Medical Coverage Policy

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Stem Cell Transplantation: Blood Cancers

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Related Coverage Resources

Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost
Stem Cell Transplantation: Non-cancer Disorders
Stem Cell Transplantation: Solid Tumors
Transplantation Donor Charges
Umbilical Cord Blood Banking

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the
Overview

This Coverage Policy addresses hematopoietic stem cell transplantation (HSCT) for blood cancers such as leukemias, lymphomas and myeloma.

Coverage Policy

Coverage for hematopoietic stem cell transplantation (HSCT) varies across plans. Refer to the customer’s benefit plan document for coverage details.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lymphocytic/ Lymphoblastic Leukemia (ALL)</td>
<td>All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.</td>
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<tr>
<td></td>
<td>Allogeneic hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for the treatment of acute lymphocytic/lymphoblastic leukemia (ALL) when ANY of the following criteria are met:</td>
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<tr>
<td></td>
<td>• failed induction therapy</td>
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<td></td>
<td>• second or subsequent remission</td>
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<td></td>
<td>• B-cell lineage ALL with marrow relapse while on treatment or within six months of completing treatment</td>
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<tr>
<td></td>
<td>• T-cell lineage ALL in first or subsequent remission</td>
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<tr>
<td></td>
<td>• first remission with poor prognosis* or high risk of relapse**</td>
</tr>
</tbody>
</table>

A second allogeneic HSCT is considered medically necessary for the treatment of ALL when relapsed disease occurs more than six months after first allogeneic HSCT.

A tandem/sequential HSCT for the treatment of ALL is considered experimental, investigational or unproven.

HSCT for the treatment of ALL is considered not medically necessary when ANY of the following conditions are present:

• active central nervous system (CNS) involvement
• presence of any significant comorbid medical or psychiatric illness which would significantly compromise the clinical care and chances of survival
• advanced age in an adult

*Poor prognosis acute lymphocytic/lymphoblastic leukemia includes ANY of the following criteria:
  ➢ longer than four weeks to achieve a complete remission
  ➢ age >35 years
  ➢ white blood cell count (WBC) greater than 30 X 10^9/L (30,000/μL) in B-cell lineage ALL
  ➢ WBC greater than 50 X 10^9/L (50,000/μL) in T-cell lineage ALL
  ➢ null cell phenotype
  ➢ extramedullary disease
**Indication** | **Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria**
--- | ---
All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor. | All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.

- presence of chromosome abnormalities (e.g., t(9;22)(q34;q11) (the Philadelphia chromosome), t(4;11), t(8,14), t(2,8), (8,22), MLL gene (11q23) or t(1;19)
- complex karyotype (i.e., ≥5 chromosomal abnormalities)
- elevated beta 2 microglobulin
- deletion of chromosome 7
- trisomy 8
- hypodiploidy

**High-risk of disease relapse includes ANY of the following criteria:**

- failure to achieve a complete remission (CR) within four weeks of induction therapy
- high minimal residual disease at end of remission induction
- relapse while on chemotherapy
- first CR lasting < 24 months
- infancy (age younger than one year)
- age ≥ 10 years
- white blood cell count (WBC) > 50,000/mcL
- extramedullary disease
- presence of chromosomal abnormalities [e.g., t(9;22)(q34;q11) (the Philadelphia chromosome), t(4;11), t(8,14), t(1,19), or MLL gene (11q23)]
- hypodiploidy
- near-haploid ALL (i.e., 24 to 28 chromosomes)
- acute lymphocytic/lymphoblastic leukemia resulting from prior cancer therapy

| Acute Myeloid Leukemia (AML) | Myeloablative allogeneic HSCT is considered medically necessary for the treatment of acute myeloid leukemia (AML) when ANY of the following criteria is met:
|---|---|
| | • first remission for a high-risk* individual
| | • second or subsequent remission
| | • failed induction
| | • no induction treatment and any of the following:
| | ➢ antecedent hematological disease
| | ➢ treatment-related secondary AML

A second myeloablative allogeneic HSCT is considered medically necessary for the treatment of AML when BOTH of the following criteria are met:

- relapse of disease occurring more than six months after first allogeneic HSCT
- second or subsequent remission

**Reduced-intensity or non-myeloablative allogeneic HSCT** is considered medically necessary for the treatment of AML when the criteria for an allogeneic HSCT are met but a myeloablative regimen is contraindicated because of age or comorbidity.

**Autologous HSCT** is considered medically necessary for the treatment of AML when allogeneic HSCT is not available or is not appropriate and EITHER of the following criteria is met:

- first remission for a high risk* individual
- second or subsequent remission
### Indication | Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria
--- | ---
**Tandem HSCT** is considered experimental, investigational or unproven for the treatment of AML

*High-risk includes ANY of the following:*
- multiple cytogenetic abnormalities
- requiring more than one cycle to achieve remission
- disease refractory to chemotherapy
- white blood cell (WBC) count > 100,000/ml³
- French-American-British (FAB) subtype M4 and M5
- chromosome translocations t(10;11), t(1;22), t(6;9), t(9;22)
- abnormalities of chromosome 7 or 5, the long arm of chromosome 3, or 11q23
- trisomy 8
- antigen CD34 and/or P-glycoprotein (MDR1 gene product)
- internal tandem duplication mutations of the FLT3 gene
- history of CNS involvement
- systemic infection at diagnosis
- treatment-induced AML
- history of myelodysplastic syndrome

#### Amyloidosis (systemic light-chain)

Autologous HSCT is considered medically necessary for the treatment of amyloidosis (systemic light-chain) when ALL of the following criteria are met:

- Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (i.e., at a minimum, ambulatory and able to perform most, if not all, self-care)
- ≤ two organs significantly involved with amyloid
- asymptomatic or compensated cardiac function (i.e., absence of congestive heart failure, echocardiographic left ventricular ejection fraction > 30%, interventricular septal thickness < 15 mm)
- adequate pulmonary status as noted on pulmonary function testing, oxygen saturation results on room air and a DLCO > 50% predicted
- adequate liver function (i.e., bilirubin < 3.0 mg/DL)
- adequate renal function (i.e., creatinine clearance > 51 ml/min, serum creatinine ≤ 2.0 ml/dL)
- absence of severe or multiple comorbidities that would increase risk of poor result or death

A second autologous HSCT for the treatment of recurrent or refractory amyloidosis (systemic light-chain) is considered experimental, investigational or unproven.

The following procedures for the treatment of amyloidosis (systemic light-chain) are considered experimental, investigational or unproven:
- tandem autologous HSCT
- allogeneic HSCT

#### Chronic Lymphocytic Leukemia (CLL)

Allogeneic HSCT is considered medically necessary for the treatment of chronic lymphocytic leukemia (CLL) that is not responsive to standard therapy.

Autologous HSCT is considered medically necessary for the treatment of CLL in an individual in complete or good partial remission.

#### Chronic Myeloid Leukemia (CML)

Allogeneic HSCT is considered medically necessary for the treatment of chronic myeloid leukemia (CML) in ANY of the following:
### Indication | Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria
--- | ---
Chronic Myelomonocytic Leukemia (CMML) | All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
- hematologic remission not reached after three months of tyrosine kinase inhibitor (TKI) therapy
- no cytogenetic response or those in cytogenetic relapse at 6, 12, or 18 months after achieving initial hematologic remission after three months of TKI therapy
- molecular remission not reached by 12 months of TKI therapy
- disease progression on TKI therapy to accelerated phase or blast crisis
- an individual who is not a candidate for TKI therapy

Autologous HSCT for the treatment of CML is considered experimental, investigational or unproven.

### Hodgkin Lymphoma | Allogeneic HSCT is considered medically necessary for the treatment of chronic myelomonocytic leukemia (CMML).

Autologous HSCT for the treatment of CMML is considered experimental, investigational or unproven.

### Hodgkin Lymphoma | Autologous HSCT is considered medically necessary for the treatment of refractory, primary progressive or recurrent Hodgkin lymphoma.

Myeloablative allogeneic HSCT is considered medically necessary for the treatment of refractory, primary progressive, or recurrent Hodgkin lymphoma when the individual is not a candidate for autologous HSCT.

Nonmyeloablative allogeneic HSCT is considered medically necessary for the treatment of Hodgkin lymphoma that is relapsed or refractory after prior HSCT.

Each of the following procedures for the treatment of Hodgkin lymphoma is considered experimental, investigational or unproven:
- nonmyeloablative allogeneic HSCT for any other indication
- tandem HSCT

### Juvenile Myelomonocytic Leukemia (JMML) | Allogeneic HSCT is considered medically necessary for the treatment of juvenile myelomonocytic leukemia (JMML).

Autologous HSCT for the treatment of JMML is considered experimental, investigational or unproven.

### Multiple Myeloma (MM) | Autologous HSCT for the treatment of active (i.e., symptomatic) multiple myeloma (MM) is considered medically necessary for EITHER of the following indications:
- after response to primary therapy
- refractory to primary therapy in an individual with relapse or progressive disease

A second or tandem autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary following autologous HSCT.

A third autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary in an individual with progressive disease following a previous autologous HSCT.
Indication | Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria
---|---
| All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.

**Indication** | **Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria**
---|---
**Myelodysplastic Syndromes** | Allogeneic HSCT is considered medically necessary for the treatment of an individual with intermediate- or high-risk myelodysplastic syndrome (MDS).

**Autologous HSCT is considered medically necessary for the treatment of intermediate- or high-risk MDS when ALL of the following criteria are met:**
- individual is in complete remission
- individual is not a candidate for allogeneic HSCT
- an appropriately-matched HLA donor is not available

**Non-Hodgkin Lymphoma (NHL)** | Autologous HSCT is considered medically necessary for the treatment of an adult with stage II, or stage III or stage IV non-Hodgkin lymphoma (NHL).

Allogeneic HSCT is considered medically necessary for the treatment of an adult with stage II, stage III or stage IV non-Hodgkin lymphoma NHL who is not a candidate for autologous HSCT.

Myeloablative allogeneic or autologous HSCT as medically necessary for the treatment of a child with recurrent NHL with chemosensitive disease.

