Regence

Medical Policy Manual Transplant, Policy No. 45.28

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

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Next Review: January 2025
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic hematopoietic cell transplant (HCT) using a myeloablative conditioning regimen may be considered **medically necessary** to treat any one of the following:

1. Poor- to intermediate-risk AML in first complete remission (CR1) (i.e., abnormal cytogenetics; see Policy Guidelines for information on risk stratification)
2. Primary refractory AML for which intensified induction chemotherapy is planned to achieve complete remission (i.e., leukemia that does not achieve a complete remission after conventional-dose chemotherapy)
3. Relapsed AML for which intensified induction chemotherapy is planned to achieve second complete remission (CR2) or beyond
4. Relapsed AML following prior autologous HCT in patients who are medically able to tolerate intensified induction chemotherapy, and for whom that chemotherapy is planned to achieve complete remission

II. Allogeneic HCT using a reduced-intensity conditioning regimen may be considered **medically necessary** as a treatment of AML in patients who are in complete marrow and extramedullary remission (CR1 and beyond), and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen (see Policy Guidelines).

III. Autologous HCT may be considered **medically necessary** to treat AML for any indication other than as first line treatment (e.g., first or second remission or relapsed AML if responsive to intensified induction chemotherapy).

IV. Hematopoietic cell transplantation is considered **investigational** to treat AML for any other circumstance other than those listed above, including but not limited to an autologous HCT as first line treatment.

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

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

RISK STRATIFICATION

The National Comprehensive Cancer Network (NCCN) preferred risk stratification for Non-APL AML is based on large datasets from consortia group, multi-center trials. NCCN algorithms for individual patient prognosis and management guidance are based on the following table:[1]

Table 1. European LeukemiaNET Risk Stratification by Genetics in Non-APL

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;22.1); *RUNX1-RUNX1T1* inv(16)(p13.q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK::NUP214* t(v;11q23.3)/*KMT2A*-rearranged t(9;22)(q34.1;q11.2)/*BCR-ABL1* t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* inv(3)(q21.3q26) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)*

Risk Category	Genetic Abnormality
	t(3q26.2;v)/*MECOM(EVI1)*-rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Mutated *ASXL1, BCOR, EXH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* Mutated *TP53*

Autologous HCT is used for consolidation treatment of intermediate- to poor-risk disease in complete remission, among patients for whom a suitable donor is not available. Favorable-risk AML often responds well to chemotherapy with prolonged remission if not cure.

REDUCED INTENSITY CONDITIONING

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HCT. These include those whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient whose disease relapses following a conventional myeloablative allogeneic HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HCT if a complete remission could be re-induced with chemotherapy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION

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

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

CROSS REFERENCES

1. Genetic Testing for Myeloid Neoplasms and Leukemia, Genetic Testing, Policy No. 59
2. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
3. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
4. Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Transplant, Policy No. 45.24

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives

HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called “graft versus tumor” effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II gene loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional (“classical”) practice of *allogeneic* HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of *autologous* HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to be delivered at doses that could otherwise not be given without stem cells, which are infused to “rescue” hematopoiesis after high dose therapy. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the conditioning with lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell

engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term “reduced-intensity conditioning” (RIC) will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) (sometimes called “acute nonlymphocytic leukemia” [ANLL]) refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. AML is characterized by proliferation of myeloblasts, coupled with low production of mature red blood cells, platelets, and often non-lymphocytic white blood cells (granulocytes, monocytes). Clinical signs and symptoms are associated with neutropenia, thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. About 13,000 new cases are diagnosed annually.

The pathogenesis of AML is unclear. It can be subdivided according to resemblance to different subtypes of normal myeloid precursors using the French-American-British (FAB) classification. This system classifies leukemias from M0–M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization (WHO) subsequently incorporated clinical, immunophenotypic and a wide variety of cytogenetic abnormalities that occur in 50% to 60% of AML cases into a classification system that can be used to guide treatment according to prognostic risk categories (see Policy Guidelines). In 2016, the WHO system updated subcategories of AML including: 1) AML with recurrent genetic abnormalities; 2) AML with myelodysplasia-related changes; 3) therapy-related AML myeloid neoplasms; 4) AML not otherwise specified (NOS); 5) myeloid sarcoma; and 5) myeloid proliferations related to Down syndrome.

