use of high dose chemotherapy for glioblastoma multiforme due to its uniformly poor prognosis, the published literature is relatively scant, consisting primarily of single institution case series. The following are representative examples.

Bouffet and colleagues reported on a series of 22 children and young adults with high-grade gliomas treated with high dose chemotherapy and autologous stem cell support. The response rate was 29% with one complete and three partial responses. However, the authors concluded that survival with high dose chemotherapy was no better than that reported with conventional treatments. Heideman and colleagues reported on a case series of 13 pediatric patients with bulky disease or recurrent disease treated with high dose chemotherapy and radiotherapy. While the overall response rate was 31%, the authors similarly concluded that overall survival was no better than conventional treatment regimens. Finlay and colleagues reported on a 1996 case series of 45 children and young adults with a variety of recurrent CNS tumors, including gliomas, medulloblastomas, ependymomas, and primitive neuroectodermal tumors. Of the 18 patients with high-grade gliomas, the response rate was 29%. The median survival of this group was 12.7 months. Of the 5 long-term survivors, all had high-grade glioma with minimal residual disease at the time of high dose chemotherapy. Based in part on these results, the authors recommend aggressive surgical debulking before high dose chemotherapy is even considered.

Studies focusing on the use of high dose chemotherapy in adults with glioblastoma multiforme report results similar to those in children, i.e., high dose chemotherapy appears most successful in those with minimal disease at the time of treatment, with an occasional long-term survivor. Cairncross and colleagues treated 20 adults with chemosensitive oligodendrogliomas with high dose thiotepa followed by autologous stem cell transplant. Four patients (20%) died of treatment related toxicities; 4 had complete response and 16 had a partial response. Four patients (20%) are alive and tumor-free at a median 31 months after high dose thiotepa. The authors considered the results to be disappointing.

Researchers agree that Phase III trials are needed to confirm these preliminary findings, particularly to control for patient selection bias. For example, because of the morbidity and mortality of high dose chemotherapy, candidates for this aggressive therapy are typically in better physical condition with a better prognosis than the overall group of patients with the disease. Therefore the evaluation of high dose therapy should ideally include a control group for comparison, since any survival benefit associated with high dose chemotherapy could be related to the improved prognosis entirely independent of any effect of high dose chemotherapy. To date, there have been no controlled clinical trials published.

A search of the National Cancer Institute database on ongoing clinical trials (PDQ database) identified 3 phase II trials in adult patients with brain tumors that included high dose chemotherapy; two of the studies focused on oligodendroglioma and one focused on glioblastoma multiforme or brain stem tumors. In children one phase II study was identified focusing on children less than 10 years old with newly diagnosed malignant brain tumors. This study includes children with malignant gliomas as well as medulloblastomas or other tumors derived from neuroectodermal cells. There were no phase III studies identified.



High Dose Chemotherapy with Hematopoietic Stem Cell Support for Breast Cancer

Breast Cancer

Breast cancer is commonly categorized according to the stage of disease. High dose therapy has been investigated as a treatment of high risk Stage II disease, Stage III, and Stage IV disease defined as follows:

High Risk Stage II

Involvement of 4 or more axillary lymph nodes without spreading outside the axilla

Stage IIIA:

Presence of fixed axillary lymph nodes, OR

Primary tumor larger than 5 cm with involvement of axillary lymph nodes

Stage IIIB:

Presence of brawny induration of skin overlying the breast due to involvement of dermal lymphatics (also known as inflammatory breast cancer; OR

Any size primary tumor, but involvement of ipsilateral internal mammary arteries

Stage IV:

Presence of distant metastases (Involvement of the axilla, chest wall, internal mammary arteries, or contralateral breast is defined as locoregional disease, and does not constitute distant disease.)

Scientific Evidence

Breast cancer affects 1 in 9 American women during their lifetimes and is the second leading cause of cancer death among women. Life expectancy after diagnosis varies by the stage of cancer at the time of diagnosis. The prognosis for high-risk primary breast cancer, that is, stage II or stage III breast cancer with extensive axillary lymph node involvement, or for inflammatory breast cancer, is poor despite surgery, radiotherapy, and standard-dose chemotherapy, and the 5-year survival for patients with stage IV metastatic breast cancer is less than 10%. The fact that breast cancers become resistant to standard chemotherapy regimens has led researchers to investigate whether anticancer drugs can kill breast cancer cells more effectively when given in much higher doses than used in standard chemotherapy. Since HDC is highly toxic to the bone marrow and causes a profound suppression of hematopoietic activity, blood stem cells are harvested from the peripheral circulation or from the bone marrow of the patient and then returned after treatment to aid in regeneration of the hematopoietic system, a procedure known as autologous stem cell support (AuSCS). The pivotal question regarding HDC/AuSCS is the following:

- Does HDC/AuSCS improve disease-free or overall survival for patients with metastatic, inflammatory, or high-risk primary breast cancer compared with standard-dose chemotherapy?

Findings: Until recently, the only evidence regarding the efficacy of HDC/AuSCS for the treatment of metastatic or high-risk primary breast cancer has come from nonrandomized phase II clinical trials and retrospective studies. The results of these studies held some promise that HDC/AuSCS might be more effective than standard-dose chemotherapy, since tumor response rates were higher than those reported for conventional chemotherapy, and some authors reported increased disease-free survival. However, rates of treatment-related morbidity and mortality were high, and there was no definitive evidence that the initial superior response rates translated into better long-term survival or higher probability of cure. When preliminary results of randomized clinical trials comparing HDC/AuSCS with standard-dose chemotherapy began to be published in 1998, the promising early results of the



phase II trials were not confirmed. To date, there are no randomized trials that report any disease-free or overall survival advantage with HDC/AuSCS for patients with high-risk breast cancer, defined as patients with an operable primary tumor but extensive involvement of axillary lymph nodes, and only one that describes superior results for metastatic breast cancer. This one randomized trial provides very weak evidence at best, since the principal investigator has since been charged with scientific misconduct connected with a subsequent clinical trial, and there are concerns regarding the adequacy of the “standard-dose” therapy administered in this trial.

As of March 2000, only relatively small randomized trials comparing HDC/AuSCS with standard-dose chemotherapy for metastatic and high-risk primary breast cancer have been published, and there have been no reports from randomized trials regarding the efficacy of HDC/AuSCS for inflammatory breast cancer. Although interim results of several ongoing, large-scale, randomized, clinical trials of HDC/AuSCS have been reported at professional meetings, data collection is incomplete, and study results have not yet been published in the peer-reviewed scientific literature.

While HDC-related mortality and morbidity has decreased somewhat with improved use of supportive measures to facilitate the restoration of bone marrow function, it is still higher than that associated with standard-dose chemotherapy. Recent studies have shown that potential late complications of HDC include development of leukemia or other malignancies, and cognitive impairment due to central nervous system toxicity, in addition to the more immediate toxic effects on the heart, liver, gastrointestinal, and hematopoietic systems.

Results from studies published in the last several years indicate that, for many patients, peripheral blood stem cell transplantation (PBSCT) can be more effective, with lower morbidity and cost than autologous bone marrow transplantation (AuBMT), and support a trend toward use of PBSCT for patients who have undergone HDC. A number of experimental approaches are being used to purge cancerous cells from the collected material in an attempt to prevent reintroduction of cancer cells during stem cell transplant. In addition, growth factors, or cytokines, are being used to increase the number of circulating stem cells and enhance collection prior to HDC, or to stimulate recovery of immune function after treatment. Other techniques being investigated for patients with advanced breast cancer include tandem transplants, where the HDC and stem cell rescue are performed twice. At the present time, there have been no randomized controlled studies to evaluate the effect of these procedures on patient survival, and no optimal HDC regimens have been identified.