The following procedures for the treatment of NHL are considered experimental, investigational or unproven:
- autologous OR allogeneic HSCT for stage I disease in an adult
- non-myeloablative allogeneic HSCT in a child
- tandem autologous OR allogeneic HSCT in an adult or a child

(For primary CNS lymphoma, see CP 0534 Stem Cell Transplantation: Solid Tumors)

**POEMS Syndrome** | Autologous HSCT is considered medically necessary for the treatment of POEMS syndrome.

**Primary Central Nervous System (CNS) Lymphoma** | Refer to CP 0534 Stem Cell Transplantation: Solid Tumors.

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**General Background**

Hematopoietic stem cell transplantation (HSCT), also called hematopoietic cell transplantation (HCT) or stem cell transplant, is a type of treatment for cancer (and a few other conditions as well). Bone marrow produces all of the different cells that make up the blood, such as red blood cells, white blood cells, and platelets. All of the cells of the immune system are also made in the bone marrow. All of these cells develop from a type of precursor cell found in the bone marrow, called a “hematopoietic stem cell.” Hematopoietic stem cells are found in the peripheral blood and the bone marrow; therefore stem cells can be collected or harvested from either location.

Some of the most effective treatments for cancer, such as chemotherapy and radiation, are toxic to the bone marrow. In general, the higher the dose, the more toxic the effects on the bone marrow. After the treatment, a healthy supply of stem cells is reintroduced, or transplanted. The transplanted cells then reestablish the blood cell production process in the bone marrow. HSCT is a method of replacing immature blood-forming cells in the bone marrow that have been destroyed by drugs, radiation, or disease. It may be allogeneic (i.e., using a person’s own stem cells) or allogeneic (i.e., using stem cells donated by someone else).
• Autologous transplant — In autologous transplantation, an individual's own hematopoietic stem cells are removed before the high dose chemotherapy or radiation is given, and they are then frozen for storage and later use. After chemotherapy or radiation is complete, the harvested cells are thawed and returned to the individual, like a transfusion.

• Allogeneic transplant — In allogeneic transplantation, the hematopoietic stem cells come from a donor, ideally a brother or sister with a similar genetic makeup. If an individual does not have a suitably matched sibling, an unrelated person with a similar genetic makeup may be used. Under some circumstances, a parent or child who is only half-matched can also be used; this is termed a haploidentical transplant. In other circumstances, umbilical cord blood may be used in an umbilical cord blood transplant.

• Myeloablative transplant — A myeloablative transplantation uses very high doses of chemotherapy or radiation prior to transplantation with autologous or allogeneic hematopoietic stem cells.

• Non-myeloablative transplant — A non-myeloablative transplantation, sometimes referred to as a "mini" or reduced intensity transplant, allows an individual to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells. This approach may be recommended for a variety of reasons including age, type of disease, other medical issues, or prior therapies (UpToDate, 2018).

Contraindications
Many factors affect the outcome of a tissue transplantation; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications for HSCT include (but are not limited to):

• poor cardiac function (ejection fraction less than 45%)
• poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal), unless related to disease
• poor renal function (creatinine clearance less than 50 mL/min)
• poor pulmonary function (diffusion capacity less than 60% of predicted)
• presence of human immunodeficiency virus or active hepatitis B, hepatitis C or human T-cell lymphotropic virus type 1 (HTLV-1)
• Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Blood Cancers
Most blood cancers start in the bone marrow where blood is produced. Stem cells in bone marrow mature and develop into three types of blood cells: red blood cells, white blood cells, or platelets. In most blood cancers, the normal blood cell development process is interrupted by uncontrolled growth of an abnormal type of blood cell.

There are three main types of blood cancers:

• Leukemia, a type of cancer found in blood and bone marrow, is caused by the rapid production of abnormal white blood cells. The high number of abnormal white blood cells are not able to fight infection, and they impair the ability of the bone marrow to produce red blood cells and platelets. Leukemia can be either acute or chronic. Chronic leukemia progresses more slowly than acute leukemia, which requires immediate treatment. Leukemia is also classified as lymphoblastic/lymphocytic or myeloid/myelogenous. Lymphocytic/Lymphoblastic leukemia refers to abnormal cell growth in the marrow cells that become lymphocytes, a type of white blood cell that plays a role in the immune system. In myeloid leukemia, abnormal cell growth occurs in the marrow cells that mature into red blood cells, white blood cells, and platelets. There are four broad classifications of leukemia:
  ➢ Acute lymphoblastic/lymphocytic leukemia (ALL)
  ➢ Acute myeloid/myelogenous leukemia (AML)
  ➢ Chronic lymphocytic leukemia (CLL)
- **Chronic myeloid leukemia (CML)**

- **Lymphoma** is a type of blood cancer that affects the lymphatic system, which removes excess fluids from the body and produces immune cells. Lymphocytes are a type of white blood cell that fight infection. Abnormal lymphocytes become lymphoma cells, which multiply and collect in lymph nodes and other tissues. Over time, these cancerous cells impair the immune system. Lymphomas are divided into two categories:
  - Non-Hodgkin lymphoma: Non-Hodgkin's lymphomas are the most common. There are about 61 known types of non-Hodgkin lymphoma. About 85 percent of non-Hodgkin's lymphomas diagnosed in the U.S. are B-cell lymphomas, which means they originated from this type of cell. B-cell lymphomas grow quickly (high-grade) or slowly (low-grade). There are over a dozen types of B-cell non-Hodgkin lymphomas. The rest are T-cell lymphomas, named after a different cancerous white blood cell, or lymphocyte.
  - Hodgkin lymphoma: The Hodgkin’s lymphomas are the rarest types of the disease and are characterized by Reed-Sternberg cells. There are six different subtypes of Hodgkin’s lymphoma.

- **Myeloma (multiple myeloma)** is a cancer of the plasma cells. Because myeloma frequently occurs at many sites in the bone marrow, it is often referred to as ‘multiple myeloma’ (MM). Plasma cells are white blood cells that produce disease- and infection-fighting antibodies. The plasma cells make an abnormal protein (antibody) known by several different names, including monoclonal immunoglobulin, monoclonal protein (M-protein), M-spike, or paraprotein.

  There are other plasma cell disorders that also have abnormal plasma cells but do not meet the criteria to be called active multiple myeloma. These other plasma cell disorders include but are not limited to:
  - Smoldering multiple myeloma (SMM)
  - Light chain amyloidosis.
  - POEMS syndrome

**Myelodysplastic Syndromes (MDS)** - conditions that can occur when the blood-forming cells in the bone marrow become abnormal (dysplastic). There are several different types of MDS, based on how many types of blood cells are affected and other factors.

**Professional Societies/Organizations**

The table below includes information and recommendations from the following sources:

1. The American Society for Blood and Marrow Transplantation (ASBMT) Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation (Majhail, et al., 2015). The key to values within the table are as follows:
   - N indicates Not generally recommended
   - C: standard of care, clinical evidence available
   - S: standard of care
   - R: standard of care, rare indication
   - D: developmental
   - CR1: first complete response
   - CR2: second CR
   - CR3: third CR.


### American Society for Blood and Marrow Transplantation (2015)

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cancer Type</th>
<th>American Society for Blood and Marrow Transplantation (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Lymphocytic/Lymphoblastic Leukemia (ALL)</strong></td>
<td></td>
<td>(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)</td>
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<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
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</thead>
<tbody>
<tr>
<td>1st Complete Response (CR), low risk</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; CR, high risk</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>2nd CR</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; CR</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
<td>N</td>
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<table>
<thead>
<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Complete response (CR), low risk</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; CR, high risk</td>
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<tr>
<td>2nd CR</td>
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<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; CR</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
<td>N</td>
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Note: The American Society for Transplantation and Cellular Therapy (ASTCT) (previously known as the American Society for Blood and Marrow Transplantation (ASBMT) has a guideline ‘in press’ as of August 2019 for Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia (DeFilipp, et al., 2019).

**NCCN GUIDELINES™ Acute Lymphoblastic Leukemia (v.2.2019, May 15, 2019)**

**Ph+ ALL Consolidation Therapy**

Allogeneic HCT is noted as an option. Footnotes include:

- Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplantation. (ALL-3, ALL-4)
- Data suggests that for younger patients age ≤21 years, allogeneic HCT may not offer an advantage over chemotherapy + TKIs. (ALL-3)
- Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities and social support. (ALL-3, ALL-4)

**NCCN Recommendations for Ph+ ALL (AYA Patients)**

Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities and social support.

The optimal timing of HCT is unclear; however, for fit patients, additional therapy may be considered to eliminate MRD prior to transplantation.

In younger patients age ≤21 years emerging data suggests that allogeneic HCT may not confer an advantage over chemotherapy combined with TKIs. (MS-24; MS-25)

**NCCN Recommendations for Ph+ ALL**

The optimal time for a patient to receive allogeneic hematopoietic cell transplantation (HCT) is unclear; however, for fit patients, additional therapy may be considered to eliminate minimal residual disease (MRD) before transplantation. (MS-25)

Allogeneic HCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HCT. (MS-26)
Cancer

**Ph- ALL Consolidation Therapy**

Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplantation (ALL-5, ALL-6). Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities and social support. (ALL-5, ALL-6)

Although long term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. Allogeneic HCT is noted as an option, including MRD+, MRD-, and MRD unavailable. For MRD- and MRD unavailable, consider allogeneic HCT, especially if high-risk features. (ALL-5, ALL-6, ALL-7)

If second remission is achieved prior to transplant and patient has not had a prior HCT, consolidative HCT is recommended. (ALL-8)

**NCCN Recommendations for Adult patients Ph- ALL**

For relatively fit patients:
- (If MRD status negative) Consolidation with allogeneic HCT may be considered especially if the patient has a high risk features.
- (If MRD status positive) allogenic HCT may be considered.
- (If MRD status unknown) allogeneic HCT is recommended especially if the patient has a high risk features. (MS-42, MS-43)

For patients with relapsed/refractory (R/R) Ph- ALL

Consolidative allogeneic HCT should be strongly considered if transplant-naïve patients experience a second CR prior to transplant. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or donor lymphocyte infusion (DLI). However the roll of allogeneic HCT following treatment with tisagenlecleucel is unclear. (MS-43)

**Treatment of Older Adults with ALL**

For appropriate fit individuals achieving remission, consideration of autologous or reduced intensity allogeneic SCT may be appropriate. (ALL- D, 7 of 8)

**NCCN GUIDELINES™ Pediatric Acute Lymphoblastic Leukemia (v.1.2020, May 30, 2019) (new guideline)**

NCCN Principles of Hematopoietic stem cell transplant are listed on pages PEDALL-J, pages 1-3, of 5) and provide detailed indications for:
- HSCT (B-cell) in First Remission
- HSCT (B-cell) in Non-First Remission Settings
- HSCT (T-cell)

**NCI Adult Acute Lymphoblastic Leukemia Treatment (PDQ®) February 8, 2019**

**Treatment for Untreated Adult ALL**

If there are appropriate available donors and if the patient is younger than 55 years, bone marrow transplantation may be a consideration in the management of this disease.

