I. Description

Use of hematopoietic stem cell transplantation (HSCT) has been investigated for treatment of patients with epithelial ovarian cancer. Hematopoietic stem cells are infused to restore bone marrow function after cytotoxic doses of chemotherapeutic agents with or without whole body radiotherapy.

The evidence for HSCT in individuals who have advanced-stage epithelial ovarian cancer includes 3 randomized trials and data from case series and registries. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment related morbidity and mortality. The evidence has not shown an improvement in health outcomes, including survival, with the use of HSCT versus conventional standard doses of chemotherapy.

Background

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. Bone marrow stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

HSCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults is largely experimental. Initial enthusiasm for the use of autologous transplantation with the use of high-dose chemotherapy (HDC) for solid tumors has waned with the realization that dose intensification often fails to improve survival, even in tumors with a linear-dose response to chemotherapy. With the advent of reduced-intensity conditioning (RIC) allogeneic
transplant, interest has shifted to determinants of alloreactivity to metastatic solid tumors via a graft-versus-tumor effect of donor-derived T cells.

**Epithelial Ovarian Cancer**

Several different types of malignancies can arise in the ovary; epithelial carcinoma is the most common. Epithelial ovarian cancer is the fifth most common cause of cancer death in women. New cases and deaths from ovarian cancer in the United States in 2015 are estimated at 21,290 and 14,180, respectively. Most ovarian cancer patients present with widespread disease, and annual mortality is approximately 65% of the incidence rate.

Current management of advanced epithelial ovarian cancer is cytoreductive surgery in addition to combination chemotherapy. Approximately 75% of patients present with International Federation of Gynecology and Obstetrics stage 3 to 4 ovarian cancer and are treated with the combination of paclitaxel plus a platinum analog, the preferred regimen for newly diagnosed advanced disease. The use of platinum and taxanes has improved progression-free survival and overall survival in advanced disease to between 16 and 21 months and 32 and 57 months, respectively. However, most of these women develop recurrences and die of the disease, as chemotherapy drug resistance leads to uncontrolled cancer growth.

HDC has been investigated as a way to overcome drug resistance. However, limited data exist on this treatment approach; the ideal patient population and best treatment regimen remain to be established. HSCT has been studied in a variety of patient groups with ovarian cancer as follows:

- to consolidate remission after induction therapy
- to treat relapse after a durable response to platinum-based chemotherapy
- to treat tumors that relapsed after less than 6 months
- to treat refractory tumors

**Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation CFR title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations. However, cytotoxic drugs used in high-dose chemotherapy (HDC) require, and generally have received, FDA approval. HDC is an off-label use of approved drugs.

**II. Policy**

A. Autologous or allogeneic hematopoietic stem cell transplantation to treat epithelial ovarian cancer is not covered as it is not known to be effective in improving health outcomes.

B. Stem cell transplantation to treat germ cell tumors of the ovary is considered separately in the Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors policy.

**III. Administrative Guidelines**

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<thead>
<tr>
<th>CPT Codes</th>
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<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
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<tr>
<td>HCPCS Codes</td>
<td>Description</td>
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<tr>
<td>Q0083 - Q0085</td>
<td>Chemotherapy, administration code range</td>
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<tr>
<td>J9000 - J9999</td>
<td>Chemotherapy drug code range</td>
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<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
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<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care on the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)</td>
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### IV. Rationale

This evidence review was originally based on a 1998 TEC Assessment, “High-dose chemotherapy with autologous stem cell support for epithelial ovarian cancer” that reached the following conclusions:

- Data were unavailable from randomized controlled trials for any of the patient groups studied (see Description). Thus, the Assessment was able to compare outcomes only indirectly, using separate studies of high-dose chemotherapy (HDC) and conventional dose regimens. Although some results reported after HDC appeared encouraging, indirect comparisons did not permit conclusions.

- In previously untreated patients, reported response rates suggested that HDC increased objective response rates compared with patients given conventional-dose chemotherapy. However, this comparison was flawed by age bias and by differences in performance status and other baseline characteristics of patients included in the 2 sets of studies. Response duration and survival data were unavailable for comparison. Treatment-related mortality was greater after HDC.

- In previously treated patients, objective response rates after HDC also were reportedly higher than after conventional-dose regimens. Subgroup analyses showed higher response rates among platinum-sensitive, optimally debulked patients. Minimum values of the ranges reported across studies for median response duration and survival after HDC were similar to those reported after conventional-dose chemotherapy. However, the maxima for these ranges suggested improved response duration and overall survival (OS) after HDC. In contrast, data from the Autologous Blood and Marrow Transplant Registry did not show similarly high survival for comparable subgroups. Comparison with conventional-dose chemotherapy was again biased due to differences in age distributions, performance status, and other baseline characteristics of patients included in studies of high-dose or conventional chemotherapies.

The 1998 TEC Assessment did not identify any studies reporting outcomes of allogeneic transplants for patients with ovarian cancer. A separate 1999 TEC Assessment evaluated the use of HDC with allogeneic stem cell support (HDC/AlloSCS) as salvage therapy after a failed prior course of HDC with autologous stem cell support (HDC/AuSCS). There were no data regarding outcomes of this strategy as therapy for epithelial ovarian cancer.
This policy has been updated at regular intervals with literature searches of the MEDLINE database; the most recent update covered the period through December 18, 2015. Experience with hematopoietic stem-cell transplantation (HSCT) in epithelial ovarian cancer is primarily derived from registry data and phase 2 trials. Over the last 20 years, more than 1000 patients have been entered on transplant registries in Europe and in the United States. Many registry patients were treated after relapse and others in nonrandomized studies using HDC as first-line treatment. Case selection and retrospective review make interpretation of registry and nonrandomized data difficult. Survival analyses from registry data and clinical trials suggested a possible benefit in treating ovarian cancer patients with HSCT.

