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Medical Policy Manual Transplant, Policy No. 45.23

Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphomas

Effective: January 1, 2019

Next Review: September 2019
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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

Transplantation is performed to restore bone marrow function following bone-marrow-toxic doses of chemotherapy.

MEDICAL POLICY CRITERIA

Notes:

- See Appendix I for a glossary of terms.
- Hematopoietic cell transplantation (HCT) in the treatment of Hodgkin's lymphoma is addressed in medical policy Transplant No. 45.30.
- HCT in the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma are considered separately in medical policy Transplant No. 45.35
- HCT in the treatment of Waldenstrom macroglobulinemia, a lymphoplasmacytic lymphoma, is considered separately in medical policy Transplant No. 45.40

I. Autologous hematopoietic cell transplantation may be considered **medically necessary** for treatment of non-Hodgkin's lymphomas except as an initial treatment for NHL.

II. Autologous hematopoietic cell transplantation is considered **investigational** as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for non-Hodgkin's lymphomas.

III. Reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation may be considered **medically necessary** for treatment of non-Hodgkin's lymphomas when all of the following criteria are met (see Policy Guidelines):

  A. All of the medical necessity criteria for myeloablative allogeneic hematopoietic cell transplantation are met; and

  B. The patient does not qualify for a myeloablative allogeneic hematopoietic cell transplantation (see Policy Guidelines).

IV. Myeloablative allogeneic hematopoietic cell transplantation may be considered **medically necessary** for treatment of non-Hodgkin's lymphomas except as an initial treatment.

V. Myeloablative allogeneic hematopoietic cell transplantation is considered **investigational** as an initial treatment (i.e., without a full course of standard-dose induction chemotherapy) for non-Hodgkin's lymphomas.

VI. Tandem hematopoietic cell transplantation (e.g., autologous - autologous, autologous - allogeneic) is considered **investigational** to treat patients with any stage, grade, or subtype of non-Hodgkin's lymphomas.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant
- Documentation of Relapse Risk Prognostic Factors
- For patients with a reduced-intensity conditioning (RIC) regimen, documentation supporting reasons patient is unable to tolerate a myeloablative conditioning regimen.

REDUCED-INTENSITY CONDITIONING

Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic stem-cell transplant (SCT) but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, or prior intensive chemotherapy) preclude use of a standard conditioning regimen.

In patients who qualify for a myeloablative allogeneic hematopoietic HCT on the basis of overall health and disease status, allogeneic HCT using either myeloablative or RIC may be considered. However, a myeloablative conditioning regimen with allogeneic HCT may benefit

younger patients with good performance status and minimal comorbidities more than allogeneic HCT with RIC.

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Transplant, Policy No. 45.30
4. Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma, Transplant, Policy No. 45.35
5. Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia, Transplant, Policy No. 45.40

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic 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 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 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 cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. 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 gene 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 HCT

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 (myeloablative chemotherapy). This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy (i.e., therapy that is intended to eliminate residual cancer cells after initial therapy) when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional (“classical”) practice of *allogeneic* HCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and the subsequent graft-versus-

malignancy (GVM) effect that develops 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. While such treatment may eliminate the malignant cells, patients are as likely to die from opportunistic infections, graft-versus-host disease (GVHD), and/or organ failure as from the underlying malignancy.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC 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 traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce adverse effects secondary to bone marrow toxicity, while retaining the beneficial graft-versus-malignancy effect of allogeneic transplantation. These regimens do not initially eradicate the patient's hematopoietic ability, allowing relatively prompt hematopoietic recovery (e.g., 28 days or less) even without a transplant. Patients who undergo RIC with allogeneic cell transplant 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. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC allotransplantation. They represent a continuum in their effects, from nearly totally myeloablation, to minimal myeloablation with lymphoablation.

Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality (NRM) and relapse due to residual disease. For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

TANDEM HCT

Tandem transplants usually are defined as the planned administration of two successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic stem cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use non-myeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.

NON-HODGKIN'S LYMPHOMA (NHL)

A heterogeneous group of lymphoproliferative malignancies, NHL usually originates in lymphoid tissue. Historically, uniform treatment of patients with NHL was hampered by the lack of a uniform classification system. In 1982, the Working Formulation (WF) was developed to unify different classification systems into one.[1] The WF divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type. Since our understanding of NHL has improved, the diagnosis has become more sophisticated and includes the incorporation of new immunophenotyping and genetic techniques. As a result, the WF has become outdated.

European and American pathologists proposed a new classification, the Revised European American Lymphoma (REAL) Classification[2], and an updated version of the REAL system, the new World Health Organization (WHO) classification.[3] The WHO classification recognizes three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and lymphoma.

Within the B-cell and T-cell categories, two subdivisions are recognized: precursor neoplasms, which correspond to the earliest stages of differentiation, and more mature differentiated neoplasms.

2008 WHO CLASSIFICATION[4]

In the lists below, the asterisk (*) represents provisional entities or provisional subtypes of other neoplasms. Diseases shown in italics are newly included in the 2008 WHO classification.

The Mature B-Cell Neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Splenic marginal zone lymphoma

Hairy cell leukemia

Splenic lymphoma/leukemia, unclassifiable

- *Splenic diffuse red pulp small B-cell lymphoma**
- *Hairy cell leukemia-variant**

Lymphoplasmacytic lymphoma

- Waldenström macroglobulinemia

Heavy chain diseases

- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease

Plasma cell myeloma

Solitary plasmacytoma of bone

Extraosseous plasmacytoma

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Nodal marginal zone B-cell lymphoma (MZL)

- *Pediatric type nodal MZL*

Follicular lymphoma

- *Pediatric type follicular lymphoma*

Primary cutaneous follicle center lymphoma

Mantle cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified

- T cell/histiocyte rich large B-cell lymphoma
- *DLBCL associated with chronic inflammation*
- *Epstein-Barr virus (EBV)$^+$ DLBCL of the elderly*

Lymphomatoid granulomatosis

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

Primary cutaneous DLBCL, leg type

ALK$^+$ large B-cell lymphoma

Plasmablastic lymphoma

Primary effusion lymphoma

Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease

Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin's lymphoma

The Mature T-Cell and NK-Cell Neoplasms

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorder of NK-cells*

Aggressive NK cell leukemia

Systemic EBV$^+$ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)

