Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

Policy # 00054
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous and allogeneic hematopoietic cell transplantation (HCT) to treat advanced stage epithelial ovarian cancer to be **investigational.***

Background/Overview

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
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.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. FDA 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.

Centers for Medicare and Medicaid Services (CMS)
The Centers for Medicare and 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)."

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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

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

- Data were unavailable from randomized controlled trials 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 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 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

In 2007, Mobus et al 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).

In 2008, Papadimitriou et al 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

In 2012, Sabatier et al retrospectively reviewed 163 patients with advanced or metastatic (International Federation of Gynecology and Obstetrics stage IIIC 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

For individuals who have advanced-stage epithelial ovarian cancer who receive HCT, the evidence includes randomized trials and data from case series and registries. Relevant outcomes are overall survival, 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.

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Policy History

Original Effective Date: 01/28/2002
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12/06/2001 Medical Policy Committee review.
01/28/2002 Managed Care Advisory Council approval.
05/07/2004 Medical Director review

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05/18/2004	Medical Policy Committee review. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for treatment of ovarian epithelial cancer policy developed separately from current HDC with Hematopoietic Stem Cell Support policy. Format revision. No substance change to policy.
06/28/2004	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006	Medical Director Review
08/09/2006	Medical Policy Committee approval
08/06/2008	Medical Director Review
08/20/2008	Medical Policy Committee approval. No change to coverage eligibility.
08/06/2009	Medical Policy Committee approval
08/26/2009	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Title changed.
12/01/2010	Medical Policy Committee approval
12/15/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding update
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Removed the word “Stem” from title and policy.
11/15/2017	Coding update
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Added “advanced stage” to investigational statement.

Next Scheduled Review Date: 6/2019

Coding

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Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C56.1-C56.9 C57.00-C57.02 C57.10-C57.12 C57.20-C57.22 C57.3-C57.4

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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