**Standard Treatment Options for Adult ALL in Remission**

Postremission therapy, Autologous or allogeneic bone marrow transplant (BMT).

**Standard Treatment Options for Recurrent Adult ALL:**
- reinduction chemotherapy followed by alloBMT
Cancer

- blinatumomab followed by alloBMT
- inotuzumab ozogamicin followed by alloBMT

**NCI Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®) August 6, 2019**

**Standard Treatment Options for Newly Diagnosed ALL**

Most patients with persistent leukemia at the end of the 4-week induction phase have a poor prognosis and may benefit from an allogeneic hematopoietic stem cell transplant (HSCT) once CR is achieved.

**Standard Postinduction Treatment Options for Childhood ALL**

There are limited data regarding the outcome of very high-risk patients treated with allogeneic HSCT in first CR. Controversy exists regarding which subpopulations could potentially benefit from HSCT.

**Postinduction Treatment for Specific ALL Subgroups**

- The role of allogeneic HSCT during first remission in infants with MLL (KMT2A) gene rearrangements remains controversial.
- Adolescents and Young Adults With ALL: Given the relatively favorable outcome that can be obtained in these patients with chemotherapy regimens used for high-risk pediatric ALL, there is no role for the routine use of allogeneic HSCT for adolescents and young adults with ALL in first remission.
- Ph+ (BCR-ABL1–positive) ALL: Outcome of results for Ph+ ALL demonstrated a better outcome after HSCT if imatinib was given before or after transplant.

**Postreinduction therapy for patients achieving a second complete remission**

- Early-relapsing precursor B-cell ALL: For precursor B-cell patients with an early marrow relapse, allogeneic transplant from a human leukocyte antigen (HLA)-identical sibling or matched unrelated donor that is performed in second remission has been reported in most studies to result in higher leukemia-free survival than a chemotherapy approach.
- Late-relapsing precursor B-cell ALL: For patients with a late marrow relapse of precursor B-cell ALL, a primary chemotherapy approach after achievement of second CR has resulted in survival rates of approximately 50%, and it is not clear whether allogeneic transplantation is associated with superior cure rate.
- T-cell ALL: For patients with T-cell ALL who achieved remission after bone marrow relapse, outcomes with postreinduction chemotherapy alone have generally been poor, and these patients are usually treated with allogeneic HSCT in second CR, regardless of time to relapse.

**Treatment Options for Second and Subsequent Bone Marrow Relapse**

Although there are no studies directly comparing chemotherapy with HSCT for patients in third or subsequent CR, because cure with chemotherapy alone is rare, transplant is generally considered a reasonable approach for those achieving remission.

**HSCT for First and Subsequent Bone Marrow Relapse**

Components of the transplant process that have been shown to be important in improving or predicting outcome of HSCT for children with ALL include:

- Total-body irradiation (TBI)-containing transplant preparative regimens.
- MRD detection just before transplant.
- MRD detection posttransplant.
- Donor type and HLA match.
- Role of GVHD/graft-versus-leukemia (GVL) in ALL and immune modulation after transplant to prevent relapse.
Cancer

Intrathecal medication after HSCT to prevent relapse: The use of post-HSCT intrathecal chemotherapy chemoprophylaxis is controversial.

Relapse after allogeneic HSCT for relapsed ALL: For patients relapsing after an allogeneic HSCT for ALL, a second ablative allogeneic HSCT may be feasible.

Treatment of Isolated Extramedullary Relapse, Isolated CNS relapse

Standard treatment options for childhood ALL that has recurred in the CNS include systemic and intrathecal chemotherapy, cranial or craniospinal radiation and HSCT.

Acute Myeloid Leukemia (AML)

American Society for Blood and Marrow Transplantation (2015)
(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Complete Response (CR), low risk</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1st CR, intermediate risk</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>1st CR, high risk</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>2nd CR</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Complete response (CR), low risk</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>1st CR, intermediate risk</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>1st CR, high risk</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>2nd CR</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>3rd CR</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia, CR1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia, CR2, molecular remission</td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia, CR2, not in molecular remission</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia, CR3+</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia, Not in remission</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia, Relapse after autologous transplant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Therapy-related acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), CR1</td>
<td>S</td>
<td>N</td>
</tr>
</tbody>
</table>

NCCN GUIDELINES™ Acute Myeloid Leukemia (v.1.2020, Aug 13, 2019)

Acute promyelocytic leukemia (APL) Therapy for Relapse/Additional Therapy
- PCR negative: autologous HCT
- PCR positive: matched sibling or alternate donor HCT. (AML-6)
<table>
<thead>
<tr>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AML age &lt; 60 years</strong>&lt;br&gt;After specific chemotherapy regimens, inductions failure, option is matched sibling or alternate donor HCT. (AML-2, AML-3)&lt;br&gt;Post-remission therapy, HCT (AML – 4)</td>
</tr>
<tr>
<td><strong>AML age ≥60</strong>&lt;br&gt;After induction, with residual disease, reduced intensity allogeneic HCT (AML-7)&lt;br&gt;Post-remission therapy, allogeneic HCT (AML-8)&lt;br&gt;Post-induction therapy, allogeneic HCT (AML-9)</td>
</tr>
<tr>
<td><strong>Surveillance and relapse/refractory disease</strong>&lt;br&gt;matched sibling or alternate donor HCT (AML-10)</td>
</tr>
<tr>
<td><strong>Management of Relapsed Acute Promyelocytic Leukemia (APL)</strong>&lt;br&gt;• NCCN notes that following completion of the first cycle of consolidations, if the patient does not enter molecular remission, a matched sibling or alternate donor HCT or clinical trial is recommended. (MS-24)&lt;br&gt;• It should be noted that only limited evidence from retrospective exist in regards to the role of autologous and allogenic HCT following relapse of APL in the era of arsenic trioxide (ATO) therapy. (MS-25)&lt;br&gt;• Patients who achieve a molecular remission after second-line therapy should be considered for autologous HCT if they do not have contradictions to high-dose therapy. (MS-26)</td>
</tr>
<tr>
<td><strong>NCCN Recommendations for Management of AML in Patients Younger than 60 years,</strong>&lt;br&gt;• favorable-risk cytogenetics: There are not sufficient data to evaluate the use of allogeneic HCT in first remission for patients with AML and favorable-risk cytogenetics outside a clinical trial (MS-38)&lt;br&gt;• intermediate-risk cytogenetics: The panel members agreed that transplant-based options (either matched sibling or alternate donor allogeneic HCT or three to four cycles of high-dose cytarabine (HIdAC) afforded a lower risk of relapse and a somewhat higher risk of DFS when given as consolidation for patients with intermediate-risk cytogenetics. (MS-38) The role of autologous HCT in the intermediate-risk outside of clinical trials is diminishing due to improvements in allogeneic transplants, which are expanding the pool of potential donors outside the family setting. The consensus of the panel is autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial. MS-38)&lt;br&gt;• unfavorable cytogenetics: If remission is observed, consolidation therapy is recommended, and strong consideration should be given to allogeneic HCT with matched sibling or matched alternative donor as part of consolidation strategy.(MS-38)</td>
</tr>
<tr>
<td><strong>Management of AML in Patients 60 years and Older</strong>&lt;br&gt;Studies suggest that reduced-intensity conditioning (RIC) allogeneic HCT is a feasible treatment option for patients aged 60 years and older, particularly those in first CR with minimal comorbidities and who have an available donor.&lt;br&gt;RIC allogeneic HCT is considered an additional option for patients age 60 years and older as post remission therapy in those experiencing a complete response (CR) to induction therapy. (MS-49)</td>
</tr>
<tr>
<td><strong>Post Remission Surveillance and Therapy for Relapsed/Refractory AML</strong></td>
</tr>
</tbody>
</table>
Cancer

- If no sibling donor has been identified, donor search should be initiated at first relapse in appropriate patients concomitant with initiation of reinduction therapy.
- For patients younger than 60 years who have experienced a relapse and the tumor burden is low and patient has a previously identified donor, chemotherapy followed by allogeneic HCT can be considered.
- For patients 60 years and older if physically fit, options include chemotherapy followed by RIC allogeneic HCT (patient in remission or clinical trial). (MS-53)

NCI Adult Acute Myeloid Leukemia Treatment (PDQ®) February 8, 2019

Adult AML in Remission

- Allogeneic bone marrow transplantation (BMT) results in the lowest incidence of leukemic relapse, even when compared with BMT from an identical twin (syngeneic BMT).
- Most U.S. leukemia physicians agree that transplantation should be offered to AML patients in first CR in the setting of poor-risk cytogenetics and should not be offered to patients in first CR with good-risk cytogenetics.
- Because BMT can cure about 30% of patients who experience relapse following chemotherapy, some investigators suggested that allogeneic BMT can be reserved for early first relapse or second CR without compromising the number of patients who are ultimately cured; however, clinical and cytogenetic information can define certain subsets of patients with predictable better or worse prognoses in those using postremission chemotherapy.
- Allogeneic stem cell transplantation can be performed using stem cells obtained from a bone marrow harvest or a peripheral blood progenitor cell harvest.

Recurrent Adult AML

A subset of relapsed patients treated aggressively may have extended disease-free survival (DFS); however, cures in patients following a relapse are thought to be more commonly achieved using BMT. Allogeneic BMT from an HLA-matched donor in early first relapse or in second CR provides a DFS rate of approximately 30%. Transplantation in early first relapse potentially avoids the toxic effects of reinduction chemotherapy. Allogeneic BMT can salvage some patients whose disease fails to go into remission with intensive chemotherapy (primary refractory leukemia).

