BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

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HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS (cont.)

Description:

Non-Hodgkin Lymphomas:

Subtypes include, *but are not limited to:*

- Follicular lymphoma
- Mantle cell lymphoma
- Peripheral t-cell lymphoma (NK-cell neoplasms, t-cell neoplasms)
- Other aggressive subtypes (anaplastic large cell lymphoma, Burkitt's lymphoma, diffuse large B cell lymphoma
- Other indolent subtypes (cutaneous t-cell lymphoma, marginal zone lymphoma)

Hematopoietic Cell Transplantation (HCT):
Hematopoietic stem cells form blood and immune cells. HCT is a procedure in which hematopoietic stem cells are infused into a recipient with deficient bone marrow function. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after a delivery. HCT may also be referred to as bone marrow transplant (BMT) or stem cell transplantation (SCT).

High-Dose Chemotherapy (HDC):
HDC is the administration of myelotoxic agents at doses sufficient to cause bone marrow failure. Myeloablative chemotherapy eradicates cancerous cells from the blood and bone marrow and inhibits the immune response against the donor bone marrow. HDC may be given with or without total body radiation.

Nonmyeloablative Chemotherapy With Allogeneic Hematopoietic Cell Transplantation (HCT):
Nonmyeloablative or reduced-intensity conditioning (RIC) is the administration of a lower dose of chemotherapy that is sufficient to eradicate the hematopoietic cells but does not completely destroy the bone marrow. RIC regimens attempt to reduce adverse effects secondary to bone marrow toxicity and allow for relatively prompt hematopoietic recovery. Nonmyeloablative chemotherapy may also be referred to as RIC, "mini transplant" or "transplant lite".

Donor Types:

- Allogeneic: From a third-party donor
- Autologous: From an individual's own bone marrow and/or circulating blood

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Definitions:

Refractory/Primary Refractory:
The disease is resistant to treatment and does not achieve a complete remission.

Relapse:
The recurrence of a disease or symptoms after apparent recovery.

Remission:
Period of time when cancer is responding to treatment or is under control. In complete remission, all signs and symptoms of the disease have disappeared.

Tandem Transplant:
Two successive cycles of high-dose chemotherapy, each followed by infusion of autologous stem cells, whether or not there is evidence of persistent disease following the first treatment.

Criteria:

All stem cell transplants will be reviewed by the medical director(s) and/or clinical advisor(s).

Pretransplantation Evaluation:

Human Leukocyte Antigen (HLA) typing and Matched Unrelated Donor (MUD) searches may be approved by the coordinator if medical necessity criteria are met. HLA typing may use serologic tissue and/or DNA (gene) for more precise matching.

The psychosocial criteria listed below must only be met prior to the actual transplant procedure.

- Pretransplantation evaluation with documentation of **ALL** of the following:

  1. Psychosocial screen with documentation of **ALL** of the following:

     - Drug/alcohol screen with documentation of **ONE** of the following:

       - No drug/alcohol abuse by history
       - Drug and alcohol free for a period greater than or equal to 6 months

     - Behavioral health disorder screening with documentation of **ONE** of the following:

       - No behavioral health disorder by history and physical exam
       - Behavioral health disorder treated

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

- Pretransplantation evaluation with documentation of **ALL** of the following: (cont.)

  2. Adequate social/family support
  3. Performance status[1] with documentation of **ONE** of the following:

     - Karnofsky score greater than or equal to 70%
     - Eastern Cooperative Oncology Group (ECOG) score 0-2
     - For ages 10 or under: Lansky Play score greater than or equal to 70. A Lansky Play score less than 70 **will be reviewed by the medical director(s) and/or clinical advisor(s)**.

[1] Performance status tables are located at the end of the Criteria section.

Pretransplantation Neurological Evaluation:

- Neurological screen with documentation of **ONE** of the following:

  - Neurological exam normal by history and physical exam
  - Neurological exam with positive symptoms/findings and **ONE** of the following:

    - Normal cytology by LP
    - Abnormal cytology by LP and CNS disease treated

Follicular Lymphoma:

- HDC with autologous HCT or HDC with allogeneic HCT using a myeloablative conditioning regimen for an individual with follicular lymphoma is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Pretransplantation evaluation criteria above
  2. **ANY** of the following:

     - As salvage therapy for individuals who do not achieve complete remission after first-line treatment (induction) with a full course of standard-dose chemotherapy
     - To achieve or consolidate complete remission for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has undergone transformation to a higher grade.