Molecular studies have identified a number of genetic abnormalities that also can be used to guide prognosis and management of AML. Cytogenetically normal AML (CN-AML) is the largest defined subgroup of AML, comprising about 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic mutations that affect outcomes, of which six have been identified. The *FLT3* gene that encodes FMS-like receptor tyrosine kinase (TK) 3, a growth factor active in hematopoiesis, is mutated in 33%–49% of CN-AML cases; among those, 28%–33% consist of internal tandem duplications (ITD), 5%–14% are missense mutations in exon 20 of the TK activation loop, and the rest are point mutations in the juxtamembrane domain. All *FLT3* mutations result in a constitutively activated protein, and confer a poor prognosis. Several pharmaceutical agents that inhibit the *FLT3* TK are under investigation.

Complete remissions can be achieved initially using combination chemotherapy in up to 80% of AML patients. However, the high incidence of relapse has prompted research into a variety of post-remission strategies using either allogeneic or autologous HCT.

EVIDENCE SUMMARY

Hematopoietic cell transplantation (HCT) has been investigated as consolidation therapy for patients whose disease enters complete remission following initial induction treatment, or as

salvage therapy in patients who experience disease relapse or have disease that is refractory to induction chemotherapy.

CONSOLIDATION THERAPY IN REMISSION

Allogeneic HCT

In order to understand the impact of allogeneic HCT as consolidation therapy in remission, well-designed randomized controlled trials (RCTs) are preferred. However, these are often difficult to perform given the populations involved. Therefore, this evidence section includes meta-analyses of nonrandomized studies and larger nonrandomized studies in addition to RCTs. Systematic Reviews

Bornhäuser (2023) conducted an open-label, 2-arm, multicenter RCT in Germany to assess the ideal post-remission strategy in intermediate-risk AML in CR1.[2] Adults with AML (age 18 to 60 years) in CR1 or CR with incomplete blood cell count recovery after conventional induction therapy who had availability of a human leukocyte antigen-matched sibling or unrelated donor were included. Subjects were randomized 1:1 to receive allo-HCT or high-dose cytarabine (HiDAC) for consolidation and salvage HCT only in cases of relapse. The primary outcomes was overall survival (OS) and disease free survival (DFS). Incidence of relapse, treatment-related mortality, and quality of life measures according to the Medical Outcomes Study 36-Item Short-Form Health Survey were secondary outcomes. One hundred forty-three patients (mean age, 48.2 years, standard deviation, 9.8 years; 57% male) with AML were randomized. At 2 years, the probability of survival was 74% (95% CI, 62% to 83%) after primary allo-HCT and 84% (95% CI, 73% to 92%) after HiDAC (p=.22). Disease-free survival at 2 years was 69% (95% CI, 57% to 80%) after HCT compared with 40% (95% CI, 28% to 53%) after HiDAC (p=.001). The cumulative incidence of relapse at 2 years with allo-HCT was 20% (95% CI, 13% to 31%) compared with 58% (95% CI, 47% to 71%; p<.001) with HiDAC and nonrelapse mortality after allo-HCT was 9% (95% CI, 5% to 19%) versus 2% (95% CI, 0% to 11%) after HiDAC (p=.005). All 41 participants who relapsed after HiDAC proceeded to receive allo-HCT. There were no differences in quality of life measures between groups. Of note, this trial was closed earlier than anticipated due to slow patient accrual, which was a limitation. Additional limitations included the lack of stratification based on minimal residual disease (MRD) and the use of a cytogenetic classifier at trial initiation (2012) which led to inclusion of some favorable-risk patients, which current guidelines would not recommend allo-HCT in CR1. In conclusion, primary allo-HCT during CR1 was not associated with superior OS compared to HiDAC in adults with intermediate-risk AML <60 years, although some secondary endpoints had promising results and were hypothesis generating.

Kharfan-Dabaja (2022) published a systematic review to assess the totality of evidence on the role of a second allo-HCT in patients with AML.[3] Clinical outcome data relating to benefits (CR, overall survival [OS], and progression-free/disease-free survival [PFS/DFS]) and harms (acute and chronic graft-versus-host disease, non-relapse mortality [NRM], and relapse) were included in this study. A second allo-HCT resulted in pooled CR, OS, PFS/DFS, NRM and relapse rates of 67%, 34%, 30%, 27%, and 51%, respectively. OS was 2-fold higher when the second allo-HCT was performed in CR (38% versus 17%) and 3-fold higher in patients who had a later relapse from the first allo-HCT (34% versus 10%). The authors reported that the procedure appears to be more effective when performed in CR and in patients who had a later relapse from the first allo-HCT. But, even when receiving the second allo-HCT in CR, the

relapse rates exceeded 50%. This analysis was limited to patients receiving a second allo-HCT for the sole purpose of treating AML relapse and must be analyzed with caution.

