Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Bone Marrow/Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Description/Background

Though cancer incidence along with overall mortality has been declining in the United States, certain population groups continue to have an increased risk of cancer progression and mortality due to social, economic, and environmental disadvantages.(1) The National Cancer Institute has published statistics on cancer disparities in relation to various criteria including specific racial and ethnic groups, gender, and geography. Some key incidence and mortality statistics in the United States are as follows: incidence rates of lung, colorectal, and cervical cancers are increased in rural Appalachia compared to urban areas; American Indians/Alaska Natives have increased mortality rates from kidney, liver, and intrahepatic bile duct cancer compared to other racial and ethnic groups; Black men are twice as likely to die of prostate cancer than White men.

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow immune 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 a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for HCT

Myeloablative (Conventional) Conditioning

The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. After graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT

Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC/NMA is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

HCT in Solid Tumors in Adults

HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors in adults 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.(2)

HCT as a treatment of ovarian cancer, germ cell tumors, ependymoma or malignant glioma is addressed in separately in related policies. See Related Policy section below. HCT as a treatment of 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., renal cell carcinoma, 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.

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

Bone marrow/autologous or allogeneic hematopoietic cell transplant is considered experimental/ investigational for specified indications (see exclusionary guidelines). It has not been scientifically demonstrated to improve individual clinical outcomes.

Inclusionary and Exclusionary Guidelines

Exclusions:
The use of BMTs in specified solid tumors in adults continues to be experimental/ investigational. These tumors include the following:

- Cancer of the bile duct
- Cancer of the fallopian tubes
- Cervical cancer
- Colon cancer
- Esophageal cancer
- Gall bladder cancer
- Lung cancer, any histology
- Malignant melanoma
- Nasopharyngeal cancer
- Neuroendocrine tumors
- Pancreatic cancer
- Paranasal sinus cancer
- Prostate cancer
- Rectal cancer
- Renal cell cancer
- Soft tissue sarcomas
- Stomach cancer
- Thyroid tumors
- Tumors of the thymus
- Tumors of unknown primary origin
- Uterine cancer

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	81267	81268
81270	81271	81272	81273	81274	81275
81276	81277	81278	81279	81280	81281
81282	81283	86812	86813	86816	86817
86821	86822	S2140	S2142	S2150	

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 a 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.

AUTOLOGOUS HCT IN SOLID TUMORS

Adult Soft Tissue Sarcomas

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with adult soft tissue sarcomas.

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

Populations
The relevant population of interest are adults with soft tissue sarcomas.

Interventions
The therapy being considered is autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
In general, the 5-year survival rate for soft-tissue sarcomas is 65%. The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a 5-year survival estimate of 16%.(3) A variety of single-agent and combination regimens are used for treatment, with targeted therapies available for some subtypes.(4) Based on initial observations that patients who achieved complete remission (CR) had longer survival; several phase I and II trials using autologous HCT were conducted in the 1990s to improve outcomes.(5) These trials were composed of sample size ranging from 2–55, yielding overall response rates (ORRs) from 20% to 65%, with CR ranging from 10% to 43%. The longest reported five-year progression-free survival (PFS) rate was 21%, and 5-year overall survival (OS) rate was 32%.(5) One study of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease prior to HCT.(6) In another phase II study, 21 of 55 (38%) patients responded to doxorubicin-based induction chemotherapy, but estimated 5-year OS did not differ statistically different between those who did (14%) and did not (3%) receive an autologous HCT (p=0.08).(7)

Systemic Reviews
In 2017, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy (HDC) for nonrhabdomyosarcoma soft tissue sarcomas.(8) One RCT

assessing 83 patients was identified.(9) 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%. In 2014, Peinemann and Labeit conducted another systematic review that included an RCT (described above) and 61 single-arm studies.(10) The pooled risk of treatment-related mortality across 61 single-arm studies was 15 (5.1%) of 294 patients.

Randomized Controlled Trials

A 2019 RCT evaluated the use of autologous HCT following high-dose chemotherapy for Ewing Sarcoma in patients younger than 50years of age with only pulmonary or pleural metastases.(11) The median age of patients was 14.2 years (range, 1.0 to 47.8 years). Induction chemotherapy for all patients consisted of 6 chemotherapy courses combining vincristine, ifosfamide, doxorubicin, and etoposide and 1 course of vincristine, dactinomycin, and ifosfamide. Patients were then randomized to receive either high-dose chemotherapy with autologous HCT without whole-lung irradiation (n=144) or standard-dose chemotherapy with whole-lung irradiation(n=143). Median follow-up was 8.1 years. No significant differences in survival outcomes between treatment groups were observed. Event-free survival was 50.6% versus 56.6% at 3 years and 43.1% versus 52.9% at 8 years, for standard-dose chemotherapy and high-dose chemotherapy with autologous HCT, respectively (HR, 0.79; 95% CI, 0.56 to 1.10; p=.16). The HR for OS was 1.00 (95% CI, 0.70 to 1.44; p=.99). Four patients died as a result of toxicity from high-dose chemotherapy with autologous HCT, and none died after standard-dose chemotherapy. Investigators concluded there is no clear benefit from high-dose chemotherapy with autologous HCT compared with standard-dose chemotherapy.