However, as outlined here, no randomized trial has provided evidence that HSCT in ovarian cancer provides any outcome benefit.

In 2012, Sabatier et al reported on a retrospective review of 163 patients with advanced or metastatic (Federation of Gynecology and Obstetrics [FIGO] stage3c/4) epithelial ovarian cancer who were treated at a single institution in France. All patients received cytoreductive surgery and combination platinum/taxane chemotherapy. Investigators compared median progression-free survival (PFS) and OS between 60 patients who received subsequent HDC with autologous HSCT support and 103 patients who did not. HDC regimens varied, but all contained alkylating agents. At a median follow-up of 47.5 months, PFS in the high-dose and standard chemotherapy groups was 20.1 and 18.1 months, respectively (p value not reported). OS was 47.3 and 41.3 months, respectively (p=0.29). In prespecified subgroup analyses, median PFS was significantly longer in women younger than age 50 years who received HDC compared with women who received standard chemotherapy (81.7 months vs 11 months; p=0.02); in women older than 50 years, median PFS did not differ statistically between groups (17.9 months vs 18.3 months; p=0.81). Similarly, median OS was significantly longer in women younger than age 50 years who received high-dose chemotherapy compared with women who received standard chemotherapy (54.6 months vs 36 months; p=0.05) but not in women older than 50 years (49.5 months vs 42 months; p value not reported). The authors recommended further study of HDC with autologous HSCT support in patients younger than 50 years.

In 2008, Papadimitriou et al reported on the use of HDC with stem cell support as consolidation therapy in patients with advanced epithelial ovarian cancer (FIGO stage IIC-IV). Patients who achieved first clinical complete remission after conventional chemotherapy were randomly assigned to receive or not receive high-dose melphalan and autologous stem-cell transplant. A total of 80 patients were enrolled in the trial. Of 37 patients allocated to HDC, 11 (30%) did not receive the treatment either due to refusal or failure of peripheral blood stem cell mobilization. In an intention-to-treat analysis, there were no significant differences between the 2 arms in time-to-disease progression (p=0.059) or OS (p=0.38).

In 2007, Mobus et al reported on a trial of 149 patients with untreated ovarian cancer who were randomly assigned, after debulking surgery, to standard chemotherapy or sequential HDC and peripheral blood stem cell support. This was the first randomized trial comparing HDC with standard chemotherapy as first-line treatment of ovarian cancer, and the investigators found no statistically significant difference in PFS or OS between the 2 treatments. Median patient age was 50 years (range, 20–65) a (FIGO) stage was 2b/2c in 4%, stage 3 in 78%, and stage 4 in 17%.
Seventy-six percent of patients in the HDC arm received all scheduled chemotherapy cycles. After a median follow-up of 38 months, PFS was 20.5 months in the standard chemotherapy arm and 29.6 months in the HDC arm (hazard ratio [HR] 0.84; 95% confidence interval [CI], 0.56 to 1.26; p=0.40). Median OS was 62.8 months in the standard chemotherapy arm and 54.4 months in the HDC arm (HR= 1.17; 95% CI, 0.71 to 1.94; p=0.54).

In 2004, Curé et al reported on outcomes in advanced ovarian cancer patients randomly assigned after second-look surgery to receive either HDC with peripheral blood stem cell support or conventional-dose maintenance chemotherapy. Results were presented in abstract form and have yet to be published. Patients were younger than age 60 years with FIGO stage 3/4 disease sensitive to first-line chemotherapy. Enrolled were 110 patients (57 high-dose and 53 conventional-dose chemotherapy). Median follow-up was 60 months. No difference was seen in disease-free survival or OS between the 2 treatment arms. Disease-free survival in the conventional- and high-dose groups was 12.2 months (95% CI, 7.3 to 17.1) and 17.5 months (95% CI, 5.2 to 29.9) (p=0.22), respectively. OS was 42.5 months (95% CI, 28.8 to 56.6) and 49.7 months (95% CI, 29.9 to 69.4), respectively (p=0.43).

Ongoing and Unpublished Clinical Trials
A search of Clinical Trials.gov in December 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for HSCT in patients who have advanced-stage epithelial ovarian cancer includes 3 randomized trials and data from case series and registries. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. The evidence has not shown an improvement in health outcomes, including survival, with the use of HSCT versus conventional standard doses of chemotherapy.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
The current NCCN guidelines (v.2.2015) do not address Hematopoietic Stem Cell Transplant for ovarian cancer for either newly diagnosed patients, nor for patients with relapsed/refractory disease.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare and Medicaid Services (CMS) currently have the following national noncoverage decision on autologous stem cell transplantation: “Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following condition[s]: Solid tumors (other than neuroblastoma).”

V. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is
intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References

6. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem cell support for relapse following high-dose chemotherapy with autologous stem cell support for non-lymphoid solid tumors. TEC Assessments. 1999; Volume 14, Tab 11.