Masetti (2022) published an up-to-date meta-analysis of studies comparing allo-HSCT in first complete remission (CR1) with chemotherapy alone as a post-remission treatment in high-risk pediatric AML.[4] The literature search strategy identified 10 cohorts from 9 studies performing as-treated analysis. The quantitative synthesis showed improved overall survival (OS) (relative risk, 1.15; 95% confidence interval [CI], 1.06-1.24; P = 0.0006) and disease-free survival (relative risk, 1.31; 95% CI, 1.17-1.47; P = 0.0001) in the allo-HSCT group, with increased relapse rate in the chemotherapy group (relative risk, 1.26; 95% CI, 1.07-1.49; P = 0.006. The authors report that further research should focus on individualizing allo-HSCT indications based on molecular stratification and MRD monitoring.

Shahzad (2022) published a systematic review to evaluate outcomes after allogeneic hematopoietic stem cell transplantation (HSCT) in TP53-mutated acute myeloid leukemia (AML) for 279 patients from eight studies.[5] This study reported a pooled 2-year overall survival of 29.7% (95% CI 0.17-0.43, n = 82/248). The pooled relapse rate was 61.4% (95% CI 0.41-0.79, n = 139/247) at a median follow-up time of 2 (0.26-3) years. Three-year progression-free survival and non-relapse mortality were reported by one study as 7.5% and 32.5%, respectively. The authors report that the outcomes of HSCT for TP53-mutated AML are poor; however, HSCT confers a survival advantage as compared to non-transplant palliative therapies.

A 2015 meta-analysis examined prospective trials of adult patients with intermediate risk AML in first complete remission (CR1) who underwent either allogeneic or autologous HSCT.[6] The analysis included nine prospective, controlled studies that enrolled a total of 1950 patients between the years 1987 and 2011, with study sizes ranging from 32 patients to 713. Allogeneic HSCT was associated with significantly better relapse-free survival (RFS), overall survival (OS), and relapse rate (RR) than autologous HSCT and/or chemotherapy (hazard ratio [HR],0.684; 95% confidence interval [CI], 0.48 to 0.95; HR=0.76; 95% CI 0.61 to 0.95; HR=0.58; 95% CI 0.45 to 0.75, respectively). Treatment related mortality (TRM) was significantly higher following allogeneic HSCT than autologous HSCT (HR=3.09; 95% CI 1.38 to 6.92). However, a subgroup analysis showed no OS benefit for allogeneic HSCT over autologous HSCT (HR=0.99; 95% CI 0.70 to 1.39).

A meta-analysis of allogeneic HSCT in patients with AML in first complete remission (CR1) pooled data from five studies that included a total of 3,100 patients.[7] Among those patients, 1,151 received allogeneic HSCT, and 1,949 were given alternative therapies including chemotherapy and autologous HSCT. All of the studies employed natural randomization based on donor availability, and an intention-to-treat analysis, with overall survival (OS) and disease-free survival (DFS) as outcomes of interest. This analysis showed a significant advantage of allogeneic HSCT in terms of OS for the entire cohort (fixed-effects model HR=1.17 95% CI 1.06 to 1.30; p=0.003; random-effects model HR=1.15, 95% CI 1.01 to 1.32; p=0.037) even though none of the individual studies did so. Meta-regression analysis showed that the effect of allogeneic HSCT on OS differed depending on the cytogenetic risk groups of patients, suggesting significant benefit for poor-risk patients (HR=1.39, 95% CI not reported), indeterminate benefit for intermediate-risk cases, and no benefit in better-risk patients compared to alternative approaches. The authors caution that the compiled studies used different definitions of risk categories (e.g., SWOG, MRC, EORTC/GIMEMA), but examination shows cytogenetic categories in those definitions are very similar to the recent guidelines from

the NCCN outlined in the Policy Guidelines.[8] Furthermore, the statistical power of the meta-regression analysis is limited by small numbers of cases. However, the results of this meta-analysis are supported in general by data compiled in other reviews.[9-12] Together, the body of evidence in the context of clinical review of this policy clearly supports the conclusion that myeloablative allogeneic HSCT may be considered medically necessary for patients with poor- to intermediate-risk AML in CR1. Because better-risk AML typically responds well to conventional induction chemotherapy, allogeneic HSCT may be reserved for treatment of relapsed disease in these patients.