Conclusions: Results from a number of nonrandomized phase II clinical trials of HDC/AuSCS for patients with metastatic or high-risk primary breast cancer have suggested that this therapy could provide superior tumor response rates and might improve survival. However, retrospective analysis of these studies indicates that patient selection bias may have been a major factor in producing the encouraging results since patients selected for HDC are typically younger and have better prognostic features than patients selected for standard-dose chemotherapy. Recently published randomized phase III trials comparing HDC/AuSCS with standard-dose chemotherapy have not demonstrated any significant difference in tumor response or survival between the two treatments but have documented a higher rate of morbidity and mortality associated with HDC/AuSCS. To date, the published randomized trials have involved relatively small cohorts of patients with metastatic or high-risk primary breast cancer, and none have addressed the effect of HDC/AuSCS in patients with inflammatory breast cancer. Definitive conclusions regarding the efficacy of HDC/AuSCS must await the completion and publication of large-scale randomized clinical trials with adequate long-term follow-up.

Policy/Criteria

High dose chemotherapy followed by autologous stem cell support (HDC/AuSCS) is considered investigational to treat all stages of breast cancer, including Stage I, II, III, or IV disease.

Tandem autologous transplantation (i.e., two or more courses of high dose chemotherapy with autologous stem cell support) is considered investigational as a treatment of breast cancer.

High dose chemotherapy with allogeneic stem cell support is considered investigational as a treatment of breast cancer.



Tandem Transplant

A February 2002 updated search of the literature reveals a number of phase I and II clinical trials reporting preliminary results of a variety of strategies of tandem high-dose chemotherapy followed by stem cell support. The trials use as many as 4 high dose chemotherapy courses, fourteen to twenty-eight days apart. Some of the trials use the same high-dose regimen while others use different drug combinations for the various courses in the protocol. Few of the trials report survival and none randomize patients to tandem transplant or conventional chemotherapy regimens. Therefore, conclusions cannot be made concerning the safety and efficacy of tandem transplants for breast cancer.

High Dose Chemotherapy and Hematopoietic Stem Cell Support for Epithelial Ovarian Cancer

Epithelial Ovarian Cancer

Ovarian cancer is the fifth most common cancer in women, with a 1 in 70 (1.4%) occurrence. The American Cancer Society projects that, in 1998, approximately 25,400 new cases of ovarian cancer will be diagnosed in the United States and 14,500 deaths will result from the disease. Epithelial ovarian cancer accounts for approximately 90% of ovarian neoplasms. More than 80% of epithelial cancer patients are postmenopausal, and the median age of onset is 64. The signs and symptoms of epithelial ovarian cancer are vague and ambiguous. There are no reliable screening tests, and early-stage disease is often detected coincidentally during a routine pelvic examination. Over 75% of patients initially present with advanced-stage disease, and 5-year survival for these patients is reported to be from 20% to 30%. For patients with the most advanced (stage IV) disease, 5-year survival is approximately 5%. Approximately 76% of all epithelial ovarian cancer patients survive longer than 1 year after diagnosis, and 46% survive to 5 years.

Epithelial ovarian cancer will remain intraperitoneal until late in its natural history. Aggressive surgical debulking is the first-line treatment for all patients, followed by chemotherapy with a platinum-based regimen for patients with advanced disease. A recent landmark phase III randomized study of stage III and IV patients with more than 1 cm residual disease after surgical debulking has resulted in the addition of paclitaxel to platinum agents as standard of care for induction chemotherapy. Epithelial ovarian cancer is a chemotherapeutically sensitive tumor with initial response rates of 60% to 80%. Duration of initial response, however is typically short. Relapse rates of up to 60% are reported for high-risk stage I and stage II patients. In patients with stage III and stage IV disease, 70% to 90% will ultimately progress or relapse after first-line treatments. Response to conventional-dose salvage therapy is between 10% to 40%, with an average duration of 6 months and no proven association with prolonged survival. Median survival after first relapse is approximately 1 year. Most patients eventually die from drug-resistant disease. This poor prognosis has led to research into alternative therapies to overcome the pattern of cancer cell resistance to chemotherapy and to improve treatment outcomes. Such therapies include new combinations of conventional-dose regimens, dose-intensive regimens delivered directly into the peritoneal cavity or systemically at sub-myeloablative protocols, and HDC/AuSCS.

In vitro and in vivo studies document a dose response to platinum-based chemotherapy for ovarian cancer. This favorable association between response and dose intensity provides the rationale for delivering high-dose chemotherapy at myeloablative levels followed by rescue infusion of stem cells to restore normal hematologic function. Optimal dose levels for HDC/AuSCS have yet to be determined. There appears to be no evidence of benefit for doubling the dose of chemotherapy beyond 100mg/m². Numerous early phase trials of HDC/AuSCS suggest that the slope of the dose-response curve may increase again for escalation approximately five times the conventional-dose range.

Relevant questions regarding this technology for the treatment of epithelial ovarian cancer are:

- Is there evidence to support that HDC/AuSCS, compared with conventional-dose chemotherapy, improves survival of patients with epithelial ovarian cancer
- Which patients are most likely to benefit from HDC/AuSCS
- What is the treatment-related mortality associated with HDC/AuSCS for epithelial ovarian cancer?



Findings: No randomized controlled trials or controlled clinical trials reporting outcomes for ovarian cancer patients treated with HDC/AuSCS have been published in the peer-reviewed scientific literature. In the absence of such research, it is not possible to measure outcomes from HDC/AuSCS against those from conventional-dose chemotherapy since there is no basis for comparison. The National Cancer Institute (NCI) and the Gynecologic Oncology Group (GOG) are sponsoring a phase III randomized study of salvage therapy with conventional-dose versus HDC/AuSCS in chemosensitive, low-bulk stage III or stage IV epithelial ovarian cancer. Results from this trial (GOG-164) may answer the question of how HDC/AuSCS compares with conventional-dose therapy in the treatment of patients with relapsed, advanced disease. Quality-of-life indicators appropriate for patients treated with HDC/AuSCS are a matter of debate and not addressed in the specific literature selected for this review.

At present, the literature is dominated by meeting abstracts and small, uncontrolled, phase I/II case series reports. Meeting abstract data are too preliminary to adequately assess and have been excluded from this review. The three trials with at least 30 subjects suggest a role for HDC/AuSCS for some select patients, although there are extremely discordant results from the two largest trials. Uncontrolled case series data are widely acknowledged to be limited and must be interpreted with caution. At best, such data may provide important information concerning issues of morbidity and patient selection criteria but can only hint at efficacy by documenting clinical course and prognosis. The International Bone Marrow Transplant Registry report on outcomes of 390 women receiving HDC/AuSCS for ovarian cancer from 1998 to 1996 suggests benefit for some patients. However, registry data is considered at par with case series data. In the absence of published data from well-designed and executed research trials, the efficacy of HDC/AuSCS is undetermined.

Conclusions: There is no conclusive proof that HDC/AuSCS versus conventional-dose chemotherapy improves survival of patients with ovarian cancer. Patient selection criteria for this procedure have not been clearly defined. There is some preliminary data to suggest that age, degree of chemosensitivity, and tumor burden are prognostic factors associated with prolonged survival, but this is also true for conventional chemotherapy. HDC/AuSCS is associated with increased risk of treatment-related mortality, with up to 14% reported in the literature.

