



# Louisiana

## Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

**Policy #** 00059

**Original Effective Date:** 01/28/2002

**Current Effective Date:** 12/20/2017

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*Note: Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer is addressed separately in medical policy 00054.*

*Note: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors is addressed separately in medical policy 00056.*

*Note: Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma is addressed separately in medical policy 00063.*

*Note: Hematopoietic Cell Transplantation for Solid Tumors of Childhood is addressed separately in medical policy 00064.*

### **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 or allogeneic hematopoietic cell transplant (HCT) for miscellaneous solid tumors in adults including, but not limited to, the following malignancies to be **investigational\***:

- Lung cancer, any histology
- Colon cancer
- Rectal cancer
- Pancreas cancer
- Stomach cancer
- Esophageal cancer
- Gall bladder cancer
- Cancer of the bile duct
- Renal cell cancer
- Cervical cancer
- Uterine cancer
- Cancer of the fallopian tubes
- Prostate cancer
- Nasopharyngeal cancer
- Paranasal sinus cancer
- Neuroendocrine tumors

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- Soft tissue sarcomas
- Thyroid tumors
- Tumors of the thymus
- Tumors of unknown primary origin
- Malignant melanoma

### **Background/Overview**

#### **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. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or from umbilical cord blood 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 (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

#### **Conditioning for HCT**

##### ***Conventional Conditioning***

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is a result of a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility to opportunistic infections. The immune reactivity between donor T cells and malignant cells that is responsible for the GVM effect also leads to acute and chronic GVHD.

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The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

### ***Reduced-Intensity Conditioning for Allo-HCT***

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

### **HCT IN SOLID TUMORS IN ADULTS**

HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors is less well established, although it has been investigated for a variety of solid tumors. With the advent of nonmyeloablative 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.

HCT as a treatment for ovarian cancer, germ cell tumors, ependymoma, or malignant glioma is addressed separately (medical policies 00054, 00056, and 00063, respectively). HCT as a treatment for breast cancer is not addressed. This evidence review collectively addresses other solid tumors of adults for which HCT has been investigated, including lung cancer, malignant melanoma, tumors of the gastrointestinal tract (affecting the colon, rectum, pancreas, stomach, esophagus, gallbladder, or bile duct), male and female genitourinary systems (e.g., SCLC [RCC], prostate cancer, cervical cancer, uterine cancer, fallopian tube cancer), tumors of the head and neck, soft tissue sarcoma, thyroid tumors, tumors of the thymus, and tumors of unknown primary origin.

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### **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 CMS 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**

This evidence review was initially based on a 1995 TEC Assessment that focused on adult solid tumors other than breast cancer, epithelial ovarian cancer, germ cell tumors, and glial cell–derived brain cancers. Solid tumors reported in the literature identified in the Assessment included lung cancers, melanoma, tumors of gastrointestinal organs, genitourinary system tumors, tumors of the head and neck, soft tissue sarcomas of the extremities and torso, thyroid tumors, tumors of the thymus, undifferentiated tumors, and tumors of unknown primary. The Assessment offered the following conclusions:

- While 125 articles were identified that reported on the results of HCT in a variety of solid tumors, only 17 included survival data from groups of patients with the same cancer. These studies reported on 4 indications: advanced small cell lung cancer, advanced colorectal cancer, malignant melanomas, and inoperable gastric cancer.
- The evidence did not permit conclusions on the effect of HCT on patient survival.

A 1999 TEC Assessment evaluated the use of allo-HCT as a salvage therapy after a failed autologous HCT for solid tumors. The evidence was inadequate to permit conclusions.

### **AUTOLOGOUS HCT IN SOLID TUMORS OF ADULTS**

The evidence on the use of autologous HCT for the solid tumors of adults addressed in this evidence review consists primarily of small series.