Nonrandomized Studies

Few 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 II study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma.(12) 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 two 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 two groups was 23.7 months (range, 12-34 months) and 10.8 months (range 0-39 months; p=0.027), respectively.

Hartmann et al (2013) reported results from a phase II study of HDC with ifosfamide, carboplatin, and etoposide followed by peripheral blood stem-cell transplantation in patients with grade II or III histologically proven soft tissue sarcoma that were considered unresectable or marginally resectable.(13) After a median follow-up period of 50 months (range, 26-120 months) in surviving patients, the median PFS for all patients was 21 months (range, 1-94 months) and median OS was 37 months (range, 3-120 months), corresponding to five-year PFS and OS rates of 39% and 48%, respectively.

A 2020 registry study retrospectively evaluated the effectiveness of autologous HCT in the treatment of soft tissue sarcoma using data from the European Society for Blood and Marrow Transplantation database between 1996 and 2016 (N=338).(14) The PFS and OS were 8.3 and 19.8 months, respectively. The PFS and OS at 5 years were 13% and 25%, respectively. Predictors of favorable benefit with HCT were younger age, better remission status before transplantation, and melphalan-based preparative regimens. The authors concluded that

autologous HCT should not be performed on patients with soft tissue sarcoma in routine clinical practice without further investigation.

Section Summary: Adult Soft Tissue Sarcomas
Overall, 2 RCTs, several phase II studies, and a retrospective registry study have reported outcomes after autologous HCT in adults with soft tissue sarcoma. Although 1 phase II study reported longer survival for patients treated with HCT than standard chemotherapy, the RCT did not show an overall survival benefit with HCT. An RCT from 2019 also showed no survival benefits with autologous HCT.

Small Cell Lung Carcinoma

Clinical Context and Therapy Purpose
The purpose of autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with small cell lung cancer (SCLC).

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

Populations
The relevant population of interest are adults with small cell lung cancer.

Interventions
The therapy being considered is autologous hematopoietic cell transplantation.

Comparators
Comparators of interest the include standard of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described above.

Review of Evidence

Systematic Reviews
The interest in treating SCLC with autologous HCT stems from the extremely high chemosensitivity and poor prognosis of this tumor type. 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.(15) The meta-analysis consisted of 5 RCTs (3 phase III trials, 2 phase II trials), with a total of 641 patients. Reviewers found no significant increase in the odds ratio for response rate with autologous transplant versus control chemotherapy (odds ratio, 1.29; 95% CI, 0.87 to 1.93; p=.206). No statistically significant increase in OS was seen among the autologous transplant patients compared with control regimens (hazard ratio, 0.94; 95% CI, 0.80 to 1.10; p=.432). Reviewers concluded that

current evidence did not support the use of intensified chemotherapy and autologous HCT for treating SCLC.

Randomized Controlled Trials
A phase III trial randomized 318 patients with SCLC randomized patients to standard chemotherapy or HCT.(16) No statistically significant difference in response rates was seen between the II groups (response rate, 80% in the standard arm vs. 88% in the HCT group; 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) versus 14.4 months in the HCT arm (95% CI, 13.1 to 15.4; p=0.76). One randomized study and several single-arm studies of HCT and autologous HCT for SCLC are summarized in a 2007 review article.(17) Overall, most of the data from these studies, including the randomized study, showed no increased OS with autologous HCT.

Section Summary: Small Cell Lung Carcinoma
Treatment of small cell lung carcinoma with autologous HCT has been studied in a meta-analysis study, RCTs, and case series. These studies did not show a survival benefit with HCT.

Other Tumors

Review of Evidence
Uncontrolled pilot studies of HCT for patients with refractory urothelial carcinoma (18) and recurrent or advanced nasopharyngeal carcinoma (19) did not demonstrate adequate evidence of improved outcomes to alter previous conclusions. In a 2014 series (N=8) of bilateral retinoblastoma survivors with secondary osteosarcoma, two patients (of seven treated with multimodal chemotherapy) received HDC with autologous peripheral blood stem cell support.(20) The two HCT-treated patients were alive with no evidence of disease at 33.4 and 56.4 months of follow up.