The frequent recurrence of ovarian cancer has prompted interest in high dose chemotherapy and autologous stem cell support. A variety of patient groups have been studied as follows:

- As initial treatment
- Treatment of relapse after an initial favorable response to platinum-based chemotherapy
- Treatment of tumors whose initial response lasted less than 6 months
- Treatment of refractory tumors

Policy/Criteria

High dose chemotherapy with autologous or allogeneic stem cell support is considered investigational as a treatment of epithelial ovarian cancer.

Background

In patients with no prior conventional dose chemotherapy, response rates suggest that high dose therapy increases the objective response rate compared to patients treated with conventional-dose chemotherapy. Age bias, and different distributions of case types, however, may flaw this comparison. Response duration and survival data are not available for comparison. Increased treatment-related mortality is also possible with high dose therapy.

In patients with prior treatment with conventional chemotherapy, the clinical response rates for high dose chemotherapy appear to be much better than those for conventional dose regimens. Subgroup analysis shows high response rates for platinum-sensitive, optimally debulked patients. Minimum values for median response duration and survival for HDC are similar to the values from the trials of conventional dose chemotherapy; the maxima suggest markedly improved response duration and overall survival. Data from the Autologous Blood and Marrow Transplant Registry, however, do not show similarly high survival for similar subgroups. Comparison with conventional dose chemotherapy is again likely to be biased due to age and different distributions of case types.



In August 2001 Donato published preliminary results of a phase I trial in 53 women with refractory and/or recurrent ovarian cancer. All had been previously treated with paclitaxel and platinum. The high dose regimen included topotecan, melphalan, and cyclophosphamide followed by autologous stem cell transplant. Patient outcomes were documented for a median of 18 months. The overall response rate in the 30 patients with measurable disease was 93%. It was reported that toxicity was acceptable and there were no treatment-related deaths. The stated goal of this study was to develop an effective high dose chemotherapy regimen and to maximize dose intensity with acceptable toxicity. The authors state that in the setting of ovarian cancer, high dose regimens should be given only as part of a well-designed clinical trial: "Phase II data, although promising, are influenced by selection factors, and therefore efforts should be put into large randomized trials so that the role of transplantation can be more clearly defined. To date, there is no unbiased evidence to support the use of high-dose chemotherapy outside of clinical trials."

High Dose Chemotherapy with Autologous Stem Cell Support for Primitive Neuroectodermal Tumors (PNET) and Ependymoma

Primitive Neuroectodermal Tumors (PNET)

Primitive neuroectodermal tumors include medulloblastoma, neuroblastoma arising in the central nervous system, ependyoblastoma, or pineal blastoma. All show a similar histology and are principally distinguished by their site of origin. Essentially, medulloblastoma may be considered a cerebellar or posterior fossa PNET or pineoblastoma may be considered a PNET arising in the pineal gland, or neuroblastomas may be considered a central PNET. Using this conceptual framework many of the studies include PNETs in general and do not make a distinction between the site of origin. However, medulloblastoma is the most common type of PNET. Treatment focuses on optimal surgical resection with or without radiation therapy. The use of radiotherapy in children may be limited by its neurodevelopmental side effects.

Ependymoma

Ependymoma is a neuroepithelial tumor that may arise throughout the CNS, but is typically contiguous with the ventricular system. In children the tumor typically arises intracranially, while in adults a spinal cord location is more common. Ependymomas are distinct from ependyoblastomas due to their more mature histologic differentiation. For this reason, ependymomas are not formally considered a member of the PNET family.

Policy/Criteria

High dose chemotherapy (with or without associated radiotherapy) and autologous stem cell support may be considered medically necessary for the treatment of recurrent or refractory medulloblastoma and other primitive neuroectodermal tumors (PNETs). Refractory is defined as a tumor that does not achieve a complete response after initial therapy. High dose chemotherapy (with or without associated radiotherapy) and autologous stem cell support is considered investigational as a treatment of ependymoma.

High dose chemotherapy (with or without associated radiotherapy) and allogeneic stem cell support is considered investigational as a treatment of medulloblastoma, PNETs or ependymoma.

Primitive Neuroectodermal Tumors (PNET)

Initial therapy of PNETs focuses on neurosurgical resection and radiation therapy with or without adjuvant conventional chemotherapy. Sixty percent children experience a 5-year survival with this approach. In patients with primary refractive or recurrent disease, further surgery or radiation therapy is usually not an option and conventional chemotherapy is rarely successful. Therefore, high dose chemotherapy for PNET has focused primarily on recurrent disease. The most common PNET is medulloblastoma, and thus most of the data focus on this diagnosis. In the largest case series of recurrent medulloblastomas reported to date, Dunkel and colleagues reported on 23 patients with recurrent medulloblastoma treated with high dose carboplatin, thiotepa, and etoposide. Seven of the 23 patients were event-free survivors at a median of 54 months with overall survival estimated at 56% at 36 months. In contrast the median survival after recurrent medulloblastoma treated with conventional therapy may be as low as 5 months.



High dose chemotherapy is expected to be most effective when the disease burden is minimal. Dunkel and colleagues suggest increased surveillance for recurrence, or aggressive surgical debulking at the time of recurrence. The authors also acknowledge the potential existence of a patient selection bias since not all patients eligible for the protocol were enrolled. Other PNETs are uncommon and include pineal blastoma, ependymoblastoma, and central neuroblastoma. There are very little data regarding high dose therapy for these rare tumors, although it is thought that the results with medulloblastoma may be extrapolated to other PNETs.

Ependymoma

Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy typically does not play a role in the initial treatment of ependymoma. However, relapse of ependymoma is common, typically occurring at the site of origin. Treatment of recurrence is problematic; further surgical resection or radiation therapy is usually not possible. Given the poor response to conventional dose chemotherapy, high dose chemotherapy has been investigated as a possible salvage therapy. At the present time, published literature regarding high dose chemotherapy for ependymoma consists primarily of small case series. For example, Mason and colleagues reported on a case series of 15 patients with recurrent ependymoma. Five patients died of treatment related toxicities, 8 died from progressive disease, and 1 died of unrelated causes. After 25 months, 1 patient remains alive, but with tumor recurrence. The authors concluded that their high dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill and colleagues similarly reported a disappointing experience in 16 children treated with a thiotepa-based high dose regimen.

A January 2002 updated search of the literature reveals no new published data on HDC with autologous stem cell support for ependymoma since the initial data noted above. A separate literature search for data on HDC with allogeneic stem cell transplant also revealed no published data for PNETs or ependymoma.

High Dose Chemotherapy and Hematopoietic Stem Cell Support as a Treatment of Germ Cell Tumors

Germ Cell Tumors

Germ cell tumors comprise the vast majority of primary testicular neoplasms, although germ cell tumors can arise in the ovary and in extragonadal locations, such as in the retroperitoneum or mediastinum. Germ cell tumors can be classified according to their histology, stage, prognosis, or response to chemotherapy.

Histologies include seminoma, embryonal carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed germ cell tumors. Seminomas are the most common; all other types of germ cell tumors may be collectively referred to as non-seminomatous germ cell tumors.

The stage is dependent on the location of the tumor. In terms of testicular tumor, Stage I is limited to the testis, stage II is disease spread to the retroperitoneum, and Stage III disease is distant (supradiaphragmatic) disease.