#### **Adult Soft Tissue Sarcomas**

The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a median survival of 1 year and a 5-year survival estimates of less than 10%. A variety of single-agent and combination regimens are used for treatment, with targeted therapies available for some subtypes. Based on initial observations that patients who achieved CR had longer survival, several phase 1 and 2 trials using autologous HCT were conducted in the 1990s in an attempt to improve outcomes. These trials were composed of small numbers of patients (range, 2-55 patients), yielding overall response rates (ORRs) from 20% to 65%, with CR ranging from 10% to 43%. The longest reported 5-year progression-free survival (PFS) rate was 21%, and 5-year overall survival (OS) rate was 32%. One study (2007) of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease prior to

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HCT. In another phase 2 study (2006), 21 (38%) of 55 patients responded to doxorubicin-based induction chemotherapy, but estimated OS did not differ statistically between those who did (14%) and did not (3%) receive an autologous HCT ( $p=0.003$ ).

In 2014, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy (HDC) for nonrhabdomyosarcoma soft tissue sarcomas. Reviewers included 62 studies reporting on 294 transplanted patients, with a variety of soft tissue sarcomas. One randomized controlled trial (RCT) including 83 patients was identified; the remainder was single-arm studies. In the RCT, OS did not differ statistically between autologous HCT following HDC and standard-dose chemotherapy (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.70 to 2.29;  $p=0.44$ ), and the point estimate for survival at 3 years was 32.7% compared with 49.4%. The pooled treatment-related mortality rate across the single-arm studies was 15 (5.1%) of 294.

A small number of studies not included in the Cochrane review have described outcomes after HCT for soft tissue sarcoma. Kasper et al (2010) reported the results of a prospective, single-institution phase 2 study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma. After 4 courses of chemotherapy, patients with at least a partial response underwent HDC and autologous HCT ( $n=9$ ). All other patients continued chemotherapy for 2 more cycles. Median PFS for patients treated with HCT was 11.6 months (range, 8-15 months) versus 5.6 months for patients treated with standard chemotherapy ( $p=0.047$ ); median OS for the 2 groups was 23.7 months (range, 12-34 months) versus 10.8 months (range 0-39 months;  $p=0.027$ ), respectively.

Hartmann et al (2013) reported results from a phase 2 study of HDC with ifosfamide, carboplatin, and etoposide followed by peripheral blood stem cell transplantation in patients with grade 2 or 3 histologically proven soft tissue sarcoma considered unresectable or marginally resectable. After a median follow-up of 50 months (range, 26-120 months) in surviving patients, median PFS for all patients was 21 months (range, 1-94 months) and median OS was 37 months (range, 3-120 months), corresponding to 5-year PFS and OS rates of 39% and 48%, respectively.

A 2014 case report on the use of autologous HCT for treatment of an adult histiocytic sarcoma was identified, in which the patient was alive with no evidence of disease 30 months posttreatment.

### **Subsection Summary: Adult Soft Tissue Sarcomas**

Overall, 1 RCT and several small phase 2 studies have reported outcomes after autologous HCT in adults with soft tissue sarcoma. Although 1 small phase 2 study reported longer survival for patients treated with HCT than with standard chemotherapy, the available RCT did not show a survival benefit with HCT.

### **Small Cell Lung Carcinoma**

The interest in treating small cell lung carcinoma (SCLC) with HCT stems from the extremely high chemosensitivity and poor prognosis of this tumor type. A phase 3 trial (2005) of 318 patients with SCLC randomized patients to standard chemotherapy or to HCT. No statistically significant difference in response rates was seen between the 2 groups (response rate, 80% in standard arm group vs 88% in HCT group;

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difference, 8%; 95% CI, -1% to 17%;  $p=0.09$ ). There was no statistically significant difference in OS between groups, with a median OS of 13.9 months in the standard arm (95% CI, 12.1 to 15.7 months) and 14.4 months in the HCT arm (95% CI, 13.1 to 15.4 months;  $p=0.76$ ). One smaller, randomized study and several single-arm studies of HCT and autologous HCT for SCLC are summarized in a 2007 review article. Overall, most of the data from these studies, including the randomized study, showed no increased OS with autologous HCT.