Evidence from the meta-analysis cited here suggests patients with cytogenetically defined better-prognosis disease may not realize a significant survival benefit with allogeneic HSCT in CR1 that outweighs the risk of associated morbidity and non-relapse mortality (NRM). However, there is considerable genotypic heterogeneity within the three World Health Organization (WHO) cytogenetic prognostic groups that complicates generalization of clinical results based only on cytogenetics.[13] For example, patients with better-prognosis disease (for example, core-binding factor AML) based on cytogenetics, and a mutation in the *c-Kit* gene of leukemic blast cells, do just as poorly with postremission standard chemotherapy as patients with cytogenetically poor-risk AML.[14] Similarly, individuals with cytogenetically normal AML (intermediate-prognosis disease) can be subcategorized into groups with better or worse prognosis based on the mutational status of the nucleophosmin gene (*NPM1*) and the *FLT3* gene (defined above in the Policy Description). Thus, patients with mutations in *NPM1* but without *FLT3*-ITD have postremission outcomes with standard chemotherapy that are similar to those with better-prognosis cytogenetics; in contrast, patients with any other combination of mutations in those genes have outcomes similar to those with poor-prognosis cytogenetics.[15] These examples highlight the rapidly growing body of evidence for genetic mutations as additional predictors of prognosis and differential disease response to different treatments. It follows that because the earlier clinical trials compiled in the meta-analysis described here did not account for genotypic differences that affect prognosis and alter outcomes, it is difficult to use the primary trial results to draw conclusions concerning the role of allogeneic HCT in different patient risk groups.

A second meta-analysis incorporated data from 24 trials involving a total of 6,007 patients who underwent allogeneic HSCT in first complete remission [CR1].[16] Among the total, 3,638 patients were stratified and analyzed according to cytogenetic risk (547 good-, 2,499 intermediate-, 592 poor-risk AML, respectively) using a fixed-effects model. Compared with either autologous HSCT or additional consolidation chemotherapy, the HR for OS among poor-risk patients across 14 trials was 0.73 (95% CI 0.59 to 0.90; p<0.01); among intermediate-risk patients across 14 trials, the HR for OS was 0.83 (95% CI 0.74 to 0.93; p<0.01); among good-risk patients across 16 trials, the HR for OS was 1.07 (95% CI 0.83 to 1.38; p=0.59). Inter-study heterogeneity was not significant in any of these analyses. Results for DFS were very similar to those for OS in this analysis. These results concur with those from the previously cited meta-analysis and the current Policy Statements for use of allogeneic HCT as consolidation therapy for AML.

Nonrandomized Studies

In 2017, Heidrich conducted retrospective analyses of subgroups from two prospective clinical trials, including 497 patients with intermediate-risk AML who did not present with *NPM1*, *CEBPA*, or *FLT3* internal tandem duplication (ITD) variants.[17] During the initial analysis (donor vs no-donor), RFS rates were better for patients who had an available sibling donor (n=83)

than for those who lacked a matched sibling donor (49% vs 26%; HR=0.5; 95% CI 0.3 to 0.9; p=0.02); a similar improvement was seen for OS, although not statistically significant (p=0.08). The authors also conducted a time-dependent multivariate analysis to account for the significantly longer time-from-CR1 observed in patients treated with allo-HCT (median, 115 days) compared with those treated with postremission chemotherapy (median, 78 days; p<0.001). Rates of OS after five years were superior for the group who received allo-HCT than for those receiving chemotherapy (OS, 66% vs 46%, respectively; HR=0.58; 95% CI 0.37 to 0.9; p=0.02), as were rates of RFS (five-year RFS, 55% vs 31%; HR=0.51; 95% CI 0.34 to 0.76; p=0.001). The investigators acknowledged that 38% of the group assigned to post-remission chemotherapy received allo-HCT following a relapse, which might have contributed to a crossover effect.