Prognostic classification systems take into account the site of primary tumor (testis versus extragonadal), tumor marker levels, and site of visceral disease. Therapy is often dictated by the prognosis. For example, first line therapy for good and intermediate risk patients is usually 3 or 4 cycles of the combination regimen of cisplatin, bleomycin, and etoposide. Second line therapy often consists of combined therapy with vinblastine, ifosfamide, and cisplatin. Patients whose tumors are resistant to cisplatin may proceed to regimens containing carboplatin. Chemotherapy is often followed by surgery to remove residual masses. Regimens used for relapsed disease include cisplatin plus ifosfamide, combined with either etoposide or vinblastine. The probability of long-term continuous complete response diminishes with each successive relapse. Experience with repeated relapses after chemotherapy and disappointing results in poor risk patients have prompted interest in high dose chemotherapy.

Policy/Criteria

High dose chemotherapy and autologous stem cell support may be considered medically necessary as a treatment of germ cell tumors that do not achieve a complete remission, i.e., refractory germ cell tumors or those exhibiting a partial response



High dose chemotherapy and autologous stem cell support may be considered medically necessary as a treatment of patients in second complete remission or in second relapse.

High dose chemotherapy and autologous stem cell support is considered investigational as an initial treatment (i.e., in lieu of an initial course of conventional chemotherapy) of poor risk germ cell tumors or as a treatment following first relapse (i.e., in lieu of a course of conventional chemotherapy).

Tandem high dose chemotherapy and autologous stem cell support is considered investigational as a treatment of germ cell tumors.

High dose chemotherapy and allogeneic stem cell support is considered investigational as a treatment of germ cell tumors, including but not limited to its use as therapy after a prior failed high dose chemotherapy with autologous stem cell support.

High Dose Chemotherapy and Hematopoietic Stem Cell Support for Hodgkin's Disease

Hodgkin's Disease

Hodgkin's disease is a lymphoid malignancy. The hallmark of the disease is effacement of the normal lymph node architecture by a heterogeneous infiltration of normal-appearing lymphocytes, plasma cells, eosinophils, and fibroblasts. The one characteristic component, and presumably the malignant component, is the Reed Sternberg cell (or one of its variants), a large binucleate cell with prominent nucleoli. Hodgkin's disease is subdivided into four subtypes: lymphocytic predominant (15% of cases), nodular sclerosing (70%), mixed cellularity (10%), and lymphocyte depleted (5%). Both the lymphocyte predominant and nodular sclerosing variants are more common in adolescents and young adults. Mixed cellularity and lymphocyte depleted are more common in older patients and frequently are present with advanced disease.

The following staging system for HD recognizes the fact that HD is thought to typically arise in a single lymph node and spread to contiguous lymph nodes with eventual involvement of extranodal sites. The staging system attempts to distinguish patients with localized HD who can be treated with extended field radiation from those who require systemic chemotherapy.

Staging for Hodgkin's Disease

Stage I

Involvement of a single lymph node region or a lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)

Stage II

Involvement of two or more lymph node regions to the same side of the diaphragm. The number of anatomic sites should be indicated by a subscript (e.g., II₂)

Stage III

Involvement of lymph node regions or structures on both sides of the diaphragm. These patients are further subdivided as follows:

III-1: disease limited to spleen or upper abdomen

III-2: periaortic or pelvic node involvement

Stage IV

Involvement of extranodal sites beyond that designated E (see below):



A: No symptoms

B: Fever, drenching sweats, weight loss

X: Bulky disease

E: Involvement of a single extranodal site, contiguous or proximal to a known nodal site

Staging includes not only the sites of involvement, but also other factors described by the letters A, B, X, and E above, i.e., a patient could have Stage IIB HD, indicating involvement of two or more lymph node groups on the same side of the diaphragm with the presence of systemic symptoms.

Treatment of HD involves the use of radiation therapy alone (for Stage I and II disease), the use of chemotherapy (for Stage IIIB and IV), or combined radiation and chemotherapy (for patients with bulky disease and for some patients with Stage IIIA disease). The most common chemotherapy regimen consists of mechlorethamine (nitrogen mustard), Oncovin (the trade name of vincristine) procarbazine, and prednisone, otherwise known as MOPP.

Although combination chemotherapy with ABVD (Adriamycin [trade name of doxorubicin], bleomycin, vinblastine, dacarbazine) is most commonly used as a salvage therapy, it is also used as initial chemotherapy, or in an alternating schedule with MOPP in patients who present with advanced disease.

Despite the generally favorable results of irradiation and chemotherapy, relapses can occur in up to 10%-20% of those with localized disease and 30%-40% of those patients with advanced (Stage III or IV) disease. The potential for long-term cure is related to the length of the first remission. Patients with relapsing disease are generally divided into 3 categories: those who fail to achieve an initial remission (primary refractory), those with a remission lasting longer than 12 months, and those with a remission of less than 12 months. High dose chemotherapy with stem cell support has been investigated for those patients who fail to achieve an initial complete remission, those with a remission of less than 12 months or those with multiple relapses.

Policy/Criteria

High dose chemotherapy with either autologous or allogeneic stem cell support may be considered medically necessary in patients with primary refractory Hodgkin's disease, or Hodgkin's disease relapsing less than one year after completion of an initial course of chemotherapy.

High-dose chemotherapy with allogeneic stem cell support is considered investigational as a treatment of Hodgkin's disease relapsing after prior therapy with high-dose chemotherapy and autologous stem cell support.

Tandem high-dose chemotherapy and autologous stem cell support for Hodgkin's disease is considered investigational.

High Dose Chemotherapy and Hematopoietic Stem Cell Support for Non-Hodgkin's Lymphomas

Non Hodgkin's lymphomas are neoplasms arising from lymphocytes arrested at various stages of maturation. NHLs can be categorized according to their histologic type, their grade, stage, on the basis of immunophenotyping, or a combination of the above. While immunophenotyping is a rapidly evolving field, the system most commonly used in the current literature is the International Working Formulation (IWF), summarized below:

IWF Class	Histologic Type	Grade
B*	follicular, small cleave cell	Low
C*	follicular, mixed small cleaved and large cell	Low
D*	follicular large cell	intermediate
E	diffuse small cleaved cell	intermediate



F	diffuse mixed small and large cell	intermediate
G	diffuse large cell (histiocytic)	intermediate
H	Large cell immunoblastic	high
I	Lymphoblastic	high
J	small non-cleaved cell (Burkitt's lymphoma)	high

Follicular refers to an architectural pattern in which the neoplastic cells are arranged in nodules, or follicles, within the lymphocyte. Follicular lymphomas arise from a B lymphocyte. In diffuse lymphomas, the normal architecture of the lymph node is entirely effaced. Diffuse lymphomas may arise from B or T cells.

In general, intermediate and high-grade NHLs are considered unfavorable histologies that tend to progress rapidly. However, these subtypes of NHL tend to be more responsive to irradiation and/or chemotherapy. Although the low-grade lymphomas are more indolent than other types of lymphomas, they also are more rarely cured with conventional doses of radiation and/or chemotherapy. When lymphomas relapse, the histologies tend to be similar to that of the original lymphoma. However, relapsed lymphomas may also exhibit transformation, in which the histology transforms into a picture consistent with a higher-grade lymphoma. Transformed lymphomas are associated with a poor prognosis and constitute a separate category distinct from de novo high-grade lymphomas.

Policy/Criteria

High dose chemotherapy with either autologous or allogeneic stem cell support may be considered medically necessary as a salvage therapy of intermediate or high-grade lymphoma that has not undergone transformation.

High dose chemotherapy with either autologous or allogeneic stem cell support may be considered medically necessary as a therapy of relapsed low-grade follicular lymphoma that has not undergone transformation.