Jiang et al (2009) performed a meta-analysis of English-language studies through October 2008 using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC. The meta-analysis consisted of 5 RCTs (3 phase 3 trials, 2 phase 2), with a total of 641 patients. Reviewers found no significant increase in the odds ratio (OR) for response rate with autologous transplant versus control chemotherapy (OR=1.29; 95% CI, 0.87 to 1.93;  $p=0.206$ ). No statistically significant increase in OS was seen among the autologous transplant patients compared with control regimens (HR=0.94; 95% CI, 0.80 to 1.10;  $p=0.432$ ). Reviewers concluded that current evidence did not support the use of intensified chemotherapy and autologous HCT for treating SCLC.

### Other Tumors

Uncontrolled pilot studies of HCT for patients with refractory urothelial carcinoma and recurrent or advanced nasopharyngeal carcinoma did not demonstrate adequate evidence of improved outcomes to alter previous conclusions. In a 2014 small series (N=8) of bilateral retinoblastoma survivors with secondary osteosarcoma, 2 patients (of 7 treated with multimodal chemotherapy) received HDC with autologous peripheral blood stem cell support. The 2 HCT-treated patients were alive with no evidence of disease at 33.4 and 56.4 months of follow-up.

### Section Summary: Autologous HCT in Solid Tumors of Adults

Since a 1995 Technology Evaluation Center (TEC) Assessment concluded that the evidence was insufficient to draw conclusions on HCT for lung cancers, melanoma, tumors of gastrointestinal organs, genitourinary system tumors, tumors of the head and neck, soft tissue sarcomas of the extremities and torso, thyroid tumors, tumors of the thymus, undifferentiated tumors, and tumors of unknown primary in adulthood, the largest body of evidence for autologous HCT in solid tumors in adults has been in sarcomas and SCLC. For both, meta-analyses of primarily retrospective data have shown no significant benefit from HCT. For other tumor types, the evidence is limited.

### ALLO-HCT IN SOLID TUMORS OF ADULTS

The evidence base for the treatment of patients with types of solid tumors addressed in this evidence review with allo-HCT consists of single-case reports and small series.

### Mixed Tumor Types

In 2016, Omazic et al reported on long-term follow-up for 61 patients with a variety of solid tumor types considered incurable with any conventional therapy who were treated with allo-HCT from 1999 to 2012. Tumors included metastatic renal carcinoma (n=22), cholangiocarcinoma (n=17), colon cancer (n=15), prostate cancer (n=3), pancreatic adenocarcinoma (n=3), and breast cancer (n=1). Most patients (n=59)

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had undergone surgical debulking of the primary tumor, and 31 patients had previously undergone additional therapy with cytotoxic chemotherapy, radiotherapy, or immunotherapy. Conditioning was myeloablative in 23 patients, reduced-intensity in 36 patients, and nonmyeloablative in 2 patients. Over a median follow-up of 8 years, OS rates at 5 and 10 years were 15% and 9%, respectively.

### **SCLC**

Metastatic RCC has an extremely poor prognosis, with a median survival of less than 1 year and a 5-year survival of less than 5%. RCC is relatively resistant to chemotherapy but is susceptible to immune therapy, and interleukin-2 and/or interferon- $\alpha$  have induced responses and long-term PFS in 4% to 15% of patients.<sup>19</sup> In addition, 7 targeted therapies are approved by the U.S. FDA for treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizumab. Based on the susceptibility of RCC to immune therapies, the immune-based strategy of a graft-versus-tumor effect possible with an allogeneic transplant has led to an interest in its use in RCC. In 2000, Childs et al published on the first series of patients with RCC treated with nonmyeloablative allo-HCT. The investigators showed regression of the tumor in 10 (53%) of 19 patients with cytokine-refractory, metastatic RCC who received a human leukocyte antigen (HLA)-identical sibling allo-HCT. Three patients had a CR and remained in remission 16, 25, and 27 months after transplant. Four of 7 patients with a partial response were alive without disease progression 9 to 19 months after transplantation. Other pilot trials have demonstrated the graft-versus-tumor effect of allo-HCT in metastatic RCC, but most have not shown as high a response rate as the Childs study. ORRs in these pilot trials have been approximately 25%, with CR rates of approximately 8%. Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC.