Hydroa vacciniforme-like lymphoma

Adult T-cell leukemia/ lymphoma

Extranodal NK/T cell lymphoma, nasal type

Enteropathy-*associated* T-cell lymphoma

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorder

Lymphomatoid papulosis

Primary cutaneous anaplastic large-cell lymphoma

*Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma**

Primary cutaneous gamma-delta T-cell lymphoma

*Primary cutaneous small/medium CD4$^+$ T-cell lymphoma**

Peripheral T-cell lymphoma, not otherwise specified

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma (ALCL), ALK^+

Anaplastic large cell lymphoma (ALCL), ALK^-

According to data from the National Cancer Data Base, the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 32.5%, follicular lymphoma (FL) 17.1%, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) 18.6%, mantle cell lymphoma (MCL) 4.1%, peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS) 1.7%, and marginal zone (MZL) lymphomas 5%. All other subtypes each represent less than 2% of cases of NHL.[5,6]

Several subtypes of NHL have emerged with the REAL/WHO classification with unique clinical and biologic features, and they will be addressed separately throughout the policy, when necessary (specifically MCL and PTCL).

In general, the NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages.[1] Early-stage indolent NHL (stage one or 2) may be effectively treated with radiation alone.[1] Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages.[1] These patients can often be re-treated if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma[7], and median survival with conventional chemotherapy is one year or less. Follicular lymphoma (FL) is the most common indolent NHL (70%–80% of cases), and often the terms indolent lymphoma and FL are used synonymously. Also included in the indolent NHL are SLL/CLL, lymphoplasmacytic lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.

Aggressive NHL has a shorter natural history; however, 30%–60% of these patients can be cured with intensive combination chemotherapy regimens.[1] Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt lymphoma.

Oncologists developed a clinical tool to aid in predicting the prognosis of patients with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI).[8] Prior to the development of IPI in 1993, prognosis was predominantly based on disease stage.

Based on the number of risk factors present and adjusted for patient age, the IPI defines four risk groups: low, low intermediate, high intermediate, and high risk, based on five significant risk factors prognostic of overall survival (OS):

- Age older than 60 years
- Elevated serum lactate dehydrogenase (LDH) level
- Ann Arbor stage III or IV disease
- Eastern Cooperative Oncology Group (ECOG) performance status of 2, 3, or 4
- Involvement of more than one extranodal site

Risk groups are stratified according to the number of adverse factors as follows: 0 or 1 is low risk, 2 is low intermediate, 3 is high intermediate, and 4 or 5 are high risk.

Patients with two or more risk factors have a less than 50% chance of relapse-free (RFS) survival and OS at five years. Age-adjusted (aaIPI) and stage-adjusted modifications of this IPI are used for younger patients with localized disease.

Adverse risk factors for age-adjusted IPI include stage III or IV disease, elevated LDH and ECOG performance status of 2 or greater, and can be calculated as follows: 0 is low risk, 1 is low intermediate, 2 is high intermediate, and 3 is high risk.

With the success of the IPI, a separate prognostic index was developed for FL, which has multiple independent risk factors for relapse after a first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index (FLIPI) contains five adverse prognostic factors:

- Age older than 60 years
- Ann Arbor stage III-IV
- Hemoglobin level less than 12.0 g/dL
- More than four lymph node areas involved
- Elevated serum lactate dehydrogenase (LDH) level

These five factors are used to stratify patients into three categories of risk: low (0-1 risk factor), intermediate (two risk factors), or poor (three or more risk factors).[9]

Mantle Cell Lymphoma (MCL)

MCL comprises approximately 6%–8% of NHL, and has been recognized within the past 15 years as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed in 1992 by Banks [10] The number of therapeutic trials are not as numerous for MCL as for other NHL as it was not widely recognized until the REAL classification. MCL shows a strong predilection for elderly men, and the majority of cases (70%) present with disseminated (stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2–4 years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs, often within 12–18 months.[11] MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

There had been no generally established prognostic index for patients with MCL. Application of the IPI or FLIPI system to patients with MCL showed serious limitations, which included no separation of some important risk groups.[12] In addition, some of the individual IPI and FLIPI risk factors, including number of extranodal sites and number of involved nodal areas showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in patients with MCL.[12] Therefore, a new prognostic index for patients with MCL was developed, and should prove useful in comparing clinical trial results for MCL.

MCL international prognostic index (MIPI):

- Age
- ECOG performance status

- Serum LDH (calculated as a ratio of LDH to a laboratory's upper limit of normal)
- White blood cell count (WBC)
    - Zero points each are assigned for age younger than 50 years, ECOG performance 0–1, LDH ratio less than 0.67, WBC less than 6,700
    - One point each for age 50–59 years, LDH ratio 0.67–0.99, WBC 6,700–9,999.
    - Two points each for age 60–69 years, ECOG 2–4, LDH ratio 1.00–1.49, WBC 10,000–14,999
    - Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more

MIPI allows separation of three groups with significantly different prognoses:[12]

- 0–3 points=low risk, 44% of patients, median OS not reached and a five-year OS rate of 60%
- 4–5 points=intermediate risk, 35% of patients, median OS 51 months
- 6–11 points=high risk, 21% of patients, median OS 29 months

Peripheral T-Cell Lymphoma (PTCL)

Immature T-cell lymphomas are generally treated on leukemia protocols, whereas mature (peripheral) T-cell lymphomas are usually treated with chemotherapy regimens similar to those used in DLBCL.

PTCLs are less responsive to standard chemotherapy than DLBCLs and therefore carry a worse prognosis than aggressive B-cell counterparts. The poor results with conventional chemotherapy have prompted exploration of the role of HDC/SCT as first-line consolidation therapy.

STAGING

The Ann Arbor staging classification is commonly used for the staging of lymphomas and is the scheme defined in the American Joint Committee on Cancer (AJCC) Manual for Staging Cancer. Originally developed for Hodgkin's disease, this staging scheme was later expanded to include non-Hodgkin's lymphoma.

Staging of Lymphoma: Ann Arbor Classification

- Stage I

  Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)

- Stage II

  Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).

- Stage III

  Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)

- Stage IV

  Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of non-Hodgkin's lymphomas (NHL) are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of NHL, comparative clinical trials that compare this therapy with standard medical treatment, such as standard chemotherapy regimens, are needed. Further, for treatment of any of these lymphomas, 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.