High dose chemotherapy with autologous or allogeneic stem cell support is considered investigational as initial therapy of all non-Hodgkin's lymphomas.

High dose chemotherapy with autologous or allogeneic stem cell support is considered investigational as a treatment of all non-Hodgkin's lymphomas that have relapsed with transformation to a higher-grade histology.

Tandem high-dose chemotherapy and autologous stem cell transplant for non-Hodgkin's lymphoma is considered investigational.

High Dose Chemotherapy and Allogeneic Stem Cell Support for Myelodysplastic Diseases

Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) refers to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into acute myelocytic leukemia (AML). MDS can occur as a primary (i.e., idiopathic form), or be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40%-60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome (i.e., trisomy 8). The most widely accepted classification system for MDS is the French-American-British (FAB) system that identifies 5 types of MDS with increasing numbers of circulating blast cells as follows:

- Refractory anemia (RA)



- Refractory anemia with ringed sideroblasts (RARS)
- Refractory anemia with excess blasts (RAEB)
- Refractory anemia with excess blasts in transformation (RAEBT)
- Chronic myelomonocytic leukemia (CMML)

Patients either succumb to disease progression to AML or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

Myeloproliferative Disorders

The myeloproliferative disorders are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. Myeloproliferative disorders include the following:

- Polycythemia vera (PV) is characterized by an expansion of the total red cell mass. Initial treatment focuses on phlebotomy to reduce red cell mass and viscosity. However, the disease inevitably progresses and after a median survival of 15 years, patients typically succumb to thrombotic complications or leukemic evolution.
- Essential thrombocythemia (ET) is characterized by an isolated expansion of the megakaryocytic lineage. The median survival is 10 years with most deaths due to thrombotic complications.
- Agnogenic myeloid metaplasia with myelofibrosis, also known as primary myelofibrosis is characterized by marrow fibrosis, splenomegaly and extramedullary hematopoiesis.
- Chronic myeloid leukemia. This disease is considered separately in policy Transplant 31.

Policy Guidelines

Given the long natural history of myelodysplastic syndrome, high dose chemotherapy with allogeneic stem cell support is typically considered in those with increasing number of blasts, signaling a possible transformation to acute myeloid leukemia. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for high dose chemotherapy with allogeneic stem cell support when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils less 500/mm³, platelets less than 20,000/mm³).

Patients with myeloproliferative disorders may be considered candidates for high dose chemotherapy with allogeneic stem cell support when there is progression to myelofibrosis, or when there is evolution toward acute leukemia. In addition, high dose chemotherapy may be considered in patients with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder.

High Dose Chemotherapy and Hematopoietic Stem Cell Support for the Treatment of Chronic Myelogenous Leukemia

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia is a malignancy arising from a primitive hematopoietic stem cell and is characterized by the presence of a chromosomal abnormality called the "Philadelphia" chromosome. The natural history of the disease consists of an initial indolent phase, lasting a median of 3 years, that typically transforms into an accelerated phase, followed by a "blast crisis," which is usually the terminal event.

**Policy/Criteria**

High dose chemotherapy with allogeneic stem cell support may be considered medically necessary as a treatment of chronic myelogenous leukemia.

High dose chemotherapy with autologous stem cell support is considered investigational as a treatment of chronic myelogenous leukemia.

Background

Allogeneic transplant has emerged as the standard treatment of CML when a suitable stem cell donor is available. It is estimated that chronic phase patients receiving an HLA-matched sibling donor transplant have a 45%-75% probability of long-term disease free survival, while those transplanted with more advanced disease have a 15%-40% long-term survival.

Recent literature has focused on the use of nonmyeloablative chemotherapy followed by allogeneic hematopoietic stem cells for a controlled graft versus leukemia effect. This is addressed under, nonmyeloablative Allogeneic Stem Cell Transplantation for Treatment of Malignancy.

High Dose Chemotherapy with Hematopoietic Stem Cell Support for Acute Myelogenous Leukemia**Acute Myelogenous Leukemia**

Acute myelogenous leukemia (sometimes called acute non-lymphocytic leukemia [ANLL]) refers to a malignancy arising from a myeloid precursor in the bone marrow. Unlike acute lymphoblastic leukemia (ALL), AML is relatively rare in childhood, with a median age of onset at 55 years. AMLs can be further subdivided according to the cells' resemblance to different subtypes of normal myeloid precursors according to the FAB classification. This system classifies leukemias from MO-M7. AMLs may also be classified on the basis of cytogenetic abnormalities, or on the basis of immunotyping. Initial complete remissions using combination chemotherapy can be achieved in up to 80% of patients. However, high incidence of relapse has prompted research into a variety of post-remission strategies, all focusing on methods of increasing dose intensity. Strategies have included high dose ara-C, or high dose therapy using either allogeneic or autologous stem cell support.

Policy/Criteria

High dose chemotherapy with either autologous or allogeneic stem cell support may be considered medically necessary as a treatment of AML in first complete remission, as a treatment of primary refractory AML, or relapsed AML.

High dose chemotherapy with allogeneic stem cell support is considered investigational as a treatment of AML relapsing after prior therapy with high-dose chemotherapy and autologous stem cell support.

Tandem high-dose chemotherapy and autologous stem cell support for AML is considered investigational.

Policy Guidelines

Primary refractory AML is defined as leukemia that does not achieve a complete remission after conventionally dosed (i.e., non-marrow ablative) chemotherapy. High dose chemotherapy as a treatment in first complete remission is typically reserved for patients with high-risk features, which include, but are not limited to, the following characteristics:

- AML secondary to prior chemotherapy and/or radiotherapy for another malignancy
- Presence of circulating blasts at the time of diagnosis



- Difficulty in obtaining first complete remission
- Leukemias with monocytoid differentiation (FAB classification M4 or M5).
- Certain cytogenetic abnormalities, such as abnormalities of chromosome 12, deletions of chromosomes 5 and 7, or trisomy of chromosome 8.

Background

High dose chemotherapy has been investigated in two general settings, either as a type of dose intensification therapy after first complete remission or as salvage therapy after first relapse or second complete remission.

Post-Remission Therapy

In patients in first complete remission, high dose chemotherapy with allogeneic stem cell support has been shown to decrease the leukemic relapse rate, but at the price of increased treatment-related morbidity and mortality, raising the question of whether allogeneic transplant offers any real benefit as a post-remission strategy in patients in first complete remission. In addition, it is unclear whether the outcomes associated with high dose therapy are better compared to those associated with other non-marrow ablative dose intensification strategies, such as high dose ara-C. Therefore, at the present time high dose chemotherapy with allogeneic stem cell support is typically reserved for those patients with high risk factors. These factors include: AML secondary to prior chemotherapy and/or radiotherapy for another malignancy, AML preceded by a myelodysplastic syndrome, presence of circulating blasts at the time of diagnosis, difficulty in obtaining first complete remission, or leukemias with monocytoid differentiation (FAB classification M4 or M5). Certain cytogenetic abnormalities are also associated with a poor prognosis, such as abnormalities of chromosome 12, deletions of chromosomes 5 and 7, or trisomy of chromosome 8. (1) In contrast, chromosomal abnormalities with a good prognosis include translocations between chromosome 8 and 12 and 15 and 17, or an internal derangement of chromosome 16. The use of allogeneic stem cell support may be limited by older age range of AML in general and the lack of availability of a suitable donor.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B and DR histocompatibility loci. Related donors mismatched at one locus are also considered suitable donors. A matched unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently there has been interest in haploidentical donors, i.e., a parent or a child of the patient, where typically there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of graft vs. host disease and overall morbidity of the procedure may be severe, and experience with these donors is limited.