Bregni et al (2009) assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received RIC with allo-HCT from a sibling who was HLA-identical. All patients received the same conditioning regimens. Response to allograft was available in 24 patients, with a CR in 1 patient and partial response in 4 patients. Twelve patients had minor response or stable disease, and 7 had progressive disease. ORR (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (range, 12-2332+ days). The 1-year OS rate was 48% (95% CI, 28% to 68%) and the 5-year OS rate was 20% (95% CI, 4% to 36%). The authors concluded that allografting can induce long-term disease control in a small fraction of cytokine-resistant patients with RCC but that with the availability of novel targeted therapies for RCC, future treatment strategies should consider incorporating these therapies into the transplant regimen.

### **Colorectal Cancer**

Aglietta et al (2009) reported their experience with 39 patients with metastatic colorectal cancer who underwent RIC allo-HCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation centers. Patients were treated with 1 of 5 RIC regimens. End points assessed were achievement of mixed chimerism, incidence of GVHD, treatment-related mortality, and toxicities, OS, and time to treatment failure (in patients who responded to the therapy). Patient population characteristics were heterogeneous; pretransplant disease status was partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. Thirty-eight (97%) patients had had previous treatment, some with

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only chemotherapy and others with surgery, chemotherapy, or both. After transplant, tumor responses were complete and partial in 2% and 18% of patients, respectively, and 26% of patients had stable disease, for overall disease control in 46% of patients. Transplant-related mortality was 10%. Median overall follow-up was 202 days (range, 6-1020 days), after which time 33 patients had died and 6 were still alive. Tumor progression was the cause of death in 74% of patients. A comparison of OS of patients was performed after stratifying by potential prognostic factors. Achievement of response after transplantation was associated with a difference in OS, with the 18 patients who had a response having a median OS of approximately 400 days versus approximately 120 days for those who had no response ( $p < 0.001$ ). The authors concluded that the HCT approach should be reserved for patients with a partial response or stable disease after second-line therapy for metastatic colorectal cancer and that second-generation clinical trials in these patients would be warranted.

### **Pancreatic Cancer**

Kanda et al (2008) reported on the efficacy of RIC allo-HCT for advanced pancreatic cancer in 22 patients from 3 transplantation centers in Japan. RIC regimens differed across centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 having locally advanced disease. All but 1 patient received chemotherapy of various combinations before transplant, and 10 patients received localized radiation. After allo-HCT, 1 patient achieved CR, 2 patients had partial response, 2 had minor response, and 8 had stable disease, with an ORR of 23%. Median survival was 139 days, and the major cause of death was tumor progression (median duration of survival in advanced pancreatic cancer in the nontransplant setting is less than 6 months, even in patients treated with gemcitabine). Only 1 patient survived longer than 1 year after transplantation. The authors concluded that a tumor response was observed in 25% of patients with advanced pancreatic cancer who underwent allo-HCT and that the response was not durable. However, based on their observation of a relation between longer survival and the infusion of a higher number of CD34-positive cells or the development of chronic GVHD, they recommended additional study to evaluate the immunologic effect on pancreatic cancer.

