MP 8.01.23
Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

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**POLICY**

Autologous and allogeneic hematopoietic cell transplantation are considered investigational to treat advanced stage epithelial ovarian cancer.

**POLICY GUIDELINES**

Stem cell transplantation to treat germ cell tumors of the ovary is considered separately in evidence review 8.01.35.

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health.
- Some plans may participate in voluntary programs offering coverage for patients participating in National Institutes of Health–approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.
- Some contracts or certificates of coverage (e.g., Federal Employee Program) may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.
BACKGROUND

EPITHELIAL OVARIAN CANCER

Several 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 for 2017 were estimated at 22,440 and 14,080, respectively. Most ovarian cancer patients present with widespread disease, and the National Cancer Institute Surveillance, Epidemiology and Results Program reported a 46.5% five-year survival for all cases between 2007 and 2013.

Treatment

Current management for advanced epithelial ovarian cancer is cytoreductive surgery with chemotherapy. Approximately 75% of patients present with International Federation of Gynecology and Obstetrics stage III to IV ovarian cancer and are treated with paclitaxel plus a platinum analogue, the preferred regimen for the newly diagnosed advanced disease. 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, cancer recurs in most women, and they die of the disease because chemotherapy drug resistance leads to uncontrolled cancer growth.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). 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 “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in detail in evidence review 7.01.50.

HCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults is largely experimental.

HCT for Epithelial Ovarian Cancer

HCT has been investigated as a therapy to overcome drug resistance. However, limited data exist on this treatment approach; the ideal patient population and best treatment regimen remain to be established. HCT has been tested in various patient groups with ovarian cancer:

- to consolidate remission after induction therapy
- to treat relapse after a durable response to platinum-based chemotherapy
- to treat tumors that relapse 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, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.
RATIONALE

This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent update covered the period through December 21, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

Clinical Context and Therapy Purpose

The purpose of autologous or allogeneic stem cell transplantation in patients who have epithelial ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does autologous or allogeneic stem cell transplantation used as part of the treatment of ovarian cancer improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population(s) of interest are patients with advanced epithelial ovarian cancer who have undergone debulking surgery and first-line chemotherapy.

Interventions

The therapy being considered is autologous or allogeneic stem cell transplantation. HCT has been investigated as a therapy to overcome drug resistance. HCT has been tested in various patient groups with ovarian cancer to consolidate remission after induction therapy, to treat relapse after a durable response to platinum-based chemotherapy, to treat tumors that relapse after less than six months, to treat refractory tumors.

Comparators

The following practices are currently being used to make decisions about the treatment of advanced epithelial ovarian cancer: guideline-based clinical pathways for debulking surgery and platinum-based chemotherapy.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, treatment-related mortality.

Timing

Patients with advanced epithelial advanced ovarian cancer have been considered for stem cell transplantation in the setting of remission after induction therapy or relapse after first-line chemotherapy. If a transplant were to be performed follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Setting

Stem cell transplantation is performed in tertiary inpatient settings with specialized expertise.

Study Selection

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

This evidence review was informed by a 1998 TEC Assessment that reached the following conclusions:

- Data were unavailable from RCTs for any of the patient groups studied. 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 differences in performance status and other baseline characteristics of patients included in the two 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 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 1999 TEC Assessment evaluated the use of HDC with allogeneic stem cell support as salvage therapy after a failed prior course of HDC with autologous stem cell support. There were no data on outcomes of this strategy as therapy for epithelial ovarian cancer.
Experience with HCT in epithelial ovarian cancer is primarily derived from registry data and phase 2 trials. Many registry patients were treated after relapse and others in nonrandomized trials 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 have suggested a possible benefit in treating ovarian cancer patients with HCT.

Randomized Controlled Trials

Mobus et al (2007) reported on a phase 3 trial that included 149 patients with untreated ovarian cancer who were randomized, 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 investigators found no statistically significant differences in progression-free survival (PFS) or OS between treatments. The trial was powered such that a sample of 208 patients would be needed to detect an absolute improvement of 15% in PFS with a power of 80% and a 1-sided α of 5%. Median patient age was 50 years (range, 20-65 years) and International Federation of Gynecology and Obstetrics stage was IIB or IIC in 4%, stage III in 78%, and stage IV 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, 0.84; 95% confidence interval, 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 (hazard ratio, 1.17; 95% confidence interval, 0.71 to 1.94; p=0.54).

Papadimitriou et al (2008) reported on an RCT comparing the use of HDC with stem cell support as consolidation therapy in patients with advanced epithelial ovarian cancer (International Federation of Gynecology and Obstetrics stage IIC-IV). Patients who achieved first complete remission after conventional chemotherapy were randomized to receive or not, high-dose melphalan and autologous HCT. Eighty 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 arms in time-to-disease progression (p=0.059) or OS (p=0.38).

Observational Comparative Studies

Sabatier et al (2012) retrospectively reviewed 163 patients with advanced or metastatic (International Federation of Gynecology and Obstetrics stage IIIIC or IV) epithelial ovarian cancer who were treated at a single institution in France. All patients received cytoreductive surgery and combination platinum plus taxane chemotherapy. Investigators compared median PFS and OS among 60 patients who received subsequent HDC with autologous HCT 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 the standard chemotherapy groups was 20.1 months and 18.1 months, respectively (p not reported). OS was 47.3 months 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 (81.7 months) than in women who received standard chemotherapy (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, respectively; p=0.81). Similarly, median OS was significantly longer in women younger than age 50 years who received HDC (54.6 months) than in women who received standard chemotherapy (36 months; p=0.05), but not in women older than 50 years (49.5 months vs 42 months, respectively; p not reported). The authors recommended further study of HDC with autologous HCT support in patients younger than 50 years.

Summary of Evidence
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For individuals who have advanced-stage epithelial ovarian cancer who receive HCT, the evidence includes randomized trials and data from case series and registries. The relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Although some observational studies have reported longer survival in subsets of women with advanced epithelial ovarian cancer than in women treated with standard chemotherapy, none of the randomized trial evidence has shown a benefit from HCT in this population. Overall, the evidence has not shown that HCT improves health outcomes in treating epithelial ovarian cancer, including survival, compared with conventional standard doses of chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Current National Comprehensive Cancer Network guidelines (v.2.2018) do not address hematopoietic cell transplantation for epithelial ovarian cancer for patients either with newly diagnosed or with relapsed or refractory disease.3

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services currently have the following national noncoverage decision on autologous stem cell transplantation [AuSCT]: “Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following condition[s]: Solid tumors (other than neuroblastoma).”13

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in January 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

ESSENTIAL HEALTH BENEFITS

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntary offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

REFERENCES


7. 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. PMID


**CODES**

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<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
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### Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

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#### HCPCS
- Q0083-Q0085: Chemotherapy, administration code range
- J9000-J9999: Chemotherapy drug code range
- S2140: Cord blood harvesting for transplantation, allogeneic
- S2142: Cord blood derived stem-cell transplantation, allogeneic
- S2150: 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)

#### ICD-10-CM
- C56.0-C56.9: Malignant neoplasm of ovary code range

#### ICD-10-PCS
- 30243G0, 30243X0: Administration, circulatory, transfusion, central vein, percutaneous, autologous, code by substance (bone marrow,
Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

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Type of Service: Therapy
Place of Service: Inpatient/Outpatient

POLICY HISTORY

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<td>01/27/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 9, 2016; reference 12 added. Policy statement unchanged. Changed “hematopoietic stem cell transplantation” to “hematopoietic cell transplantation” per NCCN terminology</td>
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Original Policy Date: December 1999
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