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Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With previously untreated germ cell tumors	Interventions of interest are: • Autologous hematopoietic cell transplantation as first-line therapy	Comparators of interest are: • Standard-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With relapsed or refractory germ cell tumors	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Standard-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With germ cell tumors	Interventions of interest are: • Tandem autologous transplantation and sequential high-dose chemotherapy	Comparators of interest are: • Standard-dose chemotherapy • Single autologous hematopoietic cell transplantation	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With germ cell tumors	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard-dose chemotherapy • Autologous hematopoietic cell transplantation	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Therapy for germ cell tumors is generally dictated by several factors, including disease stage, tumor histology, site of tumor primary, and response to chemotherapy. Patients with unfavorable prognostic factors may be candidates for hematopoietic cell transplantation (HCT).

SUMMARY OF EVIDENCE

For individuals who have previously untreated germ cell tumors who receive autologous HCT as first-line therapy, the evidence includes RCTs. The relevant outcomes are overall survival (OS), disease-specific survival (DSS),

and treatment-related mortality (TRM) and morbidity. Results from the RCTs have shown that autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (e.g., standard-dose chemotherapy). Study sample sizes were relatively small and might have been underpowered to detect differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes an RCT and several case series. The relevant outcomes are OS, DSS, and TRM and morbidity. The single published RCT did not find improved outcomes with high-dose chemotherapy (HDC) and autologous HCT compared with standard-dose HCT. Case series had a wide range of sample sizes. Progression-free and OS rates varied by prior treatment experience, prognostic factors, number of high-dose chemotherapy and autologous stem cell transplantation cycles and whether additional consolidation treatment such as radiation therapy was included. However, two- and three-year progression-free survival rates of 50-60% have consistently been achieved. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive tandem autologous transplantation and sequential HDC, the evidence includes an RCT, several retrospective cohort studies, and a comparative effectiveness review. The relevant outcomes are OS, DSS, and TRM and morbidity. The RCT reported a higher rate of TRM with sequential HDC compared with single HDC. However, five-year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (i.e., first vs. subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk-stratify patients. Tandem autologous transplant or transplant with sequential HDC has not shown a benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes. However, clinical input supported the use of this approach to salvage treatment.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. The relevant outcomes are OS, DSS, and TRM and morbidity. There were no RCTs or nonrandomized comparative studies evaluating allogeneic HCT for germ cell tumors. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2010 found strong support for autologous HCT as a treatment of relapsed or refractory germ cell tumors, and for tandem autologous transplant or transplant with sequential HDC as salvage therapy for testicular tumors and as treatment of platinum-refractory testicular tumors. Input was generally consistent with recommendations in national and international guidelines. Thus, these indications may be considered medically necessary.

POLICY

Single autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** as salvage therapy for germ-cell tumors:

- in patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; or
- in patients with unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease. (See Policy Guidelines for prognostic factors.)

Tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered **medically necessary** for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

Autologous HCT is considered **investigational** as a component of first-line treatment for germ-cell tumors.

Allogeneic HCT is considered **investigational** to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous HCT.

POLICY GUIDELINES

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

The favorable and unfavorable prognostic factors listed below are derived from the current National Comprehensive Cancer Network guidelines and the DeVita et al's textbook *Cancer: Principles and Practice of Oncology (2015, pp. 988-1004)*.

Patients with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response to initial chemotherapy, low levels of serum markers, and low volume disease. Patients with unfavorable prognostic factors are those with an extratesticular primary site, an incomplete response to initial therapy, high levels of serum markers, high-volume disease, or relapsing mediastinal nonseminomatous germ cell tumors.

MEDICARE ADVANTAGE

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

BACKGROUND

GERM CELL TUMORS

Germ cell tumors are composed primarily of testicular neoplasms as well as ovarian and extragonadal germ cell tumors (no primary tumor in either testis or ovary). Germ cell tumors are classified by their histology, stage, prognosis, and response to chemotherapy.

The most common testicular germ cell tumors are seminomas; all other histologic types are collectively referred to as nonseminomatous tumors. Nonseminomatous tumor types include embryonal cell tumor, yolk sac tumor, and teratomas. Malignant germ cell tumors of ovarian origin are classified as dysgerminomas or non-dysgerminomas. Similarly, non-dysgerminomas include immature teratomas, embryonal cell tumors, yolk sac tumor, polyembryoma, and mixed germ cell tumors.

Staging

Stage depends on location and extent of the tumor, using the American Joint Committee on Cancer's TNM system. TNM stages, modified by serum concentrations of markers for tumor burden (S0-3) when available, are grouped by similar prognoses. Markers used for germ cell tumors include human β -chorionic gonadotropin, lactate dehydrogenase, and α -fetoprotein. However, most patients with pure seminoma have normal α -fetoprotein concentrations. For testicular tumors, stages IA to B tumors are limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); stages IIA to C have increasing size and number of tumor-

involved lymph nodes, and at least one marker moderately elevated above the normal range (S1), and stages IIIA to C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

Germ cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, extent of the primary tumor, and serum marker levels. Good-risk pure seminomas can be at any primary site but are without nonpulmonary visceral metastases or marker elevations. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated human chorionic gonadotropin and/or lactate dehydrogenase. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated α -fetoprotein (due to the mixture with nonseminomatous components) are managed as nonseminomatous germ cell tumors. Good- and intermediate-risk nonseminomatous germ cell tumors have testicular or retroperitoneal tumors without nonpulmonary visceral metastases, and either S1 (good-risk) or S2 (intermediate) levels of marker elevations. Poor-risk tumors have mediastinal primary tumors, or nonpulmonary visceral metastases, or the highest level (S3) of marker elevations.

HEMATOPOIETIC CELL TRANSPLANTATION

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and 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. Cord blood transplantation is discussed in detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

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 (HLA) 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 6. An acceptable donor will match the patient at all or most of the HLA loci.

CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANTATION

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 cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to 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 potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

REDUCED-INTENSITY CONDITIONING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Reduced-Intensity Conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC 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 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. RIC regimens range from nearly total myeloablative to minimally myeloablative with lympho-ablation, 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. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be non-myeloablative.

REGULATORY STATUS

The 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, Title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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