Abe et al (2009) reported outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative conditioning with allo-HCT. Median age was 54 years (range, 44-62 years). All patients had advanced disease, either with metastases or peritonitis, and had received at least 1 course of chemotherapy including gemcitabine. After allo-HCT, tumor response was only observed in 2 patients—1 had complete disappearance of the primary tumor and 1 had a 20% reduction in tumor size; the remaining patients had progressive disease ( $n=2$ ) or stable disease ( $n=1$ ). Four patients died of progressive disease (median, 96 days; range, 28-209 days posttransplant). One patient died at day 57 secondary to rupture of the common bile duct from rapid tumor regression. The authors concluded that findings showed a graft-versus-tumor effect, but, to obtain durable responses, an improved conditioning regimen and new strategies to control tumor growth after nonmyeloablative allo-HCT would be needed.

### **Nasopharyngeal Cancer**

Toh et al (2011) reported on outcomes of a phase 2 trial of 21 patients with pretreated metastatic nasopharyngeal cancer. Median patient age was 48 years (range, 34-57 years), and patients had received a median of 2 previous chemotherapy regimens (range, 1-8 regimens). All patients had extensive metastases. Patients underwent a nonmyeloablative allo-HCT with sibling allografts. Seven (33%) patients

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showed a partial response and 3 (14%) achieved stable disease. Four patients were alive at 2 years, and 3 showed prolonged disease control of 344, 525, and 550 days. After a median follow-up of 209 days (range, 4-1147 days), the median PFS was 100 days (95% CI, 66 to 128 days) and median OS was 209 days (95% CI, 128 to 236 days). One- and 2-year OS rates were 29% and 19%, respectively, comparable to the median 7- to 14-month OS reported in the literature for metastatic nasopharyngeal patients treated with salvage chemotherapy without HCT.

### Section Summary: Allo-HCT in Solid Tumors of Adults

The evidence for allo-HCT in some solid tumors addressed in this review consists of single-arm series in small numbers of patients. The small numbers make comparisons with historical controls difficult.

### SUMMARY OF EVIDENCE

For individuals who have adult soft tissue sarcomas who receive HCT, the evidence includes 2 TEC Assessments, 1 RCT, and a number of phase 2 single-arm studies, some of which have been summarized in a systematic review. Relevant outcomes are OS, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Although 1 small phase 2 study reported longer survival for patients treated with HCT than with standard chemotherapy, this RCT did not show a survival benefit with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have SCLC who receive HCT, the evidence includes 2 TEC Assessments, several RCTs, and systematic reviews of these studies. Relevant outcomes are OS, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Studies published since the TEC Assessments have not reported increased OS for patients with SCLC treated with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have RCC, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive HCT, the evidence includes a TEC Assessment and small single-arm series. Relevant outcomes are OS, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Since publication of the TEC Assessments, the evidence for HCT to treat adult soft tissue sarcomas, RCC, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