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

Follicular Lymphoma: (cont.)

- If above criteria not met, HDC with autologous HCT or HDC with allogeneic HCT using a myeloablative conditioning regimen for an individual with follicular lymphoma is considered ***experimental or investigational***[2] based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

- Nonmyeloablative reduced-intensity conditioning (RIC) with allogeneic HCT for NHL (all subtypes) for an individual who meets criteria for allogeneic HCT but is medically unable to tolerate HDC is considered ***medically necessary***.

- Tandem HDC with autologous and/or allogeneic HCT for an individual with follicular lymphoma is considered ***experimental or investigational***[2] based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

Mantle Cell Lymphoma:

- HDC with allogeneic HCT for an individual with mantle cell lymphoma is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Pretransplantation evaluation and pretransplantation neurological evaluation criteria above
  2. **ANY** of the following:

     - 1st complete remission but at high risk of relapse
     - 1st complete remission not achieved
     - Relapsed lymphoma
     - Relapse with transformation
     - Salvage therapy

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS (cont.)

Criteria: (cont.)

Mantle Cell Lymphoma: (cont.)

- HDC with autologous HCT for an individual with mantle cell lymphoma is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Pretransplantation evaluation and pretransplantation neurological evaluation criteria above
  2. **ANY** of the following:

     - 1st complete remission but at high risk of relapse
     - 1st complete remission not achieved
     - Relapsed lymphoma
     - Relapse with transformation

- Nonmyeloablative reduced-intensity conditioning (RIC) with allogeneic HCT for NHL (all subtypes) for an individual who meets criteria for allogeneic HCT but is medically unable to tolerate HDC is considered ***medically necessary***.

- HCT for treatment of an individual with mantle cell lymphoma for all indications not previously listed or if above criteria not met is considered ***experimental or investigational***[2] based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

  These treatments include, *but are not limited to:*

  - HDC with autologous HCT for mantle cell lymphoma salvage therapy
  - HDC with allogeneic or autologous HCT for initial therapy
  - HDC with allogeneic HCT for mantle cell relapse after a prior course of HDC with autologous HCT if autologous HCT was less than 6 months ago
  - Tandem HDC with autologous and/or allogeneic HCT

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

Peripheral T-Cell Lymphoma (including NK-Cell Neoplasms and T-Cell Neoplasms):

- HDC with autologous HCT for an individual with peripheral T-cell lymphoma is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Pretransplantation evaluation criteria and neurological evaluation criteria above
  2. **ANY** of the following:

     - 1st complete remission but at high risk of relapse
     - 1st complete remission not achieved
     - Salvage therapy

- HDC with allogeneic HCT for salvage therapy for an individual with peripheral T-cell lymphoma is considered ***medically necessary*** with documentation of pretransplantation evaluation criteria and neurological evaluation criteria above.

- Nonmyeloablative reduced-intensity conditioning (RIC) with allogeneic HCT for NHL (all subtypes) for individual who meets criteria for allogeneic HCT but is medically unable to tolerate HDC is considered ***medically necessary***.

- HCT for treatment of an individual with peripheral T- cell lymphoma for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational***[2] based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

  These treatments include, *but are not limited to*:

  - HDC with allogeneic HCT to consolidate a first remission
  - Tandem HDC with autologous and/or allogeneic HCT

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

Other Non-Hodgkin Lymphoma Aggressive Subtypes[3]:

- HDC with allogeneic or autologous HCT for an individual with other non-Hodgkin Lymphoma aggressive subtypes is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Pretransplantation evaluation criteria above
  2. **ANY** of the following:

     - 1st complete or partial remission but at intermediate/high risk of relapse
     - 1st complete or partial remission not achieved
     - Relapsed lymphoma
     - Relapse with transformation

- Nonmyeloablative reduced-intensity conditioning (RIC) with allogeneic HCT for NHL (all subtypes) for individual who meets criteria for allogeneic HCT but is medically unable to tolerate HDC is considered ***medically necessary***.