This policy was initially based on four TEC Assessments.[13-16] Since that time, the classification of NHL has undergone significant changes, and several new and unique subtypes have emerged (e.g., mantle cell lymphoma [MCL], peripheral T-cell lymphoma [PTCL]).

INDOLENT LYMPHOMAS

HCT as First-Line Treatment for Indolent NHL

A number of systematic reviews and randomized trials have mostly failed to show improved outcomes with HCT as first-line treatment for indolent NHL. These are discussed below.

In 2012, Al Khabori performed a systematic review and meta-analysis of the use of autologous HCT in untreated, advanced follicular lymphoma.[17] Four randomized controlled trials (RCTs) comparing autologous HCT to conventional chemotherapy in 941 patients was included. Three trials reported overall survival (OS); moderate quality evidence from these trials did not show an improved OS with the use of HCT as part of the initial treatment of FL. Adverse outcomes including treatment-related mortality and the development of myelodysplastic syndrome, acute myeloid leukemia, and solid tumors, were not different between the two arms.

Schaaf conducted a systematic review and meta-analysis on the use of HCT for as treatment of follicular lymphoma (FL) for the Cochrane databases, published in 2012.[18] The researchers identified four trials focusing on HCT as first-line treatment for FL, the results of which are discussed individually below.[19-22] The primary outcome of the analysis was overall survival, and secondary outcomes included progression-free survival, treatment-related mortality, and secondary malignancies. After pooling results from the below trials, the authors concluded that there is no evidence to support the use of HCT for improved overall survival in first-line treatment of FL. Although improvements in treatment-related mortality and secondary malignancies were similarly not significantly associated with use of HCT, transplantation was significantly associated with improved progression-free survival in FL.

In a 2013 meta-analysis, Wang aimed to define the treatment effect of intensified therapy followed by autologous HCT compared with conventional therapy as first-line treatment of patients with FL in terms of OS and event-free survival (EFS).[23] The authors identified four randomized controlled trials that included 941 subjects. Results of the study indicated that no additional survival benefit was derived from the intensified therapy followed by autologous HCT. Authors did identify a significant benefit of intensified therapy followed by autologous HCT as first-line treatment in terms of EFS. Authors concluded that intensified therapy followed by autologous HCT does not improve the OS compared with conventional therapy.

In 2008, Ladetto reported the results of a Phase III, randomized, multicenter trial of patients with high-risk follicular lymphoma, treated at diagnosis.[19] A total of 134 patients were enrolled to receive either rituximab-supplemented high-dose chemotherapy (HDC) and autologous HCT or six courses of cyclophosphamide, doxorubicin (or Adriamycin®), vincristine (Oncovin®), and prednisolone (CHOP) followed by rituximab (CHOP-R). Of these patients 79% completed R-HDC and 71% completed CHOP-R. Complete remission was 85% with HCT and 62% with CHOP-R. At a median follow-up of 51 months, the four-year event-free survival (EFS) was 61% and 28% (HCT vs. CHOP-R, respectively), with no difference in overall survival (OS). Molecular remission (defined as negative results by polymerase chain reaction on two or more consecutive bone marrow samples spaced six months apart in patients who reached complete remission [CR]) was achieved in 80% of HCT and 44% of CHOP-R patients, and was the strongest independent outcome predictor. In 71% of the CHOP-R patients who had a relapse, salvage HCT was performed and achieved an 85% CR rate and a 68% three-year EFS. The authors concluded that there was no OS advantage to treating high-risk FL initially with HCT, but that relapsed/refractory FL would be the most appropriate setting for this therapy.

In 2006, Sebban reported the results of a randomized, multicenter study.[20] A total of 209 patients received cyclophosphamide, Adriamycin, etoposide, prednisolone (CHVP) plus interferon (CHVP-I arm) and 131 patients received CHOP followed by high-dose chemotherapy (HDC) with total body irradiation and autologous HCT. Response rates were similar in both groups (79% and 78% after induction therapy, respectively). After a median follow-up of 7.5 years, intent-to-treat analysis showed no difference between the two arms for OS (p=0.53) or EFS (p=0.11). The authors concluded that there was no statistically significant benefit to first-line, high-dose therapy in patients with follicular lymphoma, and that high-dose therapy should be reserved for relapsing patients.

Deconinck (2005) investigated the role of autologous HCT as initial therapy in 172 patients with follicular lymphoma considered at high risk due to the presence of either B symptoms (i.e., weight loss, fever, or night sweats), a single lymph node larger than 7 cm, more than three involved nodal sites, massive splenomegaly, or a variety of other indicators of high tumor burden.[21] The patients were randomized to receive either an immunochemotherapy regimen or a high-dose therapy followed by purged autologous HCT. While the autologous HCT group had a higher response rate and longer median EFS, there was no significant improvement in OS rate due to an excess of secondary malignancies. The authors concluded that autologous HCT cannot be recommended as the standard first-line treatment of follicular lymphoma with a high tumor burden.

In 2004, Lenz reported on the results of a trial of 307 patients with advanced stage lymphoma in first remission, including follicular lymphoma, mantle cell lymphoma, or lymphoplasmacytoid lymphoma.[22] Patients were randomized to receive either consolidative therapy with autologous HCT or interferon therapy. The five-year PFS rate was considerably higher in the

autologous HCT arm (64.7%) compared to the interferon arm (33.3%). However, the median follow-up of patients is still too short to allow any comparison of OS.

HCT for Relapsed, Indolent NHL

In the majority of patients with follicular lymphoma relapse, and with relapsed disease, cure is very unlikely, with a median survival of 4.5 years after recurrence.[24] A 2017 single-center retrospective study by Bozkaya analyzed data from 38 patients who were treated between 2004 and 2014 with high-dose chemotherapy followed by autologous stem cell transplantation.[25] All cases presented refractory or relapsed Hodgkin lymphoma (n=22) or a number of subtypes of non-Hodgkin lymphoma (n=18). Among the regimens given to patients were ifosfamide, carboplatin, and etoposide (ICE), and carmustine, etoposide, cytosine arabinoside, and melphalan (BEAM); additionally, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) were administered to Hodgkin lymphoma patients, and R-CHOP was given to those with non-Hodgkin lymphoma. Given the small sample size, multivariate analysis was precluded; however, univariate analysis found no statistically significant difference between groups, except in terms of chemosensitive vs chemoresistant cases and between patients undergoing ICE and BEAM regimens. After salvage therapy, 22 patients showed a partial response; 6 patients showed a complete response; and 8 had stable disease. The study found that the five-year OS rate was significantly higher for chemosensitive patients (50%) than for chemoresistant patients (22%; p=0.02); however, given the small size of the population, other analyses were primarily descriptive in nature, or showed no statistical significance.