NCI Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment (PDQ®) August 20, 2019

Postremission Therapy for AML

A major challenge in the treatment of children with AML is to prolong the duration of the initial remission with additional chemotherapy or hematopoietic stem cell transplantation (HSCT). Prospective trials of transplantation in children with AML suggest that overall, 60% to 70% of children with HLA-matched donors available who undergo allogeneic HSCT during their first remission experience long-term remissions, with the caveat that outcome after allogeneic HSCT is dependent on risk-classification status.

Current application of allogeneic HSCT involves incorporation of risk classification to determine whether transplantation should be pursued in first remission.

- Because of the improved outcome in patients with favorable prognostic features (low-risk cytogenetic or molecular mutations) receiving contemporary chemotherapy regimens and the lack of demonstrable superiority for HSCT in this patient population, this group of patients typically receives matched-family donor (MFD) HSCT only after first relapse and the achievement of a second CR.
**Cancer**

- There is conflicting evidence regarding the role of allogeneic HSCT in first remission for patients with intermediate-risk characteristics (neither low-risk or high-risk cytogenetics or molecular mutations). Given the improved outcome for patients with intermediate-risk AML in recent clinical trials and the burden of acute and chronic toxicities associated with allogeneic transplantation, many childhood AML treatment groups (including the COG) employ chemotherapy for intermediate-risk patients in first remission and reserve allogeneic HSCT for use after potential relapse.

- There are conflicting data regarding the role of allogeneic HSCT in first remission for patients with high-risk disease, complicated by the differing definitions of high risk used by different study groups. Many, but not all, pediatric clinical trial groups prescribe allogeneic HSCT for high-risk patients in first remission.

Because definitions of high-, intermediate-, and low-risk AML are evolving because of the ongoing association of molecular characteristics of the tumor with outcome (e.g., FLT3 internal tandem duplications, WT1 mutations, and NPM1 mutations) and response to therapy (e.g., MRD assessments post induction therapy), further analysis of subpopulations of patients treated with allogeneic HSCT will be an ongoing need in current and future clinical trials.

**Recurrent or Refractory Childhood AML and Other Myeloid Malignancies**

- Recurrent childhood AML: Treatment options for children with recurrent AML may include chemotherapy and HSCT. The selection of additional treatment after the achievement of a second complete remission depends on previous treatment and individual considerations. Consolidation chemotherapy followed by HSCT is conventionally recommended, although there are no controlled prospective data regarding the contribution of additional courses of therapy once a second complete remission is obtained. There is evidence that long-term survival can be achieved in a portion of pediatric patients who undergo a second transplant subsequent to relapse after a first myeloablative transplant.

- Refractory childhood AML (induction failure): Like patients with relapsed AML, induction failure patients are typically directed towards HSCT once they attain a remission.

**Acute Promyelocytic Leukemia (APL)**

Because of the favorable outcomes observed with chemotherapy plus ATRA and arsenic trioxide (event-free survival [EFS] rates of 70%–90%), hematopoietic stem cell transplantation is not recommended in first CR.

**Treatment of Recurrent APL:** Retrospective pediatric studies have reported 5-year EFS rates after either autologous or allogeneic transplantation approaches to be similar, at approximately 70%. Data support the use of autologous transplantation in patients who are MRD-negative in second CR who have poorly matched allogeneic donors.

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### Amyloidosis

**American Society for Blood and Marrow Transplantation (2015)**

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th></th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Amyloidosis (AL amyloidosis or immunoglobulin light chain amyloidosis)</td>
<td>N</td>
<td>C</td>
</tr>
</tbody>
</table>

**NCCN GUIDELINES™ Systemic Light chain Amyloidosis (v.1.2019, October 26, 2018)**
The NCCN panel members recommend that the treatment of systemic light-chain amyloidosis should be in the context of a clinical trial when possible because data are insufficient to identify optimal treatment of the underlying plasma cell disorder. NCCN Recommendations for primary treatment include high-dose melphalan followed by autologous stem cell transplant (SCT). (MS 6)

**NCI Plasma Cell Neoplasms (Including Multiple Myeloma) Treatment (PDQ®) July 19, 2019**

Patients with symptomatic plasma cell neoplasms advanced disease require treatment. Treatment most often is directed at reducing the tumor cell burden and reversing any complications of disease, such as renal failure, infection, hyperviscosity, or hypercalcemia, with appropriate medical management. The International Myeloma Working Group (IMWG) has published new criteria for identifying patients with active myeloma who require therapy. These criteria include Amyloidosis.

Treatment Options for Amyloidosis Associated With Plasma Cell Neoplasms:
- Chemotherapy
- Stem cell rescue

### Chronic Lymphocytic Leukemia (CLL)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk, 1st or greater remission</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>B-cell, prolymphocytic leukemia</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Transformation to high grade lymphoma</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

**American Society for Blood and Marrow Transplantation (2015)**

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

**NCCN GUIDELINES™ Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (V.1.2020, Aug 23, 2019)**

CLL/SLL without deletion of 17P/TP53 mutation, consider allogeneic HCT if without significant comorbidities in patients with CLL refractory to small molecule inhibitor therapy. (CSLL-4, CSLL-5)

Richter’s transformation, Initial therapy, consider allogeneic HCT. (HT-3)

Allogeneic Hematopoietic Cell Transplantation (HCT) can provide long term disease control and also overcome the poor prognosis associated with deletion of 17P/TP53 mutations. (MS-28)

Allogeneic Hematopoietic Cell Transplantation (HCT) can be considered for CLL/SLL refractory to small molecule inhibitor therapy in patients without significant comorbidities. (MS-29)

Allogeneic HCT can be considered for patients with disease responding to initial chemoimmunotherapy. (MS-31)

Autologous HCT may also be an appropriate therapy for patients with Richter’s transformation who have a response to initial therapy but are not a candidate for allogeneic HCT. (MS-31)

Pure red cell aplasia (PRCA): In very refractory cases, allogeneic may be necessary. (MS-35)
**Cancer**

**NCI Chronic Lymphocytic Leukemia Treatment (PDQ®) March 5, 2019**

Stage I, II, III, and IV CLL
Bone marrow and peripheral stem cell transplantations are under clinical evaluation.

Recurrent or Refractory CLL
Bone marrow and peripheral stem cell transplantations are under clinical evaluation.

**Chronic Myeloid Leukemia (CML)**

**American Society for Blood and Marrow Transplantation (2015)**
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<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic phase</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Accelerated phase</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Blast phase</td>
<td>C</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic phase 1, TKI intolerant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Chronic phase 1, TKI refractory</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Chronic phase 2+</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Accelerated phase</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Blast phase</td>
<td>S</td>
<td>N</td>
</tr>
</tbody>
</table>

**NCCN GUIDELINES™ Chronic Myeloid Leukemia (V.1.2020, Aug 26, 2019)**

Accelerated phase and blast phase CML, allogeneic HCT. (CML-4)
Indications for allogeneic HCT: Advanced phase CML at presentation or disease progression to blast phase.(CML-6)
Management of chronic phase CML, allogeneic HCT is no longer recommended as a first-line treatment option for patients with CP-CML.(MS-5)
Second line therapy, patients who do not achieve cyogenetic or molecular responses at 3, 6, or 12 months after second line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible. (MS-10)

Advanced phase CML Treatment considerations, participation in clinical trials and evaluation for allogeneic HCT is recommended for all patients with AP-CML and BP-CML. (MS-16)

Allogeneic HCT is an appropriate treatment option for the very rare patient presenting with BP-CML at diagnosis, patients with disease that is resistant to TKIs, patients with progression to AP-CML, or BP-CML while on TKI therapy, and for the rare patients intolerant to all TKIs. (MS-16)

**NCI Chronic Myelogenous Leukemia Treatment (PDQ®) February 8, 2019**

Treatment Option Overview for CML
Allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT) has also been applied with curative intent.

Chronic-Phase CML, High-dose therapy followed by allogeneic BMT or SCT
The only consistently successful curative treatment of CML has been high-dose therapy followed by allogeneic BMT or SCT. Patients younger than 60 years with an
**Cancer**

Identical twin or with HLA-identical siblings can be considered for BMT early in the chronic phase. Although the procedure is associated with considerable acute morbidity and mortality, 50% to 70% of patients transplanted in the chronic phase survive 2 to 3 years, and the results are better in younger patients, especially those younger than 20 years. The results of patients transplanted in the accelerated and blastic phases of the disease are progressively worse.

**Accelerated-Phase CML**

Treatment Options for Accelerated-Phase CML include allogeneic bone marrow transplantation (BMT) or stem cell transplantation (SCT).

**Blastic-Phase CML**

Allogeneic bone marrow transplantation (BMT) represents the only potentially curative approach in these patients. Allogeneic BMT is more effective in patients induced into a second chronic phase.

**Relapsing CML**

In case of treatment failure or suboptimal response, patients should undergo BCR/ABL kinase domain mutation analysis to help guide therapy with the newer tyrosine kinase inhibitors or with allogeneic transplantation.

**NCI Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment (PDQ®) August 20, 2019**

**Treatment of Childhood CML**

Treatment options for children with CML may include tyrosine kinase inhibitor, such as imatinib. As a result of this high level of activity, it is common to initiate imatinib treatment in children with CML rather than proceeding immediately to allogeneic stem cell transplantation.

**Treatment of Recurrent or Refractory Childhood CML**

Treatment options for children with recurrent or refractory CML may include alternative kinase inhibitors such as dasatinib or nilotinib and allogeneic HSCT. The question of whether a pediatric patient with CML should receive an allogeneic transplant when multiple TKIs are available remains unanswered; however, reports suggest that PFS does not improve when using HSCT, compared with the sustained use of imatinib.

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**CMML**

**NCCN GUIDELINES™ Myelodysplastic Syndromes (V.1.2020, Aug 27, 2019)**

Myelodysplastic/myeloproliferative neoplasms include CMML and JMML among other disorders (MS-5).