The survival outcomes with high dose chemotherapy and autologous stem cell support are similar to that associated with allogeneic stem cell support, with the decreased treatment-related mortality of autologous stem cell support counterbalancing the increased relapse rate due to the lack of a beneficial graft vs. leukemia effect. Similar to allogeneic stem cell support, it is not clear if high dose chemotherapy with autologous support results in improved outcomes compared to conventionally dosed chemotherapy or high dose ARA-C.

Refractory AML

Twenty to 40% of patients with AML will not achieve remission with conventionally dosed chemotherapy, i.e., refractory AML. High dose chemotherapy with allogeneic stem cell support can cure a subset of these patients.

Relapsed AML

A total of 50%-70% of patients with AML are expected to relapse after attaining a first complete remission. (1) Conventional chemotherapy is generally not curative once relapse occurs, even if a second complete remission can be achieved. High dose chemotherapy with either allogeneic or autologous stem cell support is associated with a prolonged disease free survival in 30%-40% of patients in first relapse or second complete remission. Due to the mortality associated with remission induction, high dose chemotherapy with allogeneic stem may be considered as the initial treatment of relapsed disease. In patients without an allogeneic donor, or who are not candidates for allogeneic stem cell support due to age or other factors, high dose chemotherapy with autologous stem cell support may be considered after a second complete remission. (Due to contamination of stem cell populations by malignant



cells, autologous stem cells are typically harvested only when the patient is in remission.) Alternatively, autologous stem cells stored at the time of first complete remission may permit the use of autologous stem cell support as an initial therapy of relapsed disease.

High Dose Chemotherapy with Hematopoietic Stem Cell Support as a Treatment of Acute Lymphocytic Leukemia

Acute Lymphocytic Leukemia (ALL)

ALL occurs in multiple forms that vary with regard to cellular morphology, cytochemistry, immunophenotype, cytogenetic abnormalities, and other prognostic features. Although adult and childhood forms of ALL vary in the distribution of these prognostic features, there is considerable overlap, particularly among late adolescents and young adults. Consequently, there is not a clear age demarcation that divides the adult and childhood forms.

However, in general, adult ALL is characterized by a predominance of immature and pleomorphic cells, more frequent co-expression of myeloid markers, a greater percentage of leukemias derived from T-cells rather than B-cells, and a higher incidence of cytogenetic abnormalities with negative prognostic implications (such as the Philadelphia chromosome). In contrast, childhood ALL cells usually have a more mature morphology, and infrequently are of T-cell origin or positive for myeloid markers or the Philadelphia chromosome. As a consequence of these differences, the adult and childhood forms of ALL respond differently to treatment and vary in their risk for relapse once remission is achieved. For example, childhood ALL is a highly curable disease, with long-term survival rates ranging from 60%-85%. Similar therapy regimens have had less favorable outcomes in adult ALL. Approximately 65%-90% of those with adult ALL achieve a complete remission, but only 20%-30% become long-term survivors.

Policy/Criteria

Children

High dose chemotherapy with allogeneic or autologous stem cell support may be considered medically necessary as a treatment of childhood ALL in first complete remission but at high risk of relapse. (For definition of high risk factors, see policy guidelines below.)

High dose chemotherapy with autologous or allogeneic stem cell support may be considered medically necessary as a treatment of childhood ALL in second or greater remission or refractory ALL.

High-dose chemotherapy and allogeneic stem cell transplant is considered investigational as a treatment of relapsing ALL after a prior course of high-dose chemotherapy and autologous stem cell support.

Tandem high-dose chemotherapy and autologous stem cell support for ALL is considered investigational.

Adults

High dose chemotherapy with allogeneic or autologous stem cell support may be considered medically necessary as a treatment of adult ALL in first complete remission but at high risk of relapse. (For definition of high risk factors, see policy guidelines below.)

High dose chemotherapy with allogeneic stem cell support may be considered medically necessary as a treatment of adult ALL in second or greater remission, or in patients with relapsed or refractory ALL.

High dose chemotherapy with autologous stem cell support is considered investigational as a treatment of adult ALL in second or greater remission or those with refractory disease.

High-dose chemotherapy and allogeneic stem cell support is considered investigational as a treatment of relapsing



ALL after a prior course of high-dose chemotherapy and autologous stem cell support.

Tandem high-dose chemotherapy and autologous stem cell support for ALL is considered investigational.

Background

Risk factors associated with a high risk of relapse following initial complete remission include:

- Age greater than 15 years
- Leukocyte count greater than $10 \times 10^9/L$
- Extramedullary disease, particularly CNS
- Chromosomal abnormalities, including Philadelphia chromosome
- Failure to achieve a complete remission within 6 weeks of the start of induction therapy

There is no clear age cut off that distinguishes adult from childhood ALL. Published data generally group outcomes according to whether the patient is treated by an adult or pediatric oncologist.

Childhood ALL

In childhood ALL, conventional chemotherapy is associated with complete remission rates of about 95% with long-term remission rates of 60%. Therefore, in patients with a first complete remission, high dose therapy is considered necessary only in those with risk factors predictive of relapse. These factors include:

- Age greater than 15 years
- Leukocyte count greater than $10 \times 10^9/L$
- Extramedullary disease, particularly CNS
- Chromosomal abnormalities, including Philadelphia chromosome

The prognosis after first relapse is related to the length of the original remission. For example, there is 40%-50% leukemia-free survival for children whose first remission was longer than 3 years, compared to only 10%-15% of those with early relapse. Thus high-dose chemotherapy may be a strong consideration in those with short remissions. At the present time, the comparative outcomes using high dose therapy with either autologous or allogeneic stem cell are unknown.

Adult ALL

- In patients in first complete remission, the data suggest equivalent survivals after high dose therapy and autologous stem cell support compared to conventional chemotherapy. In this setting the decision between high dose chemotherapy and conventional chemotherapy may reflect a choice between an intensive therapy of short duration and a considerably longer but somewhat milder treatment
- In other settings, such as in second or subsequent remissions, there were inadequate data to determine the relative effectiveness of autologous bone marrow transplant compared to conventional chemotherapy.

While high dose chemotherapy and allogeneic stem cell support may be considered an option in some adults, the increased morbidity and mortality related to graft vs. host disease, particularly in an older population, are serious limitations. In addition, unlike acute myeloid leukemia, there does not appear to be a beneficial graft vs. leukemia effect to counterbalance the increased mortality of the procedure. Finally, adults with AML treated with allogeneic transplant tend to fail because of treatment-related mortality and failure is rarely related to relapse. In contrast, in ALL, even for adults who survive the procedure, there is a significant relapse rate, and overall very few adults are long-term disease-free survivors. For these reasons, allogeneic transplant remains controversial as a treatment of adult ALL and may be routinely recommended only in the very poor risk subgroup of those with ALL in association with the Philadelphia chromosome or in patients with refractory or relapsed ALL. (4)



A 2000 TEC assessment focused on high-dose chemotherapy and allogeneic stem cell support after a prior failed course of high-dose chemotherapy and autologous stem cell support, in the treatment of a variety of malignancies, including ALL. (5) The TEC assessment found that there were insufficient data to permit conclusions about this treatment strategy.