In the European CUP trial, 89 patients with relapsed, nontransformed follicular lymphoma with partial or complete response after standard induction chemotherapy were randomized to one of three arms: three additional cycles of conventional chemotherapy (n=24), HDC and unpurged autologous HCT (n=33), or HDC with purged autologous HCT (n=32). OS at four years for the chemotherapy versus unpurged versus purged arms was 46%, 71%, and 77%, respectively. Two-year PFS was 26%, 58%, and 55%, respectively. No difference was found between the two autologous HCT arms. Although several studies have consistently shown improved DFS with autologous HCT for relapsed follicular lymphoma, this study was the first to show a difference in OS benefit.[7]

Randomized trials have shown no survival advantage to HCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit of autologous HCT for relapsed disease.

AGGRESSIVE LYMPHOMAS

HCT for First-Line Therapy for Aggressive NHL

In 2018, Fossard published a retrospective multicenter analysis of the benefit of up-front autologous HCT for peripheral T-cell lymphoma.[26] A total of 269 patients with peripheral T-cell lymphoma-not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with partial or complete response after induction were included in the analysis. Of these, 134 patients were included in the autologous HCT intention-to-treat group and 135 were not. No statistically significant survival advantage in favor of HCT was identified and no outcome difference was identified between the groups for PFS or OS. A propensity score matching analysis taking into account age, LDH, PS, stage, B symptoms, histology, induction regimen, and response quality did not identify any

significant differences. Further, subgroup analyses did not identify any other differences in response status, disease stage, or risk category.

Wang published a 2018 retrospective study of autologous HCT as first-line therapy for extranodal natural killer/T-cell lymphoma, nasal type (ENKTL).[27] All patients in the study were newly diagnosed with ENKTL. The high-dose chemotherapy plus autologous HCT (study) group included 20 patients and the control group included 60 ENKTL patients who were not willing to receive high-dose chemotherapy and autologous HCT. All patients were under the age of 60, high risk, and fit for high-dose chemotherapy and autologous HCT. All patients received induction chemotherapy with or without involved-field radiotherapy. The median follow-up time was 61.0 months. The difference between groups in OS was statistically significant (p=0.026) at five years post-diagnosis, but not at three or two years (p=0.233 and p=0.054, respectively). While the median OS of the study group was not reached, the median OS of the control group was 62.0 months. In the study group, no treatment-related mortality occurred.

A 2017 single-center cohort study by Strüßmann compared high-dose chemotherapy with subsequent autologous HCT with an early intensified regimen (six-cycle CHOP-14) that included rituximab and methotrexate in 63 patients with diffuse large B-cell lymphoma and poor prognosis.[28] All patients had an age-adjusted IPI score of 2 or 3, and demographic information was comparable for both cohorts (median ages were 48 and 53 for cohorts 1 and 2, respectively). Four cycles of R-CHOP-21 were administered to cohort 1, followed by high-dose BEAM and autologous HCT; cohort 2 was initially given 6-cycle CHOP-14, then rituximab and high-dose methotrexate. At two-year follow-up, PFS and OS rates were compared between cohorts, and patients in cohort 2 had significantly better outcomes, even when adjusted for multiple variables (including that of age-adjusted IPI score). Two-year PFS was 60.6% for those in cohort 1, compared with 93.37% in cohort 2 (hazard ratio [HR], 7.2; 95% CI, 1.64 to 31.75; p=0.009), a finding that retained statistical significance during multivariate analysis (HR=8.12; 95% CI, 1.73 to 36; p=0.006). The OS rate at two years was 69.7% for cohort 1 and 93.3% (HR=5.86; 95% CI. 1.28 to 26.8) after multivariate analysis. Also, patients in cohort 2 showed significantly higher overall response and complete remission rates (93.3% and 90%, respectively) than did patients in cohort 1 (66.7% and 63.6%); furthermore, no treatment-related mortality was reported for cohort 2 during follow-up, despite the initially intensive treatment protocol.

A 2017 phase 2 clinical trial (LNH2007-3B) by Casasnovas randomized 211 patients to receive a four-cycle regimen of either R-ACVBP or R-CHOP14, to be followed by either standard immunochemotherapy or autologous stem cell transplantation.[29] Of the 200 patients who completed the trial, 109 were assigned to R-ACVBP, and 97 were assigned to R-CHOP14; all patients had confirmed diffuse large B-cell lymphoma and had 2 or 3 risk factors according to age-adjusted IPI. Neither group achieved the primary endpoint, which was complete response (CR) greater than 50%, as defined by 2007 International Harmonization Project (IHP) criteria, with 47% (95% CI, 38% to 67%) of R-ACVBP patients and 39% (95% CI, 28% to 54%) showing CR. Investigators noted the disparity between the low response according to IHP criteria, and the improvement of outcomes predicted by positron emission tomography (PET) results and assessed by change in maximum standard uptake value (ΔSUVmax), suggesting that the latter may be a superior indicator of progression of disease than IHP criteria. PET scans were performed on all patients at baseline, after two cycles of the induction regimen (PET2), and again after four cycles of treatment (PET4); patients who showed negative results for both PET2 and PET4 were assigned to standard immunochemotherapy (n=51), while those

who showed positive results for PET2 but negative results for PET4 were recommended for autologous HCT (n=40). No statistically significant differences in outcome were observed between these groups; however, investigators observed significant differences in outcomes when they assessed ΔSUVmax in patients. At measurement of PET2, rates of four-year PFS and OS were higher for patients with ΔSUVmax greater than 66% than for those showing a smaller change in SUVmax (PFS for the respective groups was 80% vs 56%, p<0.001; OS was 87% vs 69% in patients with ΔSUVmax <66%, p=0.003). When ΔSUVmax was assessed following PET4, similar improvements were observed: the four-year PFS rate was 84% in those showing ΔSUVmax greater than 70%, compared with 35% in those with ΔSUVmax of 70% of less (p<0.001); likewise, OS rates were 91% and 57% for the respective groups (p<0.001). Differences between the potential treatments (standard chemotherapy, autologous HCT, or salvage therapy) were insignificant.