### References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults", 8.01.24, 1:2017.

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2. Carnevale-Schianca F, Ricciardi A, Capaldi A, et al. Allogeneic hemopoietic stem cell transplantation in solid tumors. *Transplant Proc.* Jul-Aug 2005;37(6):2664-2666. PMID 16182778
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-Dose Chemotherapy with Autologous Stem-Cell Support for Miscellaneous Solid Tumors In Adults. TEC Assessments. 1995;10:Tab 4.
4. 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;14:Tab 11.
5. Pedrazzoli P, Ledermann JA, Lotz JP, et al. High dose chemotherapy with autologous hematopoietic stem cell support for solid tumors other than breast cancer in adults. *Ann Oncol.* Oct 2006;17(10):1479-1488. PMID 16547069
6. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: soft tissue sarcoma. Version 1.2015. [http://www.nccn.org/professionals/physician\\_gls/pdf/sarcoma.pdf](http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf).
7. Kasper B, Dietrich S, Mechtersheimer G, et al. Large institutional experience with dose-intensive chemotherapy and stem cell support in the management of sarcoma patients. *Oncology.* 2007;73(1-2):58-64. PMID 18334832
8. Schlemmer M, Wendtner CM, Falk M, et al. Efficacy of consolidation high-dose chemotherapy with ifosfamide, carboplatin and etoposide (HD-ICE) followed by autologous peripheral blood stem cell rescue in chemosensitive patients with metastatic soft tissue sarcomas. *Oncology.* 2006;71(1-2):32-39. PMID 17344669
9. Peinemann F, Labeit AM. Autologous haematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas: a Cochrane systematic review. *BMJ Open.* 2014;4(7):e005033. PMID 25079925
10. Kasper B, Scharrenbroich I, Schmitt T, et al. Consolidation with high-dose chemotherapy and stem cell support for responding patients with metastatic soft tissue sarcomas: prospective, single-institutional phase II study. *Bone Marrow Transplant.* Jul 2010;45(7):1234-1238. PMID 19935728
11. Hartmann JT, Horger M, Kluba T, et al. A non-comparative phase II study of dose intensive chemotherapy with doxorubicin and ifosfamide followed by high dose ICE consolidation with PBST in non-resectable, high grade, adult type soft tissue sarcomas. *Invest New Drugs.* Dec 2013;31(6):1592-1601. PMID 24091981
12. Tsujimura H, Miyaki T, Yamada S, et al. Successful treatment of histiocytic sarcoma with induction chemotherapy consisting of dose-escalated CHOP plus etoposide and upfront consolidation auto-transplantation. *Int J Hematol.* Nov 2014;100(5):507-510. PMID 25062797
13. Lorigan P, Woll PJ, O'Brien ME, et al. Randomized phase III trial of dose-dense chemotherapy supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer. *J Natl Cancer Inst.* May 4 2005;97(9):666-674. PMID 15870437
14. Crivellari G, Monfardini S, Stragliotto S, et al. Increasing chemotherapy in small-cell lung cancer: from dose intensity and density to megadoses. *Oncologist.* Jan 2007;12(1):79-89. PMID 17227903
15. Jiang J, Shi HZ, Deng JM, et al. Efficacy of intensified chemotherapy with hematopoietic progenitors in small-cell lung cancer: A meta-analysis of the published literature. *Lung Cancer.* Aug 2009;65(2):214-218. PMID 19118919
16. Nishimura M, Nasu K, Ohta H, et al. High dose chemotherapy for refractory urothelial carcinoma supported by peripheral blood stem cell transplantation. *Cancer.* Nov 1 1999;86(9):1827-1831. PMID 10547557
17. Airoidi M, De Crescenzo A, Pedani F, et al. Feasibility and long-term results of autologous PBSC transplantation in recurrent undifferentiated nasopharyngeal carcinoma. *Head Neck.* Sep 2001;23(9):799-803. PMID 11505492
18. Lee JA, Choi SY, Kang HJ, et al. Treatment outcome of osteosarcoma after bilateral retinoblastoma: a retrospective study of eight cases. *Br J Ophthalmol.* Oct 2014;98(10):1355-1359. PMID 24795337
19. Imanguli MM, Childs RW. Hematopoietic stem cell transplantation for solid tumors. *Update Cancer Ther.* 2006;1(3):343-352.
20. Demirer T, Barkholt L, Blaise D, et al. Transplantation of allogeneic hematopoietic stem cells: an emerging treatment modality for solid tumors. *Nat Clin Pract Oncol.* May 2008;5(5):256-267. PMID 18398414
21. Omazic B, Remberger M, Barkholt L, et al. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for solid cancer. *Biol Blood Marrow Transplant.* Apr 2016;22(4):676-681. PMID 26740375
22. Childs R, Chernoff A, Contentin N, et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *N Engl J Med.* Sep 14 2000;343(11):750-758. PMID 10984562
23. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: kidney cancer. Version 2.2016. [http://www.nccn.org/professionals/physician\\_gls/pdf/kidney.pdf](http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf).
24. Bregni M, Bernardi M, Servida P, et al. Long-term follow-up of metastatic renal cancer patients undergoing reduced-intensity allografting. *Bone Marrow Transplant.* Aug 2009;44(4):237-242. PMID 19234510