- The following treatments for an individual with other aggressive subtypes are considered ***experimental or investigational***[2] based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

  These treatments include:

  - HDC with allogeneic or autologous HCT for initial therapy
  - Tandem HDC with autologous and/or allogeneic HCT

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

Other Non-Hodgkin Lymphoma Indolent Subtypes (not otherwise specifically addressed in this guideline) including Cutaneous T-cell lymphoma and Marginal Zone Lymphoma:

- HDC with allogeneic or autologous HCT for an individual with other non-Hodgkin Lymphoma aggressive subtypes is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Pretransplantation evaluation criteria above
  2. **ANY** of the following:

     - 1st complete or partial remission but at intermediate/high risk of relapse
     - 1st complete or partial remission not achieved
     - Relapsed lymphoma
     - Relapse with transformation

- Nonmyeloablative reduced-intensity conditioning (RIC) with allogeneic HCT for NHL (all subtypes) for individual who meets criteria for allogeneic HCT but is medically unable to tolerate HDC is considered ***medically necessary***.

- The following treatments for an individual with other indolent subtypes are considered ***experimental or investigational***[2] based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

  These treatments include:

  - HDC with allogeneic or autologous HCT for initial therapy
  - HDC with allogeneic HCT for relapse after a prior course of HDC with autologous HCT if autologous HCT was less than 6 months ago
  - Tandem HDC with autologous and/or allogeneic HCT for any subtype

[2] Although specific transplantation procedures may be considered experimental or investigational and therefore not eligible for coverage under standard medical benefits, these procedures may be eligible for coverage based upon Arizona Revised Statutes §20-2326 concerning Cancer Clinical Trials.

[3] Other subtypes include Anaplastic Large Cell Lymphoma, Burkitt's Lymphoma and Diffuse Large B Cell Lymphoma.

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

Performance Status Tables:

Eastern Cooperative Oncology Group (ECOG) Score (Also known as Zubrod Score):

0	Asymptomatic. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptomatic, fully ambulatory. Restricted in physically strenuous activity but able to carry out work of a light or sedentary nature.
2	Symptomatic, in bed less than 50% of the day. Capable of all self-care but unable to carry out any work activities.
3	Symptomatic, in bed or chair more than 50% of the day but not bedridden. Capable of only limited self-care.
4	Bedridden. Cannot perform any self-care.
5	Dead

Karnofsky Performance Score:

100%	Able to carry on normal activity, no evidence of disease.
90%	Able to carry on normal activity, minor signs or symptoms of disease.
80%	Normal activity with effort, some signs and symptoms of disease.
70%	Cares for self, unable to carry on normal activity or to work.
60%	Requires occasional assistance from others but able to care for most needs
50%	Requires considerable assistance from others and frequent medical care
40%	Disabled, requires special care and assistance.
30%	Severely disabled, hospitalization indicated, death not imminent.
20%	Very sick, hospitalization indicated, active support treatment necessary.
10%	Moribund
0%	Dead

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Criteria: (cont.)

Lansky Play Score (Also known as Lansky Play - Performance Scale):

100	Fully active, normal.
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly.
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities.
40	Mostly in bed; participates in quiet activities.
30	In bed; needs assistance even for quiet play.
20	Often sleeping; play entirely limited to very passive activities.
10	No play; does not get out of bed.
0	Unresponsive

Resources:

Literature reviewed 10/24/17. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 04/30/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.

1. 8.01.20 BCBS Association Medical Policy Reference Manual. Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas. Re-issue date 09/14/2017, issue date 12/01/1999.

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh ílínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة .للتحدث مع مترجم اتصل ب 877-475-4799.

HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN-LYMPHOMAS (cont.)

<u>Multi-Language Interpreter Services</u>: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:
اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و
اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
[تماس حاصل نمایید.

Assyrian:
[illegible] Blue Cross Blue Shield of Arizona [illegible]
[illegible] 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona
คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799