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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation for Miscellaneous Solid Tumors in Adults

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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

Hematopoietic Stem-Cell Transplantation

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. Hematopoietic stem-cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem-cells in it are antigenically "naïve" 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 HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on 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).

Conventional Preparative Conditioning for HSCT

The success of *autologous* HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of *allogeneic* HSCT 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 due to 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 pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increase susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HSCT

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 traditional 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 non-relapse 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 allogeneic HSCT 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.

HSCT in Solid Tumors in Adults

HSCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental. 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.[1]

Miscellaneous Solid Tumors in Adults

This policy collectively addresses other solid tumors of adults for which HSCT has been investigated, including lung cancer; malignant melanoma; tumors of the gastrointestinal tract (include colon, rectum,

pancreas, stomach, esophagus, gallbladder, and bile duct); male and female genitourinary systems (e.g., renal cell carcinoma, cervical carcinoma, cancer of the uterus, fallopian tubes, and prostate gland); tumors of the head and neck; soft tissue sarcoma; thyroid tumors; tumors of the thymus; and tumors of unknown primary origin.

MEDICAL POLICY CRITERIA

Note: This policy addresses only solid tumors in adults. See Cross References section below for tumors not specifically addressed in this policy.

Autologous or allogeneic stem-cell transplant is considered **investigational** for all of the following malignancies in adults*:

- Lung cancer, any histology
- Esophageal cancer
- Stomach cancer
- Colon cancer
- Rectal cancer
- Pancreas cancer
- Gall bladder cancer
- Bile duct cancer
- Renal cell cancer
- Cervical cancer
- Uterine cancer
- Fallopian tube cancer
- Prostate cancer
- Malignant melanoma
- Nasopharyngeal cancer
- Paranasal sinus cancer
- Neuroendocrine tumors
- Soft tissue sarcomas
- Osteosarcoma
- Thyroid tumors
- Thymus tumors
- Tumors of unknown primary origin

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of solid organ 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. Patient quality of life may be another primary outcome, particularly among patients living with refractory disease. In order to understand the impact of hematopoietic stem-cell transplantation for treatment of solid tumors in adults on these outcomes, well-designed randomized

controlled trials (RCTs) that compare this therapy to standard medical treatment, such as conventional standard-dose chemotherapy are needed. Further, for treatment of malignant cancers, 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

Autologous Hematopoietic Stem-Cell Transplantation (HSCT) in Solid Tumors of Adults

Literature on the use of autologous HSCT for the solid tumors of adults addressed in this policy consists of a BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment, several systematic reviews, and a small number of randomized controlled trials.

The TEC Assessment and several systematic reviews report on the use of autologous HSCT for several different types of tumors.

- A 1995 TEC Assessment found that while 125 articles were identified that reported on the results of high-dose chemotherapy (HDC) combined with autologous HSCT in a variety of solid tumors, only 17 included survival data from groups of patients with the same cancer.[2] These studies reported on 4 indications: advanced small-cell lung cancer, advanced colorectal cancer, malignant melanomas, and inoperable gastric cancer. The authors concluded that the available evidence did not permit conclusions concerning the effect of HDC on patient survival for any of the studied indications.

- A review by Nieto and Shpall also concluded that evidence was inadequate to demonstrate a survival benefit from HDC and autologous HSCT for melanoma or soft tissue sarcoma.[3]

- Pedrazzoli and colleagues published a review of autologous HSCT (AHSCT) for solid tumors in adults in 2006, concluding that insufficient evidence exists to support the use of AHSCT in small cell lung cancer and soft tissue sarcoma.[4]

- Another review published by Pedrazzoli and colleagues in 2007, concluded more broadly that "data available to date do not support the routine use of [high dose chemotherapy] with AHSCT for solid tumors other than [breast cancer] in adults."[5]

Overall, the literature on groups of indications is insufficient and does not permit conclusions about the use of this therapy in adults with solid tumors.

Urothelial Carcinoma

Limited data exist on the use of autologous HSCT for urothelial carcinoma. To date, only a single uncontrolled pilot study on HDC with HSCT for patients with refractory urothelial carcinoma has been published. This study was unable to provide evidence of improved outcomes.[6]

Nasopharyngeal Carcinoma

A single uncontrolled pilot study on HDC with autologous HSCT for patients with recurrent or advanced nasopharyngeal carcinoma fails to provide evidence to support the use of this treatment among patients with this indication.[7]

Adult Soft Tissue Sarcomas

The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a median survival of about 1 year, and less than 10% 5-year survival.[4] In general, dose-intensive doxorubicin and ifosfamide-based regimens have yielded higher response rates and prolonged DFS, but not OS. The available evidence on the use of autologous HSCT for this indication consists of a systematic review and several case series.