High Dose Chemotherapy with Hematopoietic Stem Cell Support for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Description

High dose chemotherapy

High dose chemotherapy (HDC) involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The most significant side effect of HDC is marrow ablation and thus HDC is accompanied by a reinfusion of hematopoietic stem cells in order to repopulate the bone marrow. The potential source of stem cells and harvesting techniques are described below.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well differentiated morphology. In CLL, these cells accumulate in the blood, marrow, lymph nodes, and spleen, while in SLL they are generally confined to the lymph nodes. CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other. Both tend to occur in older individuals and present as asymptomatic enlargement of the lymph nodes. Both tend to be indolent in nature but can undergo transformation to a more aggressive form of disease. Treatment regimens used for CLL are generally the same as those used for SLL and outcomes of treatment are comparable for the two diseases. Both low and intermediate risk CLL and SLL demonstrate relatively good prognoses with median survivals of 6 to 10 years, while the median survival of high risk CLL or SLL may be only 2 years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy and nearly all patients ultimately die of their disease. This natural history has prompted the investigation of high dose chemotherapy as a possible curative regimen.

Coverage/Criteria

High dose chemotherapy with either autologous or allogeneic stem cell support is considered investigational as a treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma.

Scientific Evidence

Autologous Stem Cell Transplant

- There are currently no randomized trials that report the outcomes of HDC followed by AuSCS compared to conventional therapy. Comparative studies using historical controls are subject to patient selection bias, since many patients may not be candidates for HDC due to coexisting co-morbidities. An additional difficulty in studying the outcomes of any therapy of CLL or SLL is the long follow-up periods required, due to the indolent natural history of the disease.
- There was insufficient evidence to permit scientific conclusions regarding the use of HDC followed by AuSCS as consolidation therapy in patients in complete remission.

Allogeneic Stem Cell Transplant



- No randomized trials are available that compare survival after HDC-alloSCS to conventional dose chemotherapy in patients with CLL or SLL. One retrospective analysis compared matched historical controls given conventional dose therapy to 24 patients treated with HDC-alloSCS. This study reported significantly longer survival in the transplanted group than in matched historical controls. However, several known prognostic factors were not used to match controls with those treated with HDC-alloSCS. In addition, data on baseline characteristics were inadequate to verify the similarity of the two groups. Furthermore, the samples were small and the duration of follow-up was short relative to the natural history of the disease.
- Since available evidence from published reports was inadequate to permit conclusions, and since it seemed unlikely that data from prospective controlled trials would be available anytime soon, TEC commissioned a direct comparative analysis from the International Bone Marrow Transplant Registry (IBMTR). Results of this analysis show that treatment with an allotransplant rather than with conventional dose salvage results in a 2.6 fold higher risk of dying in the first 12 months, and suggest a 2.6 lower risk after 12 months. At 60 months after treatment, the adjusted probabilities of survival were 43% and 29% respectively, for HDC-alloSCS vs. conventional therapy. This analysis suggests approximately 1.7 times greater survival at 5 years after salvage therapy with HDC-alloSCS than after conventional dose salvage treatment. For some patients, the difference in long-term survival may outweigh the increased risk of early mortality.
- However, the Cox regression model used to adjust the survival curves included only well established prognostic factors for CLL and SLL. As yet unknown and thus unmeasured covariates might widen the confidence intervals for point estimates the analysis provided. Further, few patients contributed to the last third of the survival curves. Thus it is possible that with additional follow-up the apparent plateau on the adjusted survival curve beginning three years after allotransplant might convert to a decline similar to that seen for conventionally salvaged patients. Consequently, evidence from this analysis is insufficient to permit conclusions on the net health outcome of HDC-alloSCS for relapsed or refractory CLL or SLL.

High Dose Chemotherapy with Hematopoietic Stem Cell Support in the Treatment of Multiple Myeloma and Primary Amyloidosis

Multiple Myeloma

Multiple myeloma is a systemic malignancy of relatively well-differentiated plasma cells. Management of myeloma is generally related to tumor mass at diagnosis or at the time treatment is initiated. Patients with a high tumor mass undergo systemic cytotoxic therapy, typically intermittent melphalan/prednisone (MP) or other combination therapy such as VAD (vincristine, doxorubicin and dexamethasone) or VMCP (vincristine, melphalan, cyclophosphamide and prednisone). However, multiple myeloma is rarely curable with standard dose chemotherapy, prompting interest in high dose chemotherapy with either autologous or allogeneic stem cell support. In addition, there has been interest in tandem high dose chemotherapy to further reduce the relapse rate seen with a single course of high dose chemotherapy.

Primary Amyloidosis

Primary systemic amyloidosis is a plasma cell disorder that causes extracellular deposition of insoluble protein (i.e., light chain immunoglobulins) in critical organs and tissues such as the heart, liver, kidneys, gastrointestinal tract, spleen, or nervous system. Progressive protein accumulation impairs organ function and results in organ failure and death when treatment is unsuccessful. Primary amyloidosis is not a malignancy, although it is related to multiple myeloma, also a plasma cell disorder. Clonal plasma cells are found in the marrow of patients with either disease. However, in those with primary amyloidosis the percentage of plasma cells among total marrow cells does not change much with time.

**Policy/Criteria**

High dose chemotherapy with autologous stem cell support may be considered medically necessary in the treatment of newly diagnosed or chemotherapy-responsive multiple myeloma (MM).

HDC/AUSCS is a covered benefit for chemotherapy-responsive multiple myeloma. High dose chemotherapy with autologous stem cell support is considered investigational for all other indications in treatment of multiple myeloma.

Tandem high dose chemotherapy with stem cell support in the treatment of multiple myeloma is considered medically necessary for the following:

1. Tandem autologous for newly diagnosed or responsive MM
2. Tandem autologous followed by reduced intensity conditioning (RIC) allogeneic SCT for newly diagnosed MM

High dose chemotherapy with allogeneic stem cell support, either as initial therapy of multiple myeloma, or after a prior failed course of high-dose chemotherapy and autologous stem cell support, is considered investigational.

High dose chemotherapy with autologous stem cell support is considered medically necessary in patients with primary amyloidosis.

Chemotherapy-Responsive Disease: The median survival rates reported in the reviewed studies are 40 to 58 months for the HDC/AuSCS arm versus 8 to 50 months in the conventional chemotherapy arm. Survival at 3 and 5 years is reported to be 50% to 76% and 38% to 52% in the HDC/AuSCS group compared with 10% to 81% and 12% to 35% in the conventional-dose group, respectively. One study provided strong evidence regarding the efficacy of HDC/AuSCS for multiple myeloma. Overall, patient survival and event-free survival were significantly better in the transplanted group than in the conventional-dose group. Prior controlled trials that did not randomly assign patients are difficult to interpret due to patient selection bias, particularly related to age, performance status, renal function, and other patient characteristics.

The treatment-related mortality for the HDC/AuSCS groups ranged from 4% to 11% and, for the conventional chemotherapy groups, from 0% to 5% in the studies reviewed. Although one study reported a relatively high treatment-related mortality in the high-dose arm, survival in the HDC/AuSCS group was significantly higher at 5 years.

General patient selection criteria usually included patient age younger than 60, good performance, no other serious diseases, low tumor burden, and responsiveness to chemotherapy.

Refractory Disease: Survival of patients treated with high-dose therapy was higher than those treated with standard therapy in two of the three controlled trials evaluated. However, median survival was not yet reached so survival curves were estimated based on very few subjects. Small sample sizes, nonrandom assignment, duration of follow-up, beginning of measurement for survival, and differing disease status of the patients make it impossible to draw conclusions at this time regarding the efficacy of HDC/AuSCS for primary-resistant or refractory multiple myeloma.

Treatment-related mortality rates of 13% to 17% have been reported for patients with primary-resistant or refractory multiple myeloma treated with HDC/AuSCS. These high rates may be explained by the fact that patients in those trials tended to have been heavily pretreated.