The IPSS or IPSS-R risk categories are used in the initial planning of therapeutic options. Therapeutic options for MDS include the option of high intensity therapy including allogeneic HCT. (MS-19)

**NCI Myelodysplastic/ Myeloproliferative Neoplasms Treatment (PDQ®) February 1, 2019**

The World Health Organization (WHO) classifies chronic myelomonocytic leukemia (CMML) as a myelodysplastic/myeloproliferative neoplasm (MDS/MPN). CMML is a clonal disorder of a bone marrow stem cell. Monocytosis is a major defining feature. Bone marrow transplantation (BMT) or stem cell transplantation appears to be the only current treatment that alters the natural history of CMML.

**NCI Myelodysplastic Syndromes (MDS) Treatment (PDQ®) February 1, 2019**

(Although previously classified with the myelodysplastic syndromes, CMML is now assigned to a group of overlap myelodysplastic/myeloproliferative neoplasms. Refer to
Cancer | Hodgkin Lymphoma
--- | ---
the PDQ summary on Myelodysplastic/ Myeloproliferative Neoplasms for more information.

### American Society for Blood and Marrow Transplantation (2015)
(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Complete Response (CR)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Primary refractory, sensitive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>First relapse, sensitive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>First relapse, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Second or greater relapse</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (PET negative)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>CR1 (PET positive)</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory, sensitive</td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Primary refractory, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>First relapse, sensitive</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>First relapse, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Second or greater relapse</td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Relapse after autologous transplant</td>
<td>C</td>
<td>N</td>
</tr>
</tbody>
</table>

### ASBMT
The American Society for Blood and Marrow Transplantation published separate guidelines in 2015 addressing the role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma. Those recommendations are as follows:

<table>
<thead>
<tr>
<th>Autologous stem cell transplant (ASCT)</th>
<th>Grade*</th>
<th>Highest level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>should not be offered as first-line therapy for advanced disease</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>should be offered as first-line therapy for patients who fail to achieve CR</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>should be offered as salvage therapy over nontransplantation (except localized disease, where IFRT may be considered, or patients with low-stage disease and late relapse, where chemotherapy may be considered)</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>tandem ASCT is not routinely recommended in standard-risk patients</td>
<td>C</td>
<td>2+</td>
</tr>
</tbody>
</table>

### Allogeneic hematopoietic cell transplantation (allo HCT)
<table>
<thead>
<tr>
<th>Cancer</th>
<th>should be used instead of conventional therapy for relapse after ASCT</th>
<th>B</th>
<th>2++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>all donor sources can be considered</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td></td>
<td>there are limited data for tandem ASCT/Allo HCT</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Allo HCT is preferred over ASCT as second HCT (except in late relapse)</td>
<td>C</td>
<td>2+</td>
</tr>
</tbody>
</table>

*Grades of Recommendation
A: At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C: A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D: Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

Levels of Evidence
1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++ High-quality systematic reviews of case-control or cohort studies; high-quality case control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3 Nonanalytic studies, eg, case reports or case series.
4 Expert opinion.

**NCCN GUIDELINES™ Hodgkin Lymphoma (V.2.2019, July 15, 2019)**

**Classic Hodgkin lymphoma, refractory disease**
Deauville 1-3, high dose therapy and autologous stem cell rescue HDT/ASCR (Category 1, footnote indicates Allotransplant is an option in selected patients as a Category 3 recommendation)
Deauville 4, HDT/ASCR
Deauville 5, Autologous or allogeneic SCT if response to secondary therapy (HODG-15)

**Classic Hodgkin lymphoma, suspected relapse**
Rebiopsy positive, HDT/ASCR (HODG-16)

**Relapsed or Refractory disease**
Allogeneic HSCT for select patients with relapsed or refractory disease is a Category 3 Recommendation.
**Cancer**

Allogeneic HSCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was 50%. Allogeneic HSCT with reduced intensity conditioning remains investigational. (MS-30)

**NCI Adult Hodgkin Lymphoma Treatment (PDQ®) July 26, 2019**

Standard Treatment Options for Recurrent Adult Classic HL

Patients who relapse after initial combination chemotherapy can undergo reinduction with the same or another chemotherapy regimen followed by high-dose chemotherapy and autologous bone marrow or peripheral stem cell or allogeneic bone marrow rescue.

Patients who are responsive to reinduction therapy may have a better prognosis after subsequent autologous SCT.

The use of HLA-matched sibling marrow (allogeneic transplantation) results in lower relapse rates, but the benefit may be offset by increased toxic effects. Reduced-intensity conditioning for allogeneic SCT is also under clinical evaluation.

In summary, consider allogeneic SCT for primary refractory disease with partial response or complete remission on salvage therapy.

**NCI Childhood Hodgkin Lymphoma Treatment (PDQ®) May 29, 2019**

Treatment of Primary Refractory or Recurrent Hodgkin Lymphoma in Children and Adolescents:

Chemotherapy followed by autologous hematopoietic cell transplantation (HCT): Myeloablative chemotherapy with autologous HCT is the recommended approach for patients who develop refractory disease during therapy or relapsed disease within 1 year after completing therapy.

Chemotherapy followed by allogeneic HCT: For patients who fail after autologous HCT or for patients with chemoresistant disease, allogeneic HCT has been used with encouraging results.

**JMML**

American Society for Blood and Marrow Transplantation (2015)

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile myelomonocytic leukemia</td>
<td>S</td>
<td>N</td>
</tr>
</tbody>
</table>

**NCCN GUIDELINES™ Myelodysplastic Syndromes (V.1.2020, Aug 27, 2019)**

Myelodysplastic/myeloproliferative neoplasms include CMML and JMML among other disorders (MS-5).

The IPSS or IPSS-R risk categories are used in the initial planning of therapeutic options. Therapeutic options for MDS include the option of high intensity therapy including allogeneic HCT. (MS-19)

**NCI Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment (PDQ®) Aug 20, 2019**

Treatment of JMML: HSCT currently offers the best chance of cure for JMML.

**NCI Myelodysplastic/ Myeloproliferative Neoplasms Treatment (PDQ®) February 1, 2019**

No consistently effective therapy is available for Juvenile Myelomonocytic Leukemia (JMML). Historically, more than 90% of patients have died despite the use of
Bone marrow transplantation (BMT) seems to offer the best chance of cure for JMML.

### Multiple Myeloma (MM)

**American Society for Blood and Marrow Transplantation (2015)**

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

<table>
<thead>
<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma, initial response</td>
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</tr>
<tr>
<td>Myeloma, sensitive relapse</td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Myeloma, refractory</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

**ASBMT**

The American Society for Blood and Marrow Transplantation published separate guidelines in 2015 addressing hematopoietic stem cell transplantation for multiple myeloma (Shah, et al., 2015). Those recommendations are as follows:

**Autologous hematopoietic cell transplantation (auto HCT)**

- high-dose chemotherapy (HDC) and auto HCT as consolidative therapy for patients with MM (grade* A)
- consideration of a first auto HCT for patients with refractory disease (grade C).
- that age not be used as a selection factor (grade C). However, an HCT-CI score of >2 or Karnofsky performance status <90 can warrant additional consideration before proceeding with auto-HCT.
- serious consideration of a clinical trial for patients with high-risk cytogenetics, particularly del17p or t(4:14) (grade C).
- second auto HCT is a safe and efficacious treatment modality for relapsed MM and should be considered (grade B)

**Allogeneic HCT**

- Upfront myeloablative allo HCT is not routinely recommended (grade A).
- It may be appropriate for further study in young patients with very high-risk MM, in the context of a clinical trial. Planned RIC-allo HCT after auto HCT has not been found to be superior in the majority of clinical trials and is, therefore, not recommended over auto HCT (grade A).
- Its role in high-risk subgroups requires further study. Allo HCT salvage therapy for relapsed MM has not been shown to be superior to salvage auto HCT and is not routinely recommended outside of a clinical trial (grade D).
- For younger patients with a good performance status, allo HCT can be considered, ideally in the context of a clinical trial. The role and choice maintenance after allo-HCT has not been adequately studied and is not known.

*Grades of Recommendation

A: At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.

C: A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
Cancer

D: Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

Levels of Evidence
1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
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3 Nonanalytic studies, eg, case reports or case series.
4 Expert opinion.

NCCN GUIDELINES™ Multiple Myeloma (V.1.2020, September 6, 2019)

Active symptomatic, Autologous transplantation
Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant.
Allogeneic stem cell transplant (2A) should only be used in the setting of a clinical trial.
Data do not support miniallografting alone.(MYEL 4 – 7)
Retrospective studies suggest a 2-3 year minimum length of remission for consideration of a second autologous stem cell transplant.(MYEL-6)

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients primary therapy is followed by high-dose chemotherapy with autologous SCT. (MS-8)

For transplant eligible patients, autologous SCT is an option after primary induction therapy (Cat 1) and for treatment of progressive/refractory disease after primary treatment.(MS-23)

Tandem SCT refers to a planned second course of high dose therapy and SCT within 6 months of the first course. The NCCN panel recommends collecting enough stem cells for two transplants in all eligible patients. According to the NCCN panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT. (MS-24)

A second autologous SCT can be considered at the time of disease relapse. According to the NCCN panel, repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding SCT and documented progression. (MS-24)

Allogeneic SCT
Includes with myeloablative or nonmyeloablative (mini) transplants. The NCCN guidelines consider myeloablative Allogeneic SCT an accepted option, preferably in a clinical trial in: 1) patient whose disease responds to primary therapy 2) patients with primary PD, or 3) patients with PD after an initial autologous SCT. (MS-25)

Treatment of progressive or relapsed myeloma
Cancer

Treatment options included systemic therapy, SCT (for eligible patients who did not receive SCT as part of their initial treatment) or clinical trials. For those who had autologous SCT as part of initial treatment and had a durable response or had SD, consideration must be given to a second transplant on or off clinical trial as the time of relapse/disease progression.(MS-29)

NCI Plasma Cell Neoplasms (Including Multiple Myeloma) Treatment (PDQ®) July 19, 2019

Autologous bone marrow or peripheral stem cell transplantation:
The failure of conventional therapy to cure myeloma has led investigators to test the effectiveness of much higher doses of drugs such as melphalan. The development of techniques for harvesting hemopoietic stem cells, from marrow aspirates or the peripheral blood of the patient, and infusing these cells to promote hemopoietic recovery made it possible for investigators to test very large doses of chemotherapy.