Qualls published a small retrospective study in 2017 of 20 individuals (13 men, 7 women) who were treated with autologous stem cell transplantation for systemic non-Hodgkin lymphoma with some form of central nervous system (CNS) involvement.[30] Most patients presented with diffuse large B-cell lymphoma histology (n=17 [85%]), and CNS involvement varied: the two most common types of CNS involvement were parenchymal involvement (n=12 [60%]) and leptomeningeal disease (n=9 [45%]). As an induction regimen, the majority of patients (n=13 [65%]) were given R-CHOP, or, as treatment for CNS involvement, high-dose methotrexate (HD-MTX) (n=16 [80%]). The high-dose chemotherapy regimen for all patients included thiotepa, busulfan, and cyclophosphamide (TBC), and six patients received rituximab in addition to TBC; all patients received autologous stem cell transplantation during first complete remission. PFS rates were high at one-year (84%; 95% CI, 59% to 95%) and four-year (77%; 95% CI, 48% to 91%) follow-ups. OS rates were similarly high at one year 95%; 95% CI, 68% to 99%) and four years (82%; 95% CI, 54% to 94%). The most commonly experienced side-effect of the treatment was febrile neutropenia, which was observed in 80% (n=16) of patients. Despite the small size of the study, the authors noted the rare occurrence of relevant cases, suggesting that the high survival rates observed in the study supports the use of ASCT in the first complete remission.

Several randomized trials reported on between 1997 and 2002 compared outcomes of autologous HCT used to consolidate a first CR in patients with intermediate or aggressive non-Hodgkin's lymphoma (NHL), with outcomes of an alternative strategy that delayed transplants until relapse.[31-34] As summarized in an editorial, the preponderance of evidence showed that consolidating first CRs with HCT did not improve OS for the full population of enrolled patients.[35] However, a subgroup analysis at eight years' median follow-up focused on 236 patients at high or high-intermediate risk of relapse (based on age-adjusted International Prognostic Index [IPI] scores) who were enrolled in the largest of these trials (the LNH87-2 protocol; reference 19). The subgroup analysis reported superior overall (64% vs. 49%, respectively; relative risk 1.51, p=0.04) and DFS (55% vs. 39%, respectively; relative risk 1.56, p=0.02) for patients at elevated risk of relapse who were consolidated with an autologous HCT.[36]

A large, multigroup, prospective, randomized Phase III comparison of these strategies (the S9704 trial) is ongoing to confirm results of the subgroup analysis in a larger population with diffuse large B-cell lymphoma at high- and high-intermediate risk of relapse. Nevertheless, many clinicians view the LNH87-2 subgroup analysis[37] as sufficient evidence to support use of autologous HCT to consolidate a first CR when risk of relapse is high. In contrast, editorials[35,37] and recent reviews[38-40] agree that available evidence shows no survival benefit

from autologous HCT to consolidate first CR in patients with intermediate or aggressive NHL at low- or low-intermediate risk of relapse (using age-adjusted IPI score).

Between 2005 and 2008, several reports of randomized trials showed no survival benefit to HCT as first-line therapy for aggressive lymphomas, as summarized below:

Greb (2008) undertook a systematic review and meta-analysis to determine whether HDC with autologous HCT as first-line treatment in patients with aggressive NHL improves survival compared to patients treated with conventional chemotherapy.[41] Fifteen randomized controlled trials (RCTs) including 3,079 patients were eligible for the meta-analysis. Thirteen studies with 2,018 patients showed significantly higher CR rates in the autologous HCT group (p=0.004). However, autologous HCT did not have an effect on OS when compared with conventional chemotherapy. According to the IPI, subgroup analysis of prognostic groups showed no survival differences between autologous HCT and conventional chemotherapy in 12 trials, and EFS also was not significantly different between the two groups. The authors concluded that despite higher CR rates, there is no benefit for autologous HCT as first-line treatment in aggressive NHL.

Betticher (2006) reported the results of a Phase III multicenter, randomized trial comparing sequential HDC with autologous HCT with standard CHOP as first-line therapy in 129 patients with aggressive NHL.[42] Remission rates were similar in the two groups, and after a median observation time of 48 months, there was no difference in OS with 46% in the sequential autologous HCT group and 53% in the group that received CHOP (p=0.48). The authors concluded that sequential autologous HCT did not confer any survival benefit as initial therapy in patients with aggressive NHL.

Baldissera (2006) reported on the results of a prospective RCT comparing HDC and autologous HCT to conventional chemotherapy as frontline therapy in 56 patients with high-risk aggressive NHL.[43] The five-year actuarial OS and PFS were not statistically different between the two study groups; only DFS was statistically different (97% vs. 47%, for the autologous HCT and conventional groups, respectively; p=0.02.)

Olivieri (2005) reported on a randomized study of 223 patients with aggressive NHL using upfront HDC with autologous HCT versus conventional chemotherapy (plus autologous HCT in cases of failure).[44] In the conventional group, 29 patients achieved a partial response or no response, and went on to receive HDC and autologous HCT. With a median follow-up of 62 months, there was no difference in seven-year probability of survival (60% and 57.8%; p=0.5), DFS (62% and 71%; p=0.2), and PFS (44.9% and 40.9%; p=0.7, respectively) between the two groups. The authors concluded that patients with aggressive NHL do not benefit from upfront autologous HCT.

In 2013, results of a Phase III multicenter randomized trial (SWOG-9704) of autologous HCT as consolidation for aggressive (high-intermediate or high-risk) diffuse B-cell NHL were published.[45] In this trial, 253 patients received five cycles of induction chemotherapy (CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone with [n=156, 47%] or without rituximab). Those who had at least a partial response to five cycles of induction therapy were randomly assigned to receive three additional cycles of CHOP (n=128) or one additional cycle of CHOP followed by autologous HCT (n=125). The primary efficacy end points of the trial were two-year PFS and OS. Two-year PFS rates were 69% and 55% in the HCT and control group, respectively (HR control vs HCT=1.72, 95% CI, 1.18 to 2.51, p=0.005). The two-year OS rates in the HCT and control group were 74% and 71%,

respectively (HR=1.26, 95% CI, 0.82 to 1.94, p=0.30). Unplanned exploratory analyses showed a differential treatment effect according to disease risk level. Among high-risk patients, the two-year OS rate was 82% in the HCT group and 64% in the control group (log-rank test p=0.01). The main results of this trial compared with earlier study results in not discerning a significant effect of early autologous HCT on OS among a group of patients with high-intermediate- and high-risk diffuse B-cell NHL. However, it appears that the survival curve shows a plateau among the high-risk HCT patients out to perhaps 10 years after study registration. Although this evidence was from exploratory subset analysis, it further supports the medical necessity of this approach in such cases compared with nontransplant strategies.

