Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Bone Marrow Transplant – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

Description/Background

Note: This policy does not address stem cell transplantation to treat germ cell tumors of the ovary.

The use of hematopoietic cell transplantation (HCT) has been investigated to treat 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.

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 2023 were estimated at 19,710 and 13,270, respectively.(1) Most ovarian cancer patients present with widespread disease, and the National Cancer Institute Surveillance, Epidemiology and Results Program reported a 50.8% 5-year survival for all cases between 2013 and 2019.(2)

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 analog (e.g. cisplatin), the preferred regimen for newly diagnosed advanced disease.(3,4) 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.(3) However, cancer recurs in most women and they die of the disease, because chemotherapy drug resistance leads to uncontrolled cancer growth.(4)

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 cytotoxic drugs with or without whole body radiotherapy. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or from 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.

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.

Medical Policy Statement

Autologous or allogeneic hematopoietic cell transplantation is considered experimental/investigational to treat epithelial ovarian cancer. It has not been shown to improve clinical outcomes better than established therapies.

Inclusionary and Exclusionary Guidelines **(Clinically based guidelines that may support individual consideration and pre-authorization decisions)**

N/A

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)***

Established codes:

N/A

****Other codes (investigational, not medically necessary, etc.):***

38204	38205	38206	38207	38208	38209
38210	38211	38212	38213	38214	38215
38230	38232	38240	38241	38242	S2140
S2142	S2150				

**Please check specific contract or certificate for coverage.*

Rationale

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 balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

HEMATOPOIETIC CELL TRANSPLANTATION FOR EPITHELIAL OVARIAN CANCER

Clinical Context and Therapy Purpose

The purpose of autologous or allogeneic stem cell transplantation in individuals 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 treatment of ovarian cancer improve net health outcomes?

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

Populations

The relevant population(s) of interest are individuals 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 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, disease-specific survival, change in disease status, treatment-related mortality.

Experience with hematopoietic cell transplantation (HCT) in epithelial ovarian cancer is primarily derived from registry data and phase 2 trials.(5-8) Many registry patients were treated after relapse and others in nonrandomized trials using HDC as first-line treatment. Case selection and retrospective review make the interpretation of registry and nonrandomized data difficult.(3) Survival analyses from registry data and clinical trials have suggested a possible benefit in treating ovarian cancer patients with HCT.

REVIEW OF EVIDENCE

Randomized Controlled Trials
Mobius 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.(3) 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 one-sided alpha 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 a 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).(4) Patients who achieved first clinical 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 IIIC or IV) epithelial ovarian cancer who were treated at a single institution in France.(9) 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 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 of the 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

National Comprehensive Cancer Network

Current NCCN guidelines (NCCN) on ovarian cancer including fallopian tube cancer and primary peritoneal cancer do not address hematopoietic cell transplantation for epithelial ovarian cancer for either newly diagnosed patients or for patients with relapsed or refractory disease.(10) However, use of high-dose chemotherapy with HCT received a category 2B recommendation for individuals with certain malignant germ cell tumors demonstrating abnormal tumor markers and definitive recurrent disease and a category 2A recommendation in those with persistently elevated markers and definitive residual disease. NCCN notes that "patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy."

Accordingly, NCCN guidelines on HCT only reference ovarian germ cell tumors as an indication for HCT.(11)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations

Medicare National Coverage Determinations Manual, Publication 100-3, Section 110.23, Chapter 1, Part 2; "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16
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)."(12)

Local:
There is no local coverage determination specifically addressing hematopoietic cell transplantation for epithelial ovarian cancer.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas (Autologous)
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

1. American Cancer Society. *Cancer Facts & Figures 2017,* Atlanta, Ga: American Cancer Society; 2021; http://www.cancer.org/research/cancerfactsstatistics/. Accessed December 29, 2023.
2. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Ovarian Cancer. n.d.; https://seer.cancer.gov/statfacts/html/ovary.html. Accessed December 29, 2023.
3. Mobus V, Wandt H, Frickhofen N et al. Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: Intergroup trial of the AGO-Ovar/AIO and EBMT. J Clin Oncol 2007; 25(27):4187-93.
4. Papadimitriou C, Dafni U, Anagnostopoulos A, et al. High-dose melphalan and autologous stem cell transplantation as consolidation treatment in patients with chemosensitive ovarian cancer: results of a single-institution randomized trial. *Bone Marrow Transplant.* 2008;41(6):547-554. PMID 18026149
5. Donato ML, Aleman A, Champlin RE et al. Analysis of 96 patients with advanced ovarian carcinoma treated with high-dose chemotherapy and autologous stem cell transplantation. Bone Marrow Transplant 2004; 33(12):1219-24.
6. Ledermann JA, Herd R, Maraninchi D et al. High-dose chemotherapy for ovarian carcinoma: long-term results from the Solid Tumour Registry of the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 2001; 12(5):693-9.
7. Stiff PJ, Bayer R, Kerger C et al. High-dose chemotherapy with autologous transplantation for persistent/relapsed ovarian cancer: a multivariate analysis of survival for 100 consecutively treated patients. J Clin Oncol 1997; 15(4):1309-17. PMID 9193322
8. Stiff PJ, Veum-Stone J, Lazarus HM et al. High-dose chemotherapy and autologous stem-cell transplantation for ovarian cancer: an autologous blood and marrow transplant registry report. Ann Intern Med 2000; 133(7):504-15. PMID 11015163
9. Sabatier R, Goncalves A, Bertucci F, et al. Are there candidates for high-dose chemotherapy in ovarian carcinoma? J Exp Clin Cancer Res. 2012;31:87. PMID 23072336
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf. Accessed April 5, 2024.

11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed April 5, 2024.
12. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for STEM CELL Transplantation (Formerly 110.8.1) 110.23.Effective date 1/27/16, Implementation date 10/3/16.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 5, 2024 the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/12	8/21/12	8/21/12	Topic split out from the following policies: • Allogeneic BMT – Investigational • Autologous BMT – Investigational Policy reformatted to mirror BCBSA policy.
11/1/13	8/22/13	8/27/13	Routine maintenance. No change in policy status.
3/1/15	12/12/14	12/29/14	Routine maintenance Added procedure codes S2140, S2142, and S2150 Updated references
5/1/16	2/16/16	2/16/16	Routine maintenance
5/1/17	2/21/17	2/21/17	Routine maintenance Updated references Added procedure code 38207 Changed Hematopoietic Stem Cell Transplantation to Hematopoietic Cell Transplantation per NCCN terminology change
5/1/18	2/20/18	2/20/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance. No change in policy status.
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (slp) Vendor managed: N/A
9/1/24	6/11/24		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR EPITHELIAL OVARIAN CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered* ***For FEHBP contracts only… Effective 1/1/13, Hematopoietic cell transplantation for epithelial ovarian cancer is covered.**
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.