- A systematic review by Verma and colleagues in 2008 found 3 Phase III RCTs involving SCT, none of which evaluated the therapy for first-line treatment of advanced or metastatic adult soft tissue sarcoma compared to conventional standard-dose chemotherapy.[8]

- Schlemmer and colleagues published a phase II study in 2006 on 55 patients with metastatic soft tissue sarcoma.[9] Although significantly more patients receiving autologous HSCT responded to doxorubicin-based induction chemotherapy versus the control group (14% vs. 3%; p=0.003), the estimated OS was not statistically different between those that received autologous HSCT and those that did not.

- Kasper and colleagues published results of a cases series in 2007of 21 patients with soft-tissue sarcoma, which showed a PFS and an OS benefit only in patients with no evidence of disease before receiving HDC and autologous HSCT.[10]

- In another study by Kasper and colleagues the results of a prospective, single institution phase 2 study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma were reported.[11] After 4 courses of chemotherapy, patients with at least a partial response underwent high dose chemotherapy and autologous HSCT (n=9). All other patients continued chemotherapy for two more cycles. Patients treated with HSCT had statistically significant longer PFS and OS compared with patients treated with standard chemotherapy, although only 9 of 34 patients were selected for treatment with HSCT.

In general, small sample size and limitations inherent to observational study design restrict the interpretation of these findings. Further research is needed to determine whether there is an association between autologous HSCT and OS, and if this association is uniform across all patient populations.

Small-Cell Lung Carcinoma

The interest in treating small-cell lung carcinoma (SCLC) with SCT originates from its extremely high chemosensitivity and poor prognosis. The available literature on this topic consists of 2 review articles, a single meta-analysis, and several small randomized controlled trials.

- A report from the European Group for Bone Marrow Transplantation's Solid Tumors Working Party concluded that evidence was still insufficient to establish a definite role for HDC and autologous transplantation in small-cell lung cancer.[12]

- Jiang and colleagues performed a meta-analysis of the medical literature through October 2008 of English language studies using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC.[13] The meta-analysis consisted of 5 randomized, controlled trials (3 were phase III trials and 2 were phase II), for a total of 641 patients. They found no significant increase in the likelihood of an improved response rate with autologous transplant versus control chemotherapy.

Neither did they find a statistically significant increase in OS among the autologous transplant patients compared to control regimens. The authors concluded that current evidence does not support the use of intensified chemotherapy and autologous HSCT for treating SMLC.

- In 2005, Lorigan and colleagues reported on a randomized phase III trial of 318 patients with SCLC.[14] No statistically significant difference in response rates was seen between the two groups (80% response rate in the standard arm vs. 88% in the HDC group), nor was there a statistically significant difference in OS between the two groups.

- One smaller, randomized study and several single-arm studies of HDC and autologous HSCT for SCLC are summarized in a review article by Cricellari and colleagues.[15] The authors begin the conclusion of their review with this statement, "The lesson we have learned is that the current literature indicates that there is no evidence that the treatment of SCLC can be improved by increasing the dose intensity, peak dose, or total dose of chemotherapy, and survival rates have reached a plateau, so intensification strategy should probably be abandoned."

Overall, the majority of the data from these studies, including the randomized study, showed no increased OS with autologous HSCT. At least one systematic review on this topic recommended that autologous HSCT, as a dose intensification strategy for SCLC, be abandoned in light of evidence demonstrating no clear treatment benefit.[15]

Allogeneic HSCT in Solid Tumors of Adults

The literature on allogenic HSCT in solid tumors among adults consists of a single TEC Assessment and several small case series.

Multiple Indications

- A 1999 TEC Assessment evaluated the use of HDC with allogeneic HSCT as a salvage therapy after a failed prior course of HDC with autologous HSCT for solid tumors.[16] Data were inadequate to permit conclusions.

- A review of data from the European Bone Marrow Transplantation Solid Tumors Working Party (EBMT STWP) on allogeneic HSCT for renal cell cancer, pancreatic cancer, colorectal cancer and soft-tissue sarcoma found multiple small case series ($n \leq 25$) with different conditioning regimens, varying response rates and treatment mortality rates for each indication.[17] The EBMT STWP concluded that, "Allogeneic transplantation in renal cancer and other solid tumors should be considered a developmental therapy until definitive proof of a clinical benefit is achieved by current studies."

Available reviews of allogeneic HSCT have concluded that the scientific evidence is insufficient to support the use of this therapy in adults with solid tumors.

Nasopharyngeal Carcinoma

A single report is available on the use of allogeneic HSCT for treatment of nasopharyngeal carcinoma.

Toh and colleagues reported the outcomes of a phase 2 trial of 21 patients with pretreated metastatic nasopharyngeal carcinoma.[18] Previous treatment was not uniform; patients had received a median of 2

previous chemotherapy regimens (range 1-8). All patients had extensive metastases. Patients underwent nonmyeloablative allogeneic HSCT with sibling allograft. Seven patients (33%) showed a partial response and 3 (14%) achieved stable disease. Four patients were alive at 2 years and 3 showed prolonged disease control past 344 days. One and 2-year OS rates were 29 and 19%, respectively, comparable to the median 7-14 months OS reported in the literature for metastatic nasopharyngeal patients treated with salvage chemotherapy without HSCT. However, valid and reliable conclusions based upon these results cannot be made due to limitations such as: small sample size, varied pre-HSCT treatment regimens, and lack of control group. These limitations hinder the ability to account for the many types of bias that can affect study outcomes.