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# Louisiana

## Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Policy # 00059

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

25. Aglietta M, Barkholt L, Schianca FC, et al. Reduced-intensity allogeneic hematopoietic stem cell transplantation in metastatic colorectal cancer as a novel adoptive cell therapy approach. The European Group for Blood and Marrow Transplantation Experience. *Biol Blood Marrow Transplant.* Mar 2009;15(3):326-335. PMID 19203723
26. Kanda Y, Omuro Y, Baba E, et al. Allo-SCT using reduced-intensity conditioning against advanced pancreatic cancer: a Japanese survey. *Bone Marrow Transplant.* Jul 2008;42(2):99-103. PMID 18391987
27. Abe Y, Ito T, Baba E, et al. Nonmyeloablative allogeneic hematopoietic stem cell transplantation as immunotherapy for pancreatic cancer. *Pancreas.* Oct 2009;38(7):815-819. PMID 19696692
28. Toh HC, Chia WK, Sun L, et al. Graft-vs-tumor effect in patients with advanced nasopharyngeal cancer treated with nonmyeloablative allogeneic PBSC transplantation. *Bone Marrow Transplant.* Apr 2011;46(4):573-579. PMID 20661236
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).
30. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* Nov 2015;21(11):1863-1869. PMID 26256941
31. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for STEM CELL Transplantation (110.8.1). 2010; Version 5:  
<https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?ncdid=45&ncdver=5&coverageselection=both&articletype=all&policytype=final&s=pennsylvania&keyword=stem+cell&keywordlookup=title&keywordsearchtype=and&bc=gaaaabaaaaa&>

### Policy History

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

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|------------|--|
| 12/06/2001 | Medical Policy Committee review  |
| 01/28/2002 | Managed Care Advisory Council approval   |
| 03/31/2004 | Medical Director review  |
| 05/07/2004 | Medical Director review  |
| 05/18/2004 | Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Miscellaneous Solid Tumors in Adults policy developed separately from current HDC with Hematopoietic Stem Cell Support policy. No substance change to policy.   |
| 06/28/2004 | Managed Care Advisory Council approval   |
| 07/12/2006 | Medical Director review  |
| 07/19/2006 | Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility is unchanged.  |
| 06/04/2008 | Medical Director review  |
| 06/18/2008 | Medical Policy Committee approval. Coverage eligibility is unchanged.  |
| 06/04/2009 | Medical Director review  |
| 06/17/2009 | Medical Policy Committee approval. Changed title from "High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Miscellaneous Solid Tumors in Adults" to "High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults." Coverage eligibility is unchanged.   |
| 06/03/2010 | Medical Policy Committee review  |
| 06/16/2010 | Medical Policy Implementation Committee approval. Changed title from "High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults." to "Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults." Changed the wording of the investigational statement from, "high-dose chemotherapy (HDC) with autologous or allogeneic stem cell support (SCS) for miscellaneous solid tumors" to "autologous or allogeneic stem cell transplant (SCT) for miscellaneous solid tumors." Coverage eligibility unchanged. |

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- 06/02/2011 Medical Policy Committee review
- 06/15/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 06/14/2012 Medical Policy Committee review
- 06/20/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 03/04/2013 Coding updated
- 08/01/2013 Medical Policy Committee review
- 08/21/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 12/04/2014 Medical Policy Committee review
- 12/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
- 12/03/2015 Medical Policy Committee review
- 12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 12/01/2016 Medical Policy Committee review
- 12/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 12/07/2017 Medical Policy Committee review
- 12/20/2017 Medical Policy Implementation Committee approval. "Stem" removed from title and policy. HSCT changed to HCT in policy text. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2018

### Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related diagnoses

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\*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. Food and Drug Administration (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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