ALLOGENEIC HCT IN SOLID TUMORS
The evidence base for the treatment of patients with other types of solid tumors (refractory urothelial carcinoma, recurrent or advanced nasopharyngeal carcinoma, and secondary osteosarcoma) using allogeneic hematopoietic cell transplantation (allo-HCT) consists of single-case reports and case series.(2,21,22)

Renal Cell Carcinoma

Clinical Context and Therapy Purpose
The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with renal cell carcinoma (RCC).

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

Populations
The relevant population of interest are adults with renal cell carcinoma.

Interventions
The therapy being considered is allogenic hematopoietic cell transplantation.

Comparators
Comparators of interest include the standards of care.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), treatment-related mortality (TRM), and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described above.

Review of Evidence
Metastatic renal cell carcinoma (RCC) has an extremely poor prognosis, with a median survival of less than 1 year and a 5-year survival of approximately 12%.(23) RCC is relatively resistant to chemotherapy but is susceptible to immune therapy. Interleukin-2 and/or interferon alpha have induced responses and long-term PFS in 4% to 15% of patients.(22) In addition, 10 targeted therapies are approved by the U.S. Food and Drug Administration for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, bevacizumab, cabozantinib, lenvatinib and tivozanib.(23) 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 the first series of patients with RCC treated with nonmyeloablative allo-HCT.(24) 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. Overall response rates in these pilot trials have been approximately 25%, with CR rates of approximately 8%.(21) Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC.(21)

Bregni et al (2009) assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received reduced-intensity conditioning (RIC) with allo-HCT from a sibling who was HLA-identical.(25) 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. The overall response rate (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (range, 12-2332+ days). The one-year OS rate was 48% (95% CI, 28% to 68%) and the five-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 of these therapies into the transplant regimen.

Section Summary: Allogenic HCT in Renal Cell Carcinoma

Evidence on use of HCT for RCC is based on multiple case series. In the absence of RCTs, current evidence is insufficient to conclude whether HCT results in improved overall survival among RCC patients.

Colorectal Cancer

Clinical Context and Therapy Purpose
The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with colorectal cancer (CRC).

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

Populations
The relevant population of interest are adults with colorectal cancer.

Interventions
The therapy being considered is allogenic hematopoietic cell transplantation.

Comparators
Comparators of interest include the standards of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

Review of Evidence
Aglietta et al (2009) reported their experience with 39 patients with metastatic colorectal cancer who underwent RIC allo-HCT between 1999 and 2004 at nine European Group for Blood and Marrow Transplantation centers.(26) Patients were treated with one of five RIC regimens. End points assessed were achievement of mixed chimerism, incidence of graft-versus-host disease (GVHD), treatment-related mortality, toxicities, OS, and time to treatment failure (in patients who responded to 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 previous treatment, some with 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. An assessment of the OS of patients was performed after stratifying by some 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.

Section Summary: Allo-HCT in Colorectal Cancer
Evidence on use of HCT for colorectal cancer is based on case series. In absence of RCTs, current evidence is insufficient to conclude whether HCT results in improved OS among colorectal carcinoma individuals.

Pancreatic Cancer

Clinical Context and Therapy Purpose
The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with pancreatic cancer.

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

Populations
The relevant population of interest are adults with pancreatic cancer.

Interventions
The therapy being considered is allogenic hematopoietic cell transplantation.

Comparators
Comparators of interest include the standards of care**.**

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described above.

Review of Evidence
Kanda et al (2008) reported on the efficacy of RIC allo-HCT for advanced pancreatic cancer in 22 patients from three transplantation centers in Japan.(27) RIC regimens differed across centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and seven having locally advanced disease. All but one patient received chemotherapy of various combinations before transplant, and 10 patients received localized radiation. After allo-HCT, one patient achieved CR, two 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 non-transplant setting is less than six 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 relationship 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 five patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative conditioning with allo-HCT.(28) 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 survival, 96 days; range, 28-209 days post-transplant). 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.

Omazic et al (2017) reported the outcome for 2 patients who received allogeneic HCT from HLA-identical sibling donors following resection of pancreatic ductal adenocarcinoma.(29) These patients were compared with six controls who underwent radical surgery for pancreatic ductal adenocarcinoma but did not receive HCT. Both patients receiving HCT were tumor free after nine years following diagnosis, whereas all the patients in the control group died within 4 years of diagnosis.

Section Summary: Allo-HCT in Pancreatic Cancer
Evidence on use of HCT for pancreatic cancer is based on multiple case series and a comparative study. In absence of RCTs, current evidence is insufficient to conclude whether HCT results in improved OS among individuals with pancreatic cancer.