Tandem autologous bone marrow or peripheral stem cell transplantation followed by autologous or allogeneic transplantation:
Another approach to high-dose therapy has been the use of two sequential episodes of high-dose therapy with stem cell support (tandem transplants).

Allogeneic bone marrow or peripheral stem cell transplantation:
Many patients are not young enough or healthy enough to undergo these intensive approaches. A definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses after the infusion of donor lymphocytes.

Salvage autologous bone marrow or peripheral stem cell transplantation after relapse from first transplantation
One study cited

Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Myelodysplastic Syndromes</th>
<th>American Society for Blood and Marrow Transplantation (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
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</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>High risk</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukemia</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Therapy related</td>
<td>S</td>
<td>N</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/intermediate – 1 risk</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Intermediate-2/high risk</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Therapy-related acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), CR1</td>
<td>S</td>
<td>N</td>
</tr>
</tbody>
</table>

NCCN GUIDELINES™ Myelodysplastic Syndromes (V.1.2020, Aug 27, 2019)

IPSS-R: very low, low, Intermediate
IPSS: Low/Intermediate-1
WPSS: Very low, Low, Intermediate
Clinical trial or consider allogeneic HCT for selected patients (MDS-3, MDS-4)
Cancer

IPSS-R: Intermediate, High, Very high
IPSS: Intermediate-2, High
WPSS: High, Very high

If transplant candidate. Allogeneic HCT from most suitable donor following standard or reduced-intensity conditioning regimens.
Consider allogeneic HCT or donor lymphocyte infusion if relapse after allogeneic HCT or no response. Consider second transplant or donor lymphocyte infusion immune-based therapy for appropriate patients who had a prolonged remission after first transplant. (MDS – 6)

Myeloablative therapy followed by either matched family or matched unrelated donor allogeneic HCT is the treatment of choice for children with MDS. Children with Downs’s syndrome – HCT not indicated in first complete remission. (MS-8)

High-intensity therapy includes intensive induction chemotherapy or HCT.
- The panel recommends that such treatments be given in the context of clinical trials.
- Allogeneic HCT from an HLA-matched sibling or matched unrelated donor is a preferred approach for treating select patients with MDS, particularly those with high risk disease. This includes both standard and RIC strategies. AzaC, decitabine, or other therapies may be used as a bridge to transplantation and should not be used to delay HCT.
- In patients who relapse after a prolonged remission following the first transplant, a second transplant or donor lymphocyte infusion therapy may be considered.
- Allogeneic HCT may also be considered in select lower-risk MDS patients (IPSS int-1, IPS-R, and WPSS intermediate) with severe cytopenias. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been prospectively established. (MS-30)

Therapy for high-risk patients (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High)
With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC for HCT is generally the strategy in older individuals. Studies suggest that age alone should not be an exclusionary factor for eligibility. (MS-32, MS-33)

**NCI Myelodysplastic Syndromes (MDS) Treatment (PDQ®) February 1, 2019**
Allogeneic HSCT is the only potentially curative treatment for MDS. Although HSCT represents the only treatment modality with curative potential, the relatively high morbidity and mortality of this approach limits its use. Allogeneic stem cell transplantation with reduced-intensity conditioning (RIC) has extended transplantation as a possible modality for treatment of older patients.

**NCI Myelodysplastic/ Myeloproliferative Neoplasms Treatment (PDQ®) February 1, 2019**
Myelodysplastic/ Myeloproliferative Neoplasm, Unclassifiable (MDS/ MPN-UC) (also known as mixed myeloproliferative/myelodysplastic syndrome, unclassifiable and overlap syndrome, unclassifiable) shows features of both myeloproliferative disease and myelodysplastic disease but does not meet the criteria for any of the other MDS/MPN entities.
Adult patients with MDS/MPN associated with platelet-derived growth factor receptor gene rearrangements are candidates for imatinib mesylate at standard dosages.
Because of its rare occurrence, the literature only minimally addresses other treatment options for MDS/MPN-UC. Supportive care involves treating cytopenias and infection as necessary.

**NCI Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment (PDQ) Aug 20, 2019**

Allogeneic HSCT is considered to be the optimal approach to treatment for pediatric patients with MDS. Although matched sibling transplantation is preferred, similar survival has been noted with well-matched, unrelated cord blood and haploidentical approaches.

**Treatment of Therapy-Related AML/MDS**

The goal of treatment is to achieve an initial complete remission (CR) using AML-directed regimens and then, usually, to proceed directly to hematopoietic stem cell transplantation (HSCT) with the best available donor.

### Non-Hodgkin Lymphoma (NHL)

**American Society for Blood and Marrow Transplantation (2015)**

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<thead>
<tr>
<th>Children (&lt;18 years)</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic large cell lymphoma, CR1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, Primary refractory, sensitive</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Anaplastic large cell lymphoma, Primary refractory, resistant</td>
<td>C</td>
<td>N</td>
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<tr>
<td>Anaplastic large cell lymphoma, First relapse, sensitive</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Anaplastic large cell lymphoma, First relapse, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, Second or greater relapse</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Burkitt's lymphoma, First remission</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Burkitt's lymphoma, First or greater relapse, sensitive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Burkitt's lymphoma, First or greater relapse, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR1, standard risk</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR1, high risk</td>
<td>S</td>
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<tr>
<td>Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR2</td>
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<tr>
<td>Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR3+</td>
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<tr>
<td>Cancer</td>
<td>Adults</td>
<td>Allogeneic HCT</td>
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<tr>
<td>Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), Not in remission</td>
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<tr>
<td>T-cell non-Hodgkin lymphoma, CR1, standard risk</td>
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<td>T-cell non-Hodgkin lymphoma, CR1, high risk</td>
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<tr>
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<tr>
<td>T-cell non-Hodgkin lymphoma, CR3+</td>
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<tr>
<td>T-cell non-Hodgkin lymphoma, Not in remission</td>
<td>C</td>
<td>N</td>
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</table>

<p>| Burkitt lymphoma (BL), First remission                             | C      | C              |                |
| Burkitt lymphoma, First or greater relapse, sensitive               | C      | C              |                |
| Burkitt lymphoma, First or greater relapse, resistant               | C      | N              |                |
| Burkitt lymphoma, Relapse after autologous transplant              | C      | N              |                |
| Cutaneous T-cell lymphoma, Relapse                                 | C      | C              |                |
| Cutaneous T-cell lymphoma, Relapse after autologous transplant     | C      | N              |                |
| Diffuse large B-cell lymphoma, CR 1 (PET negative)                 | N      | N              |                |
| Diffuse large B-cell lymphoma, CR 1 (PET Positive)                 | N      | C              |                |
| Diffuse large B-cell lymphoma, Primary refractory, sensitive       | C      | S              |                |
| Diffuse large B-cell lymphoma, Primary refractory, resistant       | C      | N              |                |
| Diffuse large B-cell lymphoma, First relapse, sensitive             | C      | S              |                |
| Diffuse large B-cell lymphoma, First relapse, resistant             | C      | N              |                |
| Diffuse large B-cell lymphoma, Second or greater relapse            | C      | S              |                |
| Diffuse large B-cell lymphoma, Relapse after autologous transplant | C      | N              |                |
| Follicular lymphoma, CR 1                                           | N      | C              |                |
| Follicular lymphoma, Primary refractory, sensitive                 | S      | S              |                |
| Follicular lymphoma, Primary refractory, resistant                  | S      | N              |                |
| Follicular lymphoma,                                                | S      | S              |                |</p>
<table>
<thead>
<tr>
<th>Cancer</th>
<th>First relapse, sensitive</th>
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<tbody>
<tr>
<td>Follicular lymphoma, First relapse, resistant</td>
<td>S</td>
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<tr>
<td>Follicular lymphoma, Second or greater relapse</td>
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<tr>
<td>Follicular lymphoma, Transformation to high grade lymphoma</td>
<td>C</td>
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<tr>
<td>Follicular lymphoma, Relapse after autologous transplant</td>
<td>C</td>
<td>N</td>
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<tr>
<td>Mantle cell lymphoma, CR 1/PR 1</td>
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<tr>
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<tr>
<td>Mantle cell lymphoma, Relapse after autologous transplant</td>
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<td>Plasmablastic lymphoma, Relapse</td>
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<tr>
<td>T-cell lymphoma, CR 1</td>
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<td>T-cell lymphoma, Second or greater relapse</td>
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<tr>
<td>T-cell lymphoma, Relapse after autologous transplant</td>
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<tr>
<td>Waldenstrom macroglobulinemia (WM)/ Lymphoplasmacytic lymphoma, CR 1</td>
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<tr>
<td>Waldenstrom macroglobulinemia, Primary refractory, sensitive</td>
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<tr>
<td>Waldenstrom macroglobulinemia, Primary refractory, resistant</td>
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<tr>
<td>Waldenstrom macroglobulinemia, Relapse after autologous transplant</td>
<td>R</td>
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</table>
### NCCN GUIDELINES™ B-cell Lymphoma (V.4.2019, June 18, 2019)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>First or greater relapse, sensitive</th>
<th>Waldenstrom macroglobulinemia, First or greater relapse, resistant</th>
<th>Waldenstrom macroglobulinemia, Relapse after autologous transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular lymphoma (grade 1-2)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Histologic transformation to diffuse large B-cell lymphoma: (DLBCL) high-dose therapy with autologous stem cell rescue (HDT/ASCR) or allogeneic HCT in selected cases is a treatment option (FOLL-7, FOLL-8)</td>
<td></td>
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<tr>
<td>Nodal Marginal Zone lymphoma, Histologic transformation to diffuse large B-cell lymphoma:</td>
<td></td>
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<tr>
<td>HDT/ASCR or allogeneic HCT is a treatment option (NODE-5, NODE-6)</td>
<td></td>
<td></td>
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<tr>
<td>Mantle cell lymphoma, HDT/ASCR may be appropriate (MANT-4, MANT-4)</td>
<td></td>
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</tr>
<tr>
<td>Burkitt lymphoma, Relapse or refractory disease, HDT/ASCR or allogeneic HCT is a treatment option (BURK-3)</td>
<td></td>
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<tr>
<td>Follicular lymphoma</td>
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<tr>
<td>High-dose therapy with autologous stem cell rescue (HDT/ASCR) is an appropriate consolidative therapy for patients with second or third remission. HDT/ASCR as consolidation therapy has been shown to prolong overall survival and progression-free survival in patients with relapsed or refractory disease. (MS-37).</td>
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<tr>
<td>Histologic transformation of FL to DLBCL</td>
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<tr>
<td>Consolidation therapy with HDT/ASCR with or without ISRT (if not previously given) or observation are included as treatment options for patients achieving complete remission or partial remission to initial treatment (MS-39)</td>
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<tr>
<td>Nodal Marginal Zone lymphoma</td>
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<tr>
<td>High dose therapy followed by HDT/ASCR has been associated with survival benefit in patients with relapsed or refractory disease. Allogeneic HCT may also be considered in select patients. (MS-61)</td>
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<tr>
<td>Mantle cell</td>
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<tr>
<td>HDT/ASCR as first-line consolidation after aggressive induction therapy has demonstrated promising outcomes in a number of studies (MS-80).</td>
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<tr>
<td>The panel recommends consolidation with HDT/ASCR for eligible patients in complete remission following induction therapy with aggressive regimens (MS-81)</td>
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<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
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<tr>
<td>Overall, studies found no benefit to upfront HDT/ASCR as compared with first line chemoimmunotherapy except in high-risk IPI patients, but this remains controversial. HDT/ASCR is therefore not routinely recommended. (MS-101).</td>
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<tr>
<td>Double-hit lymphoma</td>
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<tr>
<td>HDT/ASCR is done at some institutions; however, its role is not established (MS-120).</td>
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<tr>
<td>Burkitt Lymphoma, relapsed or refractory disease:</td>
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<tr>
<td>Patients should be treated in the context of a clinical trial. Autologous or allogeneic HSCT may be considered in select patients achieving a CR or PR to second line therapy. (MS-132)</td>
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</tbody>
</table>
### NCCN GUIDELINES™ T-cell Lymphomas (V.2.2019, Dec 17, 2018)