HCT for Relapsed, Aggressive NHL

Autologous HCT is the treatment of choice for relapsed or refractory aggressive NHL for patients who achieve a complete or partial response with second-line therapy.[1,5,6]

Data from randomized trials have shown conflicting results, but some have shown an overall survival benefit with HCT to consolidate a first CR in patients with aggressive B-cell lymphomas at high or high-intermediate risk of relapse.

HCT for relapsed aggressive B-cell lymphomas is the treatment of choice, as randomized studies have shown an overall survival benefit with this approach.

TANDEM TRANSPLANTS

Nonrandomized Studies

Monjanel reported on a pilot Phase II trial evaluating tandem high-dose therapy with stem-cell support between 1994 and 1999 in 45 patients with age adjusted-IPI equal to three untreated aggressive non-Hodgkin's lymphoma.[46] After induction, responders underwent tandem autologous transplantation; 31 out of 41 evaluable patients completed the program. There were four toxic deaths. The primary end point of the study was complete response rate, which was 49%. With a median follow-up of 114 months for surviving patients, the OS was 51%, and 19 of the 22 patients (86%) who reached a complete response were alive and relapse-free. Prospective evaluation of quality of life and comorbidities of surviving patients did not reveal long-term toxicities. The authors concluded that in the era of monoclonal antibodies and response-adapted therapy, the role of tandem transplantation still needs to be determined.

In a 2005 pilot study reported by Papadopoulos, 41 patients with poor-risk NHL and Hodgkin's disease were given tandem HDC with autologous HCT.[47] Thirty-one patients (76%) completed both transplants. Overall toxic death rate was 12%. The study evaluated the maximum tolerated dose of the chemotherapeutic regimen, and did not compare tandem versus single transplants for NHL.

Tarella (2007) reported on a multicenter, non-randomized, prospective trial consisting of 112 patients with previously untreated diffuse large B-cell lymphoma and age-adjusted IPI score of 2-3.[48] All patients received rituximab-supplemented, early-intensified HDC with multiple autologous HCT. Although the study concluded the treatment regimen improved patients' life expectancy, the comparisons were made with historic controls that had received conventional chemotherapy.

A retrospective analysis by Crocchiolo (2013) of 34 high-risk NHL patients who underwent autologous HCT followed closely by reduced-intensity allogeneic HCT ("tandem auto-allo") included patients treated from 2002 to 2010.[49] In this study, researchers began to identify appropriate allogeneic donors at the initiation of the salvage regimen. The patients' median age was 47 years. Histologic subtypes were: diffuse large B-cell (n=5), follicular (n=14), transformed follicular (n=4), mantle-cell (n=5), plasmacytoid lymphoma (n=1), anaplastic large T-cell (n=2), and peripheral T-cell (n=3). HLA-identical sibling donors were located for 29 patients, and 10/10-matched unrelated individuals were identified for five cases. The median interval between autologous HCT and allogeneic HCT was 77 days (range 36–197 days). At a median follow-up of 46 months since allogeneic HCT, the five-year OS was 77% and PFS was 68%. Six patients experienced disease relapse or progression, the 100-day TRM was 0%, and two-year TRM incidence was 6%. These results suggest tandem autologous-allogeneic transplantation appears feasible in high-risk NHL patients having a HLA-identical donor, but further study is necessary to establish its role in this setting.

No randomized studies have been conducted on the use of tandem HCT for the treatment of non-Hodgkin's lymphomas, and the published data consist of small numbers of patients. Therefore, the data on tandem transplants is insufficient to determine outcomes with this type of treatment.

ALLOTRANSPLANT AFTER A FAILED AUTOTRANSPLANT

An updated literature search found no prospective randomized controlled studies comparing allotransplants to alternative strategies for managing failure (progression or relapse) after an autologous HCT for NHL. The scant data are insufficient to change conclusions of the previous TEC Assessment.[15]

The paucity of outcomes data for allotransplants after a failed autologous HCT is not surprising. Patients are rarely considered eligible for this option either because their relapsed lymphoma progresses too rapidly, because their advanced physiologic age or poor health status increases the likelihood of adverse outcomes (e.g., from graft-versus-host-disease), or because they lack a well-matched donor. Nevertheless, several institutions report that a minority of patients achieved long-term DFS following an allotransplant for relapsed NHL after an autotransplant. Factors that apparently increase the likelihood of survival include a chemosensitive relapse, younger age, a long disease-free interval since the prior autotransplant, availability of an HLA-identical sibling donor, and fewer chemotherapy regimens prior to the failed autotransplant. Thus, clinical judgment can play an important role to select patients for this treatment with a reasonable likelihood that potential benefits may exceed harms.

NHL SUBTYPES NEWLY DEFINED BY THE WHO CLASSIFICATION

Mantle Cell Lymphoma (MCL)

In an attempt to improve the outcome of MCL, several Phase II trials investigated the efficacy of autologous HCT, with published results differing substantially.[12,50] Some studies found no benefit to HCT, suggested an EFS advantage, at least in a subset of patients.[12] The differing results in these studies were likely due to different time points of transplant (first vs. second remission) and other patient selection criteria.[50]

In 2005, the results of the first randomized trial were reported by Dreyling of the European MCL Network.[50] A total of 122 patients with MCL received either autologous HCT or interferon as consolidation therapy in first CR or PR. Among these patients, 43% had a low-risk, 11% had a high-intermediate risk, and 6% had a high-risk profile. Autologous HCT resulted in a PR rate of 17% and a CR rate of 81% (versus PR of 62% and CR of 37% with interferon). Survival curves for time to treatment failure (TTF) after randomization showed that autologous HCT was superior to interferon (p=0.0023). There also was significant improvement in the three-year PFS demonstrated in the autologous HCT versus interferon arm (54% and 25%, respectively; p=0.01). At the time of the reporting, no advantage was seen in OS, with a three-year OS of 83% versus 77%. The trial also suggested that the impact of autologous HCT could depend on the patient's remission status prior to the transplant, with a median PFS of 46 months in patients in CR versus 33 months in patients in PR.

