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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer

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Section: Transplant

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION[1]

The 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 following cytotoxic doses of chemotherapeutic agents with or without whole body radiation therapy.

Hematopoietic Stem-Cell Transplantation (HSCT)

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 radiation therapy. 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.

HSCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental. Initial enthusiasm for the use of autologous transplant with the use of high-dose chemotherapy and stem cells 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 exploring the generation 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 2013 are estimated at 22,240 and 14,030, respectively.[2] Most ovarian cancer patients present with widespread disease, and yearly mortality is approximately 65% of the incidence rate.[2]

The current management of advanced epithelial ovarian cancer is cytoreductive surgery followed by combination chemotherapy.[3] Approximately 75% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian cancer, and treated with the combination of paclitaxel and a platinum analog being the preferred regimen for newly diagnosed advanced disease.[3,4] The use of platinum and taxanes has improved progression-free survival (PFS) and overall survival (OS) rates in advanced disease to 16–21 months and 32–57 months, respectively.[4] However, most of these women develop recurrences and die of their disease as chemotherapy drug resistance leads to uncontrolled cancer growth.[3]

High-dose chemotherapy has been investigated as a way to overcome drug resistance. However, limited data exist on this treatment approach, and the ideal patient population and best regimen remain to be established.[3] Hematopoietic stem-cell transplantation has been studied in a variety of patient groups with ovarian cancer as follows:

- to consolidate remission after initial treatment
- 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

Note: HSCT to treat *germ cell* tumors of the ovary is considered separately in transplant policy No. 45.38.

MEDICAL POLICY CRITERIA

I. Autologous HSCT

Autologous hematopoietic stem-cell transplantation is considered **investigational** to treat epithelial ovarian cancer.

II. Allogeneic HSCT

Allogeneic hematopoietic stem-cell transplantation is considered **investigational** to treat epithelial ovarian cancer.

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Ideally, in order to understand the impact of HSCT for treatment of epithelial ovarian cancer, comparative clinical trials that compare this therapy to standard medical treatment are needed. Further, for treatment of malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

Literature Appraisal

Technology Assessments

Initially, this policy was based on a 1998 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment, "High-dose chemotherapy with autologous stem cell support for epithelial ovarian cancer"[5] 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.[5] Although some results reported after high-dose therapy appeared encouraging, the indirect comparisons did not permit conclusions.
- In previously untreated patients, reported response rates suggested that high-dose therapy increased the objective response rate compared to 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 two sets of studies. Response duration and survival data were unavailable for comparison. Treatment-related mortality was greater after high-dose therapy.
- 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 after high-dose therapy. 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 therapies.

The 1998 TEC Assessment did not identify any studies reporting outcomes of allogeneic transplants for patients with ovarian cancer.[5] 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/AuSCS.[6] There were no data regarding outcomes of this strategy as therapy for epithelial ovarian cancer.

Randomized Controlled Trials

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.[4] This was the first randomized trial comparing HDC to standard chemotherapy as first-line treatment of ovarian cancer, and the investigators found no statistically significant difference in progression-free survival (PFS) or overall survival (OS) between the two treatment options. The median patient age was 50 years (range: 20–65) and FIGO stage was IIb/IIc in 4%, III in 78%, and IV in 17%. Seventy-six percent of patients in the HDC arm received all of the 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% CI: 0.56–1.26; 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: 0.71–1.94; p=0.54).

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).[3] 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 the 37 patients allocated to HDC, 11 did not receive the treatment either due to refusal or failure of peripheral blood stem-cell mobilization. In an intent-to-treat analysis, there were no significant differences between the two arms in time-to-disease progression (p=0.059) or OS (p=0.38).

Non-randomized Trials and Registries

Experience with hematopoietic stem-cell transplantation (HSCT) in epithelial ovarian cancer comes primarily from registry data and phase II trials.[7-11] Over the last 20 years, more than 1,000 patients have been entered on transplant registries in Europe and in the United States.[4,7,8] Many of the registry patients were treated in relapse and others in non-randomized studies using HDC as first-line treatment.

Case selection and retrospective review make the interpretation of the registries and non-randomized data difficult.[4] Survival analyses from registry data and clinical trials suggested a possible benefit treating ovarian cancer patients with HSCT.[4] However, as outlined above, none of the randomized trials have provided evidence that HSCT in ovarian cancer provides any outcome benefit.

Clinical Practice Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for ovarian cancer do not address HSCT. [12]

Summary

The evidence for the use of hematopoietic stem-cell transplant (HSCT) as an adjunct to high-dose chemotherapy in epithelial ovarian cancer is based on two published randomized trials and data from case series and registries. At present, the evidence is insufficient to recommend this intervention in either first-line therapy or for patients in whom epithelial ovarian cancer has relapsed following standard chemotherapy. In addition, there are no clinical practice guidelines for professional societies that recommend HSCT for these patients. Therefore, the use of HSCT for the treatment of epithelial ovarian cancer is considered investigational.

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CROSS REFERENCES

Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant, Transplant, Policy No. 45.03

Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

Hematopoietic Stem-Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy

No. 45.27

Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38

CODES	NUMBER	DESCRIPTION
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Bone marrow; aspiration only
	38221	Bone marrow; biopsy, needle or trocar
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	J9000–	Chemotherapy drugs code range

CODES	NUMBER	DESCRIPTION
	J9999	
	Q0083–Q0085	Chemotherapy administration 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 in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)