**Peripheral T-Cell Lymphoma, ALCL, ALK positive, Stage III, IV**  
Consider consolidative HDT/ASCR for high risk IPI patients in CR1. (TCEL-3)

**Peripheral T-Cell Lymphoma, relapsed/refractory**  
Consider allogeneic HCT  
Consider autologous stem cell rescue (TCEL-5)

**Mycosis Fungoides/Sézary Syndrome, refractory disease**  
Consider allogeneic HCT. The role of allogeneic HSCT is controversial.  
(MFSS-7 - MFSS-9)

**Adult T-Cell Leukemia/Lymphoma**  
Consider allogeneic HCT (ATLL-3)

**T-cell prolymphocytic leukemia, symptomatic disease**  
Consider allogeneic HCT. Consider HDT/ASCR if a suitable donor is not available.  
(TPLL-2)

**Extranodal NK/T-cell lymphoma, nasal type**  
Complete response, Consider HCT. There are no clear data to suggest whether allogeneic or autologous HSCT is preferred and treatment should be individualized.  
Extranodal NK/T-cell lymphoma, nasal type, No response  
HCT if eligible. Allogeneic preferred if donor available (NKTL-4)

**Peripheral T-Cell Lymphoma (PTCL)**  
The generally poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as first line consolidation therapy. (MS-17)  
HDT/ASCR as first line consolidation therapy may improve outcomes in patients with AITL and EATL. (MS-18)  
Available evidence suggest that HDT/ASCR is a reasonable treatment option only in patients with disease responding to induction therapy. (MS-19)  
Findings suggest that HDT/ASCR less frequently results in durable benefit in patients with relapsed or refractory disease as compared to allogeneic HCT. This conclusion is not universal in the literature and those with relapsed ALCL and more chemosensitive relapsed disease benefit from HDT/ASCR more often than those with non-ALCL subtypes and less chemosensitive disease. Allogeneic HCT using RIC may provide a more reliable curative option for the majority of patients with relapsed or refractory PTCL. (MS-21)  
Second line systemic therapy followed by consolidation with HDT/ASCR or allogeneic HCT for those with a CR or PR is recommended for patients who are candidates for transplant. (MS-21)

**Mycosis Fungoides/Sézary Syndrome**  
Autologous HCT has been used infrequently for patients with cutaneous t-cell lymphomas (CTCL). (MS-51)  
Allogeneic HCT appears to be a promising therapeutic strategy in patients with advanced CTCL; further data are needed. (MS-52)  
Refractory or progressive disease, allogeneic HCT may be considered for patients with stage IIB – IV disease that is progressive or refractory to primary treatment options. Patients should have failed biologic options and single-agent chemotherapy. (MS-55)  

**Adult T-Cell Leukemia/Lymphoma**
### Cancer

<table>
<thead>
<tr>
<th>Allogeneic HCT should be considered for patients with acute or lymphoma subtype, if donor is available. In patients with acute or lymphoma subtypes wo achieve a response to second therapy, allogeneic HCT should be considered if a donor is available. (MS-90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-Cell Prolymphocytic Leukemia</strong></td>
</tr>
<tr>
<td>Given the poor prognosis associated with T-PLL, the panel recommends that patients be managed in a clinical trial. In patients who achieve CR or PR following initial therapy, consolidation with allogeneic HCT should be considered. Autologous HCT may be considered if a donor is not available and the patient is not physically fit to undergo allogeneic HCT. (MS-100)</td>
</tr>
<tr>
<td><strong>Extranodal NK/T-Cell Lymphoma, nasal type</strong></td>
</tr>
<tr>
<td>Participation in a clinical trial is the preferred option for all patients with ENKL at any stage. Patients with stage IV nasal disease or extranasal disease (stage I-IV) achieving a CR to induction therapy should be considered for HCT. No clear data suggests allogeneic versus autologous HCT. (MS-111)</td>
</tr>
</tbody>
</table>

### NCCN GUIDELINES™ Waldenstrom Macroglobulinemia (WM)/Lymphoplasmacytic Lymphoma (V.2.2019, Sept 14, 2018)

Therapy for previously treated WM, In selected patients, stem cell transplantation may be appropriate with either
- autologous stem cell transplant or
- allogeneic stem cell transplant (ablative or nonablative) (Should ideally be undertaken in the context of a clinical trial). (WM/LPL-B, 2 of 3)

Primary treatment, agents that limit future treatment options should be avoided in initial therapy. (MS-5)

**Therapy for previously treated WM**

It is important to avoid stem-cell damaging agents in patients who are candidates for autologous SCT. (MS-11)

SCT is an option for relapsed WM in selected patients. SCT options listed in the NCCN guideline are for high-dose therapy with autologous stem cell rescue. According to the NCCN panel, myeloablative or nonmyeloablative allogeneic SCT may be considered but in the context of a clinical trial. (M-12)

### NCI Adult Non-Hodgkin Lymphoma Treatment (PDQ®) July 26, 2019

**Indolent NHL**

- Follicular Lymphoma: Therapeutic options include watchful waiting; rituximab, an anti-CD20 monoclonal antibody, alone or with purine nucleoside analogs; oral alkylating agents; and combination chemotherapy. Radiolabeled monoclonal antibodies, vaccines, and autologous or allogeneic bone marrow or peripheral stem cell transplantation are under clinical evaluation.
- Lymphoplasmacytic Lymphoma (Waldenström Macroglobulinemia): Myeloablative therapy with autologous or allogeneic hematopoietic stem cell support is under clinical evaluation. Candidates for this approach should avoid long-term use of alkylating agents or purine nucleoside analogs, which can deplete hematopoietic stem cells.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Aggressive NHL</th>
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<tbody>
<tr>
<td>• Diffuse large B-cell lymphoma (DLBCL): The BCL2 gene and rearrangement of the MYC gene or dual overexpression of the MYC gene, or both, confer a particularly poor prognosis. Dose-intensive therapies, infusional therapies, and stem cell transplantation consolidation are being explored in this high-risk group. Patients with CNS dissemination at diagnosis or at relapse usually receive rituximab and high-doses of methotrexate and/or cytarabine followed by ASCT, but this approach has not been assessed in randomized trials.</td>
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<tr>
<td>• Follicular Large Cell Lymphoma: Treatment of follicular large cell lymphoma is more similar to treatment of aggressive NHL than it is to the treatment of indolent NHL. In support of this approach, treatment with high-dose chemotherapy and autologous hematopoietic peripheral stem cell transplantation (SCT) shows the same curative potential in patients with follicular large cell lymphoma who relapse as it does in patients with diffuse large cell lymphoma who relapse.</td>
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<td>• Angioimmunoblastic T-cell Lymphoma: Myeloablative chemotherapy and radiation therapy with autologous or allogeneic peripheral stem cell support has been described in anecdotal reports.</td>
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<tr>
<td>• Peripheral T-cell Lymphoma: Consolidation using high-dose chemotherapy with autologous or allogeneic hematopoietic stem cell support has been applied to patients with advanced-stage peripheral T-cell lymphoma after induction therapy with CHOP-based regimens and after response to reinduction therapy at first relapse. Evidence for this approach is anecdotal.</td>
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<tr>
<td>• Enteropathy-type Intestinal T-cell Lymphoma: High-dose therapy with hematopoietic stem cell rescue has been applied in first remission or at relapse. Evidence for this approach is anecdotal.</td>
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<tr>
<td>• Mantle Cell Lymphoma: Several induction chemotherapy regimens may be employed for symptomatic progressing disease. These regimens range in intensity from rituximab alone to rituximab plus bendamustine, to R-CHOP, to high-dose intensive regimens such as R-hyper C-VAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine). Some physicians use autologous or ASCT consolidation next, while others prefer rituximab maintenance, reserving high-dose consolidation for a later time. Many investigators are exploring high-dose chemoradiation immunotherapy with stem cell/marrow support or nonmyeloablative ASCT.</td>
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<tr>
<td>• Plasmablastic Lymphoma: Anecdotal reports suggest using aggressive chemotherapy for Burkitt or lymphoblastic lymphoma, followed by stem cell transplant consolidation in responding patients, when feasible.</td>
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**Aggressive, Recurrent Adult NHL**

Bone marrow transplantation (BMT) is the treatment of choice for patients whose lymphoma has relapsed. Similar success has been achieved using autologous marrow, with or without marrow purging, and allogeneic marrow.