García-Noblejas (2017) conducted a retrospective analysis of MCL patients who received autologous stem cell transplantation.[51] They found, at a mean follow-up of 54 months, progression-free survival and overall survival to be 38 and 74 months, respectively. They stratified patients as achieving CR before the transplant or not. For patients who were in CR at the time of the transplant, progression-free survival and overall survival were 49 and 97 months, respectively.

Jantunen (2011) investigated the feasibility and efficacy of autologous HCT in patients with MCL older than 65 years. In the retrospective comparison, there were no differences in relapse rate, PFS, or OS between patients with MCL under 65 years of age and the seventy-nine patients ≥65 years of age.[52]

In an International Bone Marrow Transplant Registry (IBMTR) study, 212 patients (median age 50 years) received allogeneic transplants.[53] At two years, OS was only 40%. In a study by the European Bone Marrow Transplant Group, 22 allogeneic transplant patients had EFS and OS rates of 50% and 62%, respectively, but the follow-up was too short.[54]

The literature regarding allogeneic transplantation in mantle cell lymphoma is limited. This is due, in part, to the fact that the average age of patients at diagnosis is 65 years, making them unsuitable for allogeneic transplant. In addition, the disease is relatively rare, and hence, randomized studies on the use of HCT have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with the use of autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Although a graft-versus-tumor effect has been demonstrated[55], there is currently no conclusive evidence that allogeneic transplantation is curative in mantle cell lymphoma.[56]

There have been several studies regarding reduced-intensity chemotherapy (RIC) and allogeneic HCT.[56]

Khouri reported on results of RIC allogeneic HCT in 18 patients with mantle cell lymphoma, and after a median follow-up of 26 months, the actuarial probability of EFS was 82% at three years.[57] Maris evaluated allogeneic HCT in 33 patients with relapsed and recurrent mantle cell lymphoma. At two years, the relapse and nonrelapse mortality rates were 9% and 24%, respectively, and the OS and DFS were 65% and 60%, respectively.[58] Cook retrospectively evaluated outcomes of RIC allogeneic HCT in 70 MCL patients. The five-year overall survival (OS) and progression-free survival (PFS) rates were 37% and 14% respectively. The one- and five-year non-relapse mortality (NRM) was 18% and 21% respectively.[59]

Till (2008) reported the results of the outcomes of 56 patients with MCL, treated with high-dose induction chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD) with or without rituximab followed by autologous HCT in first CR or PR (n=21), cyclophosphamide, doxorubicin (or Adriamycin), vincristine (Oncovin), and prednisolone (CHOP) with or without rituximab followed by autologous HCT in first CR or PR (n=15), or autologous HCT following disease progression (n=20).[60] OS and PFS at three years among patients transplanted in CR or PR were 93% and 63% compared with 46% and 36%, all respectively, for patients transplanted with relapsed/refractory disease. The hazard of mortality among patients transplanted with relapsed or refractory disease was 6.1 times that of patients transplanted in first CR or PR (p=.0006).

Geisler (2008) reported on 160 previously untreated patients with MCL with dose-intensified induction immunochemotherapy.[61] Responders received HDC with in vivo purged autologous HCT. Overall and CR was achieved in 96% and 54%, respectively. The six-year OS, EFS, and PFS were 70%, 56%, and 66%, respectively, with no relapses occurring after five years.

Evens reported on 25 untreated patients with MCL who received intensive induction chemotherapy, with an overall response rate of 74%.[62] Seventeen patients received a consolidative autologous (n=13) or allogeneic (n=4) HCT. Five-year EFS and OS for all patients was 35% and 50%, respectively. After a median follow-up of 66 months, the five-year EFS and OS for patients who received autologous HCT was 54% and 75%, respectively.

Budde (2011) evaluated outcomes of 118 consecutive patients with MCL who received a high-dose induction regimen before autologous HCT. The authors report that the intensive induction regimen was not associated with improved survival in the overall study population or any of the subgroups (i.e., patients who underwent autologous HCT as initial consolidation, or patients under 60 years of age).[63]

A 2007 review article by Kasamon summarized the literature on high-dose therapy for mantle cell lymphoma, and a repeat finding in several studies has been a superior result of transplantation in first CR (autologous or allogeneic) rather than in the relapsed setting.[12]

Due in part to the relative rarity of the disease, randomized studies on the use of HCT in MCL have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with the use of autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allogeneic HCT has shown prolonged disease control in the relapsed/refractory setting.

Peripheral T-Cell Lymphoma (Mature T-cell or NK-cell neoplasms)

Prospective studies with autologous HCT in patients with aggressive PTCL consist of only a few studies with small numbers of patients. A few retrospective studies have included a moderate number of patients and length of follow-up.

Rohlfing (2018) performed a single-center retrospective analysis of first-line HCT in patients diagnosed with PTCL.[64] Patients diagnosed with T-cell leukemias, ALCL ALK+, and primary cutaneous lymphomas except ALCL ALK- were excluded. Of the 97 patients included in the final analysis, autologous HCT in the first remission was intended for 63 patients (intention-to-treat group; ITT) and 34 patients were not intended to be transplanted (no intention-to-treat group; nITT). Reasons for forgoing transplant included comorbidity, higher age, low

International Prognostic Index (IPI), physician's decision, and unknown reasons. Baseline differences between the groups included age and fraction of patients receiving induction other than CHOP/CHOEP (CHOP plus etoposide; both higher in nITT) and proportion of patients with elevated lactate dehydrogenase (smaller in nITT). Of those in the ITT group, 54% underwent transplantation. Five-year OS and PFS were not statistically different between groups (46 and 23% in the ITT and group and 42 and 25% in the nITT group, respectively). In a multivariate analysis that adjusted for gender, age, IPI, PTCL subtype, and ITT, the only factor associated with significant benefits for OS was younger age.