Nasopharyngeal Cancer

Clinical Context and Therapy Purpose
The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with nasopharyngeal cancer.

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

Populations
The relevant population of interest are adults with nasopharyngeal cancer.

Interventions
The therapy being considered is allogenic hematopoietic cell transplantation.

Comparators
Comparators of interest include the standards of care.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described above.

Review of Evidence
Toh et al (2011) reported the outcomes of a phase II trial of 21 patients with pretreated metastatic nasopharyngeal carcinoma.(30) Median patient age was 48 years (range, 34-57 years), and patients had received a median of two previous chemotherapy regimens (range, 1-8 regimens). All patients had extensive metastases. Patients underwent a nonmyeloablative allo-HCT with sibling allografts. Seven (33%) patients 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 Nasopharyngeal Cancer
Evidence on use of HCT for nasopharyngeal cancer is based on a phase II trial. In absence of RCTs, current evidence is insufficient to conclude whether allo-HCT results in improved OS among nasopharyngeal cancer patients.

Mixed Tumor Types

Review of Evidence
Omazic et al (2016) 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.(31) 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) 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.

Summary of Evidence

Autologous HCT
For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes 2 randomized controlled trials (RCTs), phase II single-arm studies (some of which have been summarized in a systematic review) and a retrospective registry study. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Although a phase II RCT reported longer survival for patients treated with autologous HCT than with standard chemotherapy, this trial did not show an overall survival benefit with HCT. An RCT from 2019 also showed no survival benefits with autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes several RCTs, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Studies have not reported increased overall survival for patients with SCLC treated with autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Allo-HCT

For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes single-arm series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The evidence for allo-HCT to treat renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to case series. 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 National Comprehensive Cancer Network guidelines on the tumors addressed in this evidence review do not discuss hematopoietic cell transplantation (HCT) as a treatment option and these tumors are also not addressed in the NCCN HCT guideline.(32,33)

American Society of Blood and Marrow Transplantation

The American Society for Blood and Marrow Transplantation (2015) issued guidelines related to indications for autologous and allogeneic HCT.(34) The guidelines were updated in 2020.(35) The tumors addressed herein for which Society has provided recommendations are listed in Table 1.

Table 1. Recommendations for Use of Autologous and Allogeneic HCT

Condition	Treatment Option	2015 Recommendation	2020 Recommendation
Ewing sarcoma, high-risk	Allogeneic HCT	Not generally recommended	Developmental
	Autologous HCT	Standard of care, clinical evidence available	Standard of care, clinical evidence available
Renal cancer, metastatic	Allogeneic HCT	Developmental	Developmental
	Autologous HCT	Not generally recommended	Not generally recommended

HCT: hematopoietic cell transplantation.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT04530487	Donor Stem Cell Transplant After Chemotherapy for the Treatment of Recurrent or Refractory High-Risk Solid Tumors in Pediatric and Adolescent-Young Adults	40	May 2025
NCT04937842	Efficacy and Safety of Radiotherapy or Chemotherapy Combined with Microtransplantation in the Treatment of Advanced and Relapsed Solid Tumors	60	June 2025
NCT01505569	Alkylator-Intense Conditioning Followed by Autologous Transplantation for Patients with High Risk or Relapsed Solid or CNS Tumors	20	March 2025

NCT: national clinical trial

Government Regulations
National:

Medicare National Coverage Determinations Manual, Chapter 1, Part 2, Section 110.23, "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 non-coverage 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)."(34)

Local:
There is no local coverage determination for this topic.

(The above Medicare information is current as of the review date or 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 - Allogenic Hematopoietic Cell, for Genetic Diseases and Acquired Anemias
- BMT - Hematopoietic Cell Transplant for Treatment of Multiple Myeloma
- 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 Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT - Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia
- BMT - Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT - Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT - Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT - Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT - Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT - Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT - Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT - Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
- BMT - Malignant Astrocytomas and Gliomas, Autologous

- 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)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/25/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/11	8/16/11	8/16/11	Joint policy established. Note: This policy was generated from former combined policies on investigational bone marrow transplants
9/1/13	6/18/13	6/26/13	Routine review; rationale and references updated. Added procedure code 38204.
11/1/14	8/21/14	8/25/14	Added additional CPT codes 38230, 38232, 81370-81383, 86812-86822 and S2140, S2142. S2150
5/1/16	2/16/16	2/16/16	Routine review; rationale and references updated.
5/1/17	2/21/17	2/21/17	Routine review Added CPT code 38207 Rationale and references updated 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
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: BONE MARROW/HEMATOPOIETIC CELL TRANSPLANTATION FOR MISCELLANEOUS SOLID TUMORS IN ADULTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not 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.