**Treatment Options Under Clinical Evaluation for Aggressive, Recurrent Adult NHL**

Treatment options under clinical evaluation include SCT. The indolent lymphomas may relapse with an aggressive histology (i.e., histologic conversion). The durability of the second remission may be short, and clinical trials, such as autologous or allogeneic peripheral SCT, should be considered.

**NCI Childhood Non-Hodgkin Lymphoma Treatment (PDQ®) August 06, 2019**

Treatment options for Recurrent Burkitt and Burkitt-like lymphoma/leukemia and diffuse large B-cell lymphoma (DLBCL) include allogeneic or autologous stem cell transplantation (SCT). If remission can be achieved, high-dose therapy plus SCT.
Cancer

remains the best option for survival. However, the benefit of autologous versus allogeneic SCT is unclear.

Treatment options for Recurrent lymphocytic/lymphoblastic lymphoma include Allogeneic stem cell transplantation (SCT).

Treatment options for Recurrent Anaplastic Large cell lymphoma include Allogeneic or autologous stem cell transplantation (SCT).

Treatment options for Lymphoproliferative disease associated with primary immunodeficiency include Allogeneic stem cell transplantation (SCT).

NCI Hairy Cell Leukemia Treatment (PDQ®) March 23, 2018
No mention of stem cell transplantation.

<table>
<thead>
<tr>
<th>POEMS Syndrome</th>
<th>American Society for Blood and Marrow Transplantation (2015)</th>
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<tbody>
<tr>
<td></td>
<td>(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)</td>
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<tr>
<th>Adults</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
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<tbody>
<tr>
<td>POEMS syndrome</td>
<td>N</td>
<td>R</td>
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<tr>
<td>Plasma cell disorders, Relapse after autologous transplant</td>
<td>C</td>
<td>C</td>
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National Organization for Rare Disorders (NORD):
On a patient information webpage on POEMS Syndrome, NORD states that many patients may be offered high-dose chemotherapy with peripheral blood stem cell transplant.

Literature Review

ALL: Several randomized controlled trials (RCTs) and case studies have demonstrated improved outcomes with the use of myeloablative conditioning and allogeneic HSCT in subsets of adults with five-year overall survival (OS) rates of 28%–69% (Cornelissen, 2009; Tomblyn, 2009; Goldstone, 2008; Fielding, 2007; Vey, 2007; Oyekunle, 2006). Although variables exist, several studies have demonstrated improved outcomes with the use of myeloablative allogeneic HSCT compared with autologous HSCT or chemotherapy in selected infants and children with ALL (Eckert, 2013; Schrauder, 2006; Balduzzi, 2005; Dalle, 2005; Sanders, 2005; Klingebiel, 2005).

Data are not robust regarding improved overall survival rates for the use of autologous HSCT compared with allogeneic HSCT. However, this therapy may result in improved disease-free survival (DFS) and may be an acceptable treatment option for selected individuals who are ineligible for allogeneic HSCT (Thomas, 2004).

AML: Several randomized controlled trials, meta-analyses and retrospective reviews have demonstrated relapse (RFS)-, disease-free (DFS), and overall (OS) survival benefit with the use of myeloablative allogeneic HSCT in first complete remission for individuals with poor- and intermediate risk AML. No improvement was noted for individuals with good-risk disease (Schetelig, 2015; Li, et al., 2015; Stelljes, 2011; Koreth, 2009; Fagioli, 2008; Gassas, 2008).

Although clinical trial data are limited, non-myeloablative or reduced-intensity conditioning permits the use of allogeneic HSCT for a subset of individuals who may be unable to tolerate the toxic effects of myeloablative chemotherapy prior to allogeneic HSCT (Scott, 2017; Abdul Wahid, 2014; Lioure, 2012; Baron, 2007; Grigg, 2007; Martino, 2007).

Two meta-analyses evaluated the outcomes of autologous HSCT versus chemotherapy in six studies of adult patients with AML in first CR. Patients receiving autologous HSCT had better EFS in both studies; however,
there was no difference in OS. The studies did not address the effect in the high-risk population (Levi, 2004; Nathan, 2004).

**Amyloidosis (systemic light-chain)**: Several prospective case series and retrospective studies have demonstrated higher complete response rates in addition to improved outcomes after high-dose chemotherapy and autologous HSCT, in selected subgroups with AL amyloidosis (Chee, 2010; Cibeira, 2011; Sancharawala, 2007).

**CLL**: There are scarce randomized controlled trials evaluating the role of allogeneic hematopoietic stem-cell transplantation (HSCT) in chronic lymphocytic leukemia (CLL); however, the evidence demonstrated by several nonrandomized trials suggests that high-dose allogeneic HSCT may be potentially curative for a select population of patients with CLL based on the long-term survival of some patients who have achieved a complete remission (Moreno, 2005; Oscier, 2004).

Several case series and retrospective studies involving non-myeloablative conditioning and allogeneic HSCT have demonstrated improved remission rates, improved progression-free and overall survival rates at variable time intervals; Khouri, 2007; Brown, 2006.

Several prospective comparisons have investigated the safety and effectiveness of autologous HSCT for CLL (Reljic, 2015; Magni, 2014; Brion, 2012; Dreger, 2012; Michalet, 2011).

**CML**: The published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of CML in selected individuals. Although it remains a research interest, improved outcomes have not been demonstrated for autologous HSCT compared with conventional chemotherapy in individuals with CML and the role of autologous HSCT has not been established for this indication (Hehlman, 2008; Kebriaei, 2007).

**CMML/JMML**: Data from randomized controlled clinical trials are lacking; however, several prospective and retrospective studies have demonstrated improved overall survival (OS) with myeloablative allogeneic HSCT (Symeonidis, 2015; Yabe, 2014; Park, 2013).

**Hodgkin Lymphoma**: Rancea et al. (2013) published a Cochrane review regarding the effectiveness of high-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. The authors included three randomized controlled open-label trials with 14 publications, assessing 398 patients. Data from this systematic review suggest a survival benefit for patients with relapsed or refractory HL after first-line therapy in those treated with HDCT followed by ASCT compared to patients treated with conventional chemotherapy.

A systematic review and meta-analysis published by Rashidi et al. (2016) reported autologous HSCT outcomes of 38 studies (42 reports) involving 1850 patients. The primary endpoints were six-month, one-year, two-year and three-year relapse-free survival (RFS) and overall survival (OS). The pooled estimates for RFS were 77%, 50%, 37% and 31% at six months and one, two and three years, respectively. The corresponding outcomes for OS were 83%, 68%, 58% and 50%, respectively. Data suggests that non-durable remissions are a major shortcoming of allogeneic HSCT in Hodgkin lymphoma.

**Multiple Myeloma**: Allogeneic HSCT may include the use of a myeloablative or nonmyeloablative conditioning regimen (Kuruva, 2007; Kennedy, 2006; Rotta, 2008). Although autologous HSCT is not curative, studies demonstrate an improvement in complete response rates and prolongation of median overall survival (OS) by approximately 12 months (Giralt, 2009; Barlogie, 2006 [a-c]). Several randomized controlled trials have demonstrated improved response rates and overall survival (OS) rates with the use of tandem compared with single autologous transplantation (Kumar, 2009; Bruno, 2007).

**Myelodysplastic Syndromes**: Allogeneic HSCT offers the potential for long-term disease-free survival (DFS), and is a component of the standard of care for individuals with good performance status and no significant comorbidity for individuals with de novo and secondary myelodysplastic syndromes (Alessandrino, 2008; Kebriaei, 2005). Autologous HSCT may be appropriate in a carefully selected subset of individuals who achieve...
complete remission following induction chemotherapy and in whom suitable autologous stem-cells can be collected (Alessandrino, 2002; Kroger, 2006 de Witte, 2007).

**Non-Hodgkin Lymphoma:** The peer-reviewed published scientific literature supports the safety and effectiveness of high-dose chemotherapy with autologous HSCT as a standard treatment option for selected adults with aggressive or advanced indolent, aggressive or recurrent chemosensitive disease. There is a clear survival benefit for compared with conventional chemotherapy (Song, 2007; Oyan, 2006). Although pediatric data are not robust, there is evidence in the published peer-reviewed scientific literature supporting improvement in overall survival (OS) with autologous HSCT compared with standard chemotherapy for the treatment of stage II, stage III or stage IV NHL (Won, 2006; Sandlund, 2002).

Although data are not robust, myeloablative allogeneic HSCT is considered an acceptable treatment option for selected adults and children with NHL (Kim, 2006; Laudi, 2006; Kasamon, 2005). Non-myeloablative allogeneic HSCT may result in improved OS and is considered an acceptable treatment option for selected adults with NHL (Tomblyn, 2011; Rezvani, 2008; Vigouroux, 2007). There are scarce data in the published peer-reviewed literature regarding the safety and effectiveness of non-myeloablative allogeneic HSCT in the treatment of children with NHL.

**POEMS Syndrome:** In several small case series, slow, but progressive improvement of neurological involvement and performance status was noted after autologous HSCT (Laurenti, 2008; Dispenzieri, 2008).

**American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative**

No relevant statements.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCDs): NCD for STEM CELL Transplantation (Formerly 110.8.1) (110.23) (last updated 1/27/16) does not appear as broad in scope as Cigna Coverage Policies.
- Local Coverage Determinations (LCDs): No LCDs found.

**Use Outside of the US**

The European Society for Medical Oncology has published numerous Haematological Malignancies Practice Guidelines.

**Coding/Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>S2130</td>
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<td>Bone marrow harvesting for transplantation; autologous</td>
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<tr>
<td>S2142</td>
<td>Cord blood derived stem-cell transplantation, allogeneic</td>
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<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition</td>
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</table>

**References**

**General References**


**Acute Lymphocytic/Lymphoblastic Leukemia (ALL)**


**Acute Myeloid Leukemia (AML)**


Amyloidosis (systemic light-chain)


Chronic Lymphocytic Leukemia (CLL)


**Chronic Myeloid Leukemia (CML)**


**CMML/JMML**


**Hodgkin Disease:**


Multiple Myeloma


Myelodysplastic Syndromes


Non-Hodgkin Lymphoma


POEMS Syndrome