Yam (2017) retrospectively analyzed PTCL patients receiving either active observation (28 patients) or consolidation with autologous stem cell transplantation (20 patients). Three-year PFS was 37% and 41% for observation and transplant groups, respectively. The one-year cumulative incidence of relapse and the median PFS was not significantly different between the groups, with one-year cumulative incidence of relapse in the observation and transplant groups at 50% and 46%, respectively and median progression-free survival in the observation and ASCT groups at 15.8 and 12.8 months, respectively.

Han (2017) analyzed clinical data from 46 patients with PTCL receiving autologous stem cell transplantation as consolidation therapy.[65] Thirty-four patients with pre-transplantation CR and 12 with PR received transplantation. Median follow-up was 37 months. The five-year OS and PFS rates were 77.1% and 61.9%, respectively.

A prospective Phase II trial by Rodriguez (2007) showed that autologous HCT as first-line consolidation therapy improved treatment outcome in patients responding to induction therapy.[66] Nineteen of 26 patients who showed CR or partial response to induction therapy received an autotransplant. At two years post-transplant, OS, PFS, and DFS were 84%, 56%, and 63%, respectively.

The role of HCT in peripheral T-cell lymphoma is not well defined. Few studies have been conducted, mostly retrospectively and with small numbers of patients.[67-81] This is partly due to the rarity and heterogeneity of this group of lymphomas. In particular, studies often mix patients with PTCL-NOS (which has a poorer prognosis) with patients with ALK + ALCL which has a better prognosis (even with conventional chemotherapy regimens), and ALK- ALCL patients who have a worse prognosis than ALK+ ALCL but better than PTCL-NOS patients. There have been no randomized studies comparing chemotherapy regimens solely in patients with PTCL (i.e., some randomized studies have included PTCL with aggressive B-cell lymphomas). For frontline therapy, results from recent phase II studies with autologous HCT as consolidation offers the best survival outcomes for patients with high-risk features; however, randomized trials to confirm these findings have not been performed. No relevant data for the use of allogeneic HCT in the front-line setting are available. Patients with relapsed or refractory PTCL are generally considered incurable with chemotherapy alone. In the salvage setting, the data show that the use of HCT may improve survival outcomes similar to the results observed in corresponding aggressive B-cell lymphomas in the same treatment setting.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

Guidelines from NCCN offer the following on the use of HCT in NHL:[5,6]

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Follicular Lymphoma (grade 1-2)

For histologic transformation to diffuse large B-cell lymphoma with either multiple prior therapies or minimal or no prior chemotherapy, high-dose therapy with autologous stem cell rescue or allogeneic cell transplant may be considered. It is strongly recommended this treatment be given in the context of a clinical trial.

A second-line consolidation suggested treatment includes allogeneic cell transplant for highly selected patients.

Mantle Cell Lymphoma

In stage II bulky, III, and IV aggressive mantle cell lymphoma candidates for high-dose therapy with autologous stem cell rescue, autologous cell rescue is recommended as first-line consolidative therapy; allogeneic cell transplant may be considered as for second-line consolidation.

Diffuse Large B-Cell Lymphoma

For stage I and II diffuse large B-cell lymphoma follow-up therapy for a partial response may include high-dose therapy with autologous stem cell rescue, or clinical trial which may include allogeneic cell transplant.

For stage III and IV diffuse large B-cell lymphoma end-of-treatment response may include high-dose therapy with autologous stem cell rescue in high-risk patients (category 2B [Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.])

For relapsed/refractory disease in patients who are candidates for high-dose therapy, following second-line therapy, consolidation therapy may include high-dose therapy with autologous stem cell rescue or allogeneic hematopoietic cell transplant in select cases for those who have a complete or partial response.

Peripheral T-cell Lymphoma

Consider consolidation with high-dose therapy and stem cell rescue as first-line consolidation therapy in peripheral T-cell lymphoma patients showing a complete response to induction therapy (except those considered low-risk, e.g., ALCL ALK-positive). For relapse/refractory disease, in patients who intend to proceed to transplant and who have a complete or partial response to additional therapy, additional/consolidation therapy may include allogeneic cell transplant (non-myeloablative or ablative) or high-dose therapy with autologous stem cell rescue.

Mycosis Fungoides/Sezary Syndrome

For refractory or progressive disease in stage IIB, III, IV mycosis fungoides/Sezary syndrome patients, the role of allogeneic transplant is noted as controversial, though recommended as a treatment to consider (nonmyeloablative in stage III).

Adult T-cell Leukemia/Lymphoma

Following initial response, after two cycles, consider allogeneic cell transplant in adult T-cell leukemia/lymphoma patients.

SUMMARY

Research has shown improved survival (overall survival and/or progression-free survival) from hematopoietic cell transplantation (HCT) for non-Hodgkin's lymphomas in cases other than initial treatment. Therefore, HCT (autologous or allogeneic), including reduced intensity conditioning allogeneic HCT when criteria are met, for these indications may be considered medically necessary.

Research has not shown improved survival from hematopoietic cell transplantation (HCT) as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for treatment of non-Hodgkin's lymphomas. Therefore, HCT (autologous or allogeneic) is considered investigational for this indication.

No randomized studies have been conducted on the use of tandem hematopoietic cell transplantation (HCT) for the treatment of non-Hodgkin's lymphomas. There is not enough research to know if this treatment is safe and effective. Therefore, tandem HCT is considered investigational to treat patients with any stage, grade, or subtype of non-Hodgkin's lymphomas.

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CODES

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	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	J9000–J9999	Chemotherapy drugs code range

Codes	Number	Description
	Q0083–Q0085	Chemotherapy administration code range
	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic

APPENDIX I: Glossary of Terms used in this Policy

consolidation therapy[1] - Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.

relapse[2] - The return of a disease or the signs and symptoms of a disease after a period of improvement.

salvage therapy[3] - Treatment that is given after the cancer has not responded to other treatments.

tandem transplant[4] – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

1. NCI Dictionary of Cancer Terms | https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45654 | Accessed Sept 25 2018
2. NCI Dictionary of Cancer Terms | https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=45866 | Accessed Sept 25 2018
3. NCI Dictionary of Cancer Terms | https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44176 | Accessed Sept 25 2018
4. NCCN Guidelines Version 1.2019 Multiple Myeloma | https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf | Accessed Sept 25 2018

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