Renal Cell Carcinoma

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 less than 5%.[19] RCC is relatively resistant to chemotherapy, but is susceptible to immune therapy, and interleukin-2 (IL-2) and/or interferon alpha have induced responses and long-term PFS in 4%–15% of patients.[17] Therefore, 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. Several small case series and pilot studies exist on the use of allogeneic HSCT in RCC.

- In 2000, Childs and colleagues published a study on the first series of patients with RCC treated with nonmyeloablative allogeneic HSCT.[19] The investigators showed regression of the tumor in 10 of 19 (53%) patients with cytokine-refractory, metastatic RCC who received an HLA-identical sibling allogeneic HSCT. Three patients had a complete response, 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 to19 months after transplantation.

- Other pilot trials have demonstrated the graft-versus-tumor effect of allogeneic transplant in metastatic RCC, but most have not shown as high a response rate as the Childs' study.[20] Overall response rates in these pilot trials have been about 25%, with complete response rates of about 8%.

- Bregni and colleagues assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received a reduced intensity conditioning (RIC) allograft from a sibling who was human leukocyte antigen (HLA) identical.[21] All patients received the same conditioning regimens. Response to allograft was available in 24 patients, with a complete response in 1 patient and partial response in 4 patients. Twelve patients had minor response or stable disease, and 7 reported progressive disease. Overall response rate (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (12–2,332+). One-year OS was 48% (95% CI: 28–68), and 5-year OS was 20% (95% CI: 4–36). The authors concluded that allografting may be associated with long-term disease control in only a small fraction of cytokine-resistant patients with RCC.

Results from small, nonrandomized clinical trials should be interpreted with caution as it is not possible to account for the many types of bias that can affect study outcomes. Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with RCC.

Colorectal Cancer

A single case series is available on the use of allogeneic HSCT in patients with colorectal carcinoma.

Aglietta and colleagues reported their experience with 39 patients with metastatic colorectal cancer who underwent RIC allogeneic HSCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation (EBMT) centers.[22] Patients were treated with one of five different RIC regimens. Patient population characteristics were heterogeneous; pretransplant disease status was partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. After transplant, tumor responses were complete in 2% of patients, partial in 18%, 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 6–1,020), after which time 33 patients had died. Tumor progression was the cause of death in 74% of patients. 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=.00018). The authors concluded that the HSCT approach should probably 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 are warranted.

Pancreatic Cancer

Two small case series (n≤22) are available on the use of this technology among patients with pancreatic cancer.

- Kanda and colleagues reported on the efficacy of RIC allogeneic HSCT against advanced pancreatic cancer in 22 patients from three transplantation centers in Japan.[23] The RIC regimens differed among the centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 locally advanced disease. All but 1 patient received chemotherapy of various combinations before transplant, and 10 patients received local radiation. After HSCT, 1 patient achieved complete response, 2 patients had partial response, 2 had minor response, and 8 had stable disease, with an overall response rate 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 one-fourth of patients with advanced pancreatic cancer who underwent HSCT and that the response was not durable.

- Abe and colleagues reported the outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative allogeneic peripheral blood HSCT.[24] The median patient 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 HSCT, tumor response was only observed in 2 patients; 1 patient had complete disappearance of the primary tumor and 1 had a 20% reduction in tumor size. Four patients died of progressive disease on post-transplant day ranging from 28 to day 209 (median: 96 days).

Results from the above studies should be interpreted with caution due to the heterogeneity of patient populations (including previous treatment regimens), small sample size, and short follow-up times, all of which prevent control for biases which can affect study outcomes.

Clinical Practice Guidelines

The National Comprehensive Cancer Network guidelines on the tumors addressed in this policy do not indicate hematopoietic stem-cell transplantation as a treatment option.[25]

Summary

Based on the lack of published long-term objective outcomes from well-designed, well-executed randomized controlled clinical trials, conclusions cannot be reached concerning the effectiveness of hematopoietic stem-cell transplantation (HSCT) as a treatment option for the miscellaneous adult solid tumors addressed in this policy; therefore HSCT is considered investigational for these indications. Larger, randomized trials of longer duration are needed to evaluate the effectiveness of HSCT in improving overall survival and to determine whether HSCT offers any additional benefit compared with other standard treatments.

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CROSS REFERENCES

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Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer, Transplant, Policy No. 45.26

Hematopoietic Stem-Cell Transplantation for Breast Cancer, Transplant, Policy No. 45.29

Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33

Autologous Hematopoietic Stem-Cell Transplantation for Malignant Astrocytomas and Gliomas, Transplant, Policy No. 45.34

Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37

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

CODES	NUMBER	DESCRIPTION
	38221	Bone marrow; biopsy, needle or trocar
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	J9000–J9999	Chemotherapy drugs code range
	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)