The evidence does suggest that refractory patients who have received previous aggressive treatments are not good candidates for high-dose therapy since their survival is similar to that of patients receiving standard chemotherapy. Patients with primary-resistant disease who are treated with high-dose therapy early in the disease process may see a benefit but this has yet to be clearly established in controlled trials.



Nonmyeloablative Allogeneic Stem Cell Transplantation for Treatment of Malignancy

Description

Allogeneic transplantation of stem cells in conjunction with myeloablative chemotherapy is an established therapy for a variety of malignancies, including acute and chronic leukemias and non-Hodgkin's lymphomas. The treatment effect was originally believed to be related primarily to the chemotherapeutic ablation of the malignant cells, secondarily enhanced in many cases by a beneficial immunologic graft versus tumor effect mediated by the infused donor cells. However, pilot studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This manifests as a stable, mixed donor-host hematopoietic chimerism. Once chimerism has developed a further infusion of donor leukocytes may be given to eradicate malignant cells; i.e., to induce a graft versus tumor effect. Nonmyeloablative allogeneic transplants, also referred to as "mini-transplants" or "transplant lite," are thus thought to be potentially as effective as conventional myeloablative allogeneic transplants, but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen.

There are two general categories of patients that have been considered candidates for nonmyeloablative transplants: those who would otherwise be considered candidates for a conventional myeloablative transplant, and those who would not. In the former category, nonmyeloablative transplants could be considered as a variant of a standard chemotherapy conditioning regimen. In the latter category, nonmyeloablative transplants would be considered a novel approach, either for patients whose comorbidities preclude a standard myeloablative conditioning regimen, or in those with malignancies that have not been shown to be effectively treated with conventional myeloablative allogeneic transplants.

Note: Donor leukocyte infusions may be administered as part of the above therapy. However, donor leukocyte infusions used as a salvage regimen at relapse following a conventional myeloablative allogeneic stem cell transplant are considered separately in medical policy, Donor Lymphocyte Infusion, Medicine, Policy No. 3.

Policy/Criteria

Nonmyeloablative allogeneic stem cell transplantation may be considered medically necessary in patients who would otherwise meet patient selection criteria for high dose chemotherapy and allogeneic stem cell transplantation. These criteria are addressed in the following policy sections:

Non-Hodgkin lymphoma

Myelodysplastic diseases/ Myelodysplastic syndrome

Acute myelogenous leukemia

Hodgkin's disease, Transplant

Chronic myelogenous leukemia

Acute lymphocytic leukemia

Multiple myeloma

Chronic lymphocytic leukemia

Other applications of nonmyeloablative allogeneic stem cell transplantation are considered investigational, including its use in patients who do not meet criteria for high dose chemotherapy and allogeneic stem cell transplantation due to either age or co-morbidities, or as a treatment of other malignancies, including renal cell carcinoma or other solid tumors.

Background

This policy is based on a 2001 TEC Assessment that focused on nonmyeloablative stem cell transplant in patients who would not be considered candidates for conventional allogeneic stem cell transplant due to comorbidities. The assessment further focused on those malignancies for which conventional allogeneic stem cell transplant has a proven treatment benefit (i.e., acute and chronic myeloid leukemia, acute lymphoblastic leukemia, Hodgkin's disease, and non Hodgkin's lymphoma) and those malignancies where the treatment effectiveness of conventional



allogeneic stem cell transplant is still uncertain (multiple myeloma, chronic lymphocytic leukemia, myelodysplastic syndrome, malignancies, or solid organs). The TEC assessment did not focus on those patients who would otherwise be considered for a conventional myeloablative transplant. The rationale behind this Assessment focus was that, in the literature, it is not possible to clearly distinguish between what would be considered a myeloablative versus a nonmyeloablative conditioning regimen. Therefore, for patients who are considered candidates for a conventional allogeneic transplant, the intensity of the conditioning regimen is primarily one of physician preference. However, for patients who are not considered candidates for a conventional myeloablative transplant, nonmyeloablative transplants represent a unique approach. The following observations and conclusions regarding this latter group of patients were reported:

CML, AML, ALL, HD, NHL, Multiple myeloma, chronic lymphocytic leukemia; myelodysplastic syndrome ineligible for conventional allogeneic stem cell transplant

- The available evidence was insufficient to permit scientific conclusions. For each of the above malignancies, the sample size was inadequate even when data were pooled from all studies. In addition, the follow-up duration in all of the studies ranged from 3 months to slightly more than one year. This duration is short relative to either the natural history of these malignancies or the reported duration of survival after alternative therapies. No data were reported on results of conventional management of well-matched controls; thus, direct comparison of outcomes was not possible.

The limited evidence suggested that patients with contraindications to conventional allogeneic transplant experienced a high rate of transplant related mortality after nonmyeloablative transplant.

CODING INFORMATION

ICD-9 Codes that may support medical necessity

(List is not inclusive or a guarantee of coverage)

140.0 – 208.99	Malignant neoplasm
230.0 – 234.9	Carcinoma in Situ
235.0 – 239.9	Neoplasm of uncertain behavior
272.7	Lipidoses
277.30	Amyloidosis, unspecified
277.31	Familial Mediterranean fever
277.39	Other amyloidosis
277.5	Mucopolysaccharidosis
279.12	Wiskott-Aldrich syndrome
279.2	Combined immunity deficiency
282.41 – 282.42	Thalassemias
282.60 – 282.69	Sickle-cell diseases
284.01	Constitutional red blood cell aplasia
284.09	Other constitutional aplastic anemia
284.8	Other specified aplastic anemias
284.9	Aplastic anemia, unspecified
288.01	Congenital neutropenia
289.89	Other specified diseases of blood and blood-forming organs
340	Multiple sclerosis
701.0	Circumscribed scleroderma
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome



- 714.2 Other rheumatoid arthritis with visceral or systemic involvement
- 714.3 Juvenile chronic polyarthritis
- 714.30 Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
- 714.31 Polyarticular juvenile rheumatoid arthritis, acute
- 714.32 Pauciarticular juvenile rheumatoid arthritis
- 714.33 Monoarticular juvenile rheumatoid arthritis
- 756.52 Osteopetrosis

CPT/HCPCS Codes

- 38204 Management of recipient hematopoietic progenitor cell donor search and cell acquisition
- 38205 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
- 38206 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
- 38207 Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
- 38208 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
- 38209 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
- 38210 Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
- 38211 Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
- 38212 Transplant preparation of hematopoietic progenitor cells; red blood cell removal
- 38213 Transplant preparation of hematopoietic progenitor cells; platelet depletion
- 38214 Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
- 38215 Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer

- 38230 Bone marrow harvesting for transplantation
- 38240 Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
- 38241 Bone marrow or blood-derived peripheral stem cell transplantation; autologous
- 38242 Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

- 86367 Stem cells (i.e., CD34), total count
- 88240 Cryopreservation, freezing and storage of cells, each cell line
- 88241 Thawing and expansion of frozen cells, each aliquot
- 86812 – 86822 Tissue typing

- 96401 - 96542 Chemotherapy

Payable for Priority Medicare and Employer Group Medicare only

- G0265* Cryopreservation, freezing and storage of cells for therapeutic use, each cell line
- G0266 * Thawing and expansion of frozen cells for therapeutic use, each aliquot
- G0267* Bone marrow or peripheral stem cell harvest, modification or treatment to eliminate cell type(s) (e.g., T-cells, metastatic carcinoma)

Not payable for Medicaid or Medicare products:



S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

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