In 2017, Canaani published a retrospective analysis of 1,275 patients who underwent HCT; of these, 918 patients had normal white blood cell (WBC) counts, and the rest presented with abnormally high WBC (hyperleukocytosis).[18] For 159 patients in the latter group, WBC counts were between 50,000 and 100,000/µL; for 198 patients, WBC counts were greater than 100,000. By comparing endpoints such as relapse incidence, leukemia-free survival, nonrelapse mortality, and the occurrence of acute or chronic graft-versus-host disease (GVHD) between groups, the authors evaluated hyperleukocytosis as a potential prognostic indicator of outcomes following transplantation. At baseline, patients in the intermediate- and high-WBC groups had younger median ages (49.1 years and 48.8 years, respectively) than patients without hyperleukocytosis (median age, 52.2 years); additionally, patients with high WBC were associated with the presence of FLT3-ITD and NPM1 variants (p<0.001), and there were significant differences between groups regarding cytogenetic risk category (p<0.001) and the choice of conditioning regimen, whether myeloablative or reduced-intensity (p=0.02). In multivariate analysis, patients with hyperleukocytoses (intermediate and high WBC) were more likely to experience relapse than patients with less than 50,000/µL WBC (29% and 30% vs 22%, respectively); the HR was 1.55 (95% CI 1.14 to 2.12; p=0.004). Negative outcomes were again linked to patients with hyperleukocytosis for leukemia-free survival and OS, which were favorable for non-hyperleukocytosis patients (respective HRs were as follows: 1.38 [95% CI 1.07 to 1.78], p=0.013; and 1.4 [95% CI 1.07 to 1.87], p=0.013). Such findings were statistically significant when different types of transplantation sources (a matched sibling vs an unrelated donor) were accounted for, leading investigators to recommend the use of hyperleukocytosis as a predictor of clinical outcomes following allogeneic HCT.

A 2014 study by Stelljes compared the outcome of 185 matched pairs of patients from a large multicenter clinical trial (AMLCG99).[19] Patients younger than 60 years who underwent allogeneic HSCT in CR1 were matched to patients who received conventional postremission chemotherapy. The main matching criteria were AML type, cytogenetic risk group, patient age, and time inCR1. In the overall pairwise-compared AML population, the projected seven-year OS rate was 58% for the allogeneic HSCT and 46% for the conventional postremission treatment group (p=0.037; log-rank test). Relapse-free survival was 52% in the allogeneic HSCT group compared with 33% in the control group (p<0.001). OS was significantly better for allogeneic HSCT in patient subgroups with nonfavorable chromosomal aberrations, patients older than 45 years, and patients with secondary AML or high-risk myelodysplastic syndrome. For the entire patient cohort, postremission therapy was an independent factor for OS (HR=0.66; 95% CI, 0.49 to 0.89 for allogeneic HSCT versus conventional chemotherapy), among age, cytogenetics, and bone marrow blasts after the first induction cycle.

Autologous HCT

Systematic Reviews

A 2004 meta-analysis examined survival outcomes of autologous HSCT in CR1 versus standard chemotherapy or no further treatment in AML patients aged 15 to 55 years.[20] Two types of studies were eligible: 1) prospective cohort studies in which patients with an available sibling donor were offered allogeneic HSCT (biologic randomization) with random assignment of all others to autologous HSCT or chemotherapy (or no further treatment); and 2) randomized trials that compared autologous HSCT with chemotherapy in all patients. Among a total of 4,058 patients included in six studies, 2,989 (74%) achieved CR1; 1,044 (26%) were randomly allocated to HSCT (n=524) or chemotherapy (n=520). Of the five studies for which OS data were available, outcomes with autologous HSCT were better in three, and outcomes with chemotherapy were better in two. None of the differences reached statistical significance, nor did the pooled estimate reach statistical significance (fixed-effects model survival probability ratio=1.01; 95% CI 0.89 to 1.15, p=0.86). In all six studies, disease-free survival (DFS) was numerically superior with autologous HSCT compared to chemotherapy (or no further treatment), but only one reported a statistically significant DFS probability associated with autologous HSCT. However, the pooled estimate for DFS showed a statistically significant probability in favor of autologous HSCT at 48 months post-transplant (fixed-effects model survival probability ratio=1.24, 95% CI 1.06 to 1.44, p=0.006).

There are several possible reasons this meta-analysis did not demonstrate a statistically significant OS advantage for autologous HSCT compared to chemotherapy given the significant estimate for DFS benefit. First, the pooled data showed a 6.45% greater NRM rate in autologous HSCT recipients compared to chemotherapy recipients. Second, 14% of chemotherapy recipients whose disease relapsed ultimately achieved a sustained second remission after undergoing an allogeneic or autologous HSCT. The intent-to-treat analysis in the studies, which included the latter cases in the chemotherapy group, may have inappropriately inflated overall survival rates favoring chemotherapy. Furthermore, this analysis did not take into account potential effects of cytogenetic or molecular genetic differences among patients that are known to affect response to treatment. Finally, the dataset comprised studies performed between 1984 and 1995, during which transplant protocols and patient management evolved significantly, particularly compared to current care. Nonetheless, the evidence suggests the use of autologous HCT to treat AML in CR1 is feasible and offers improved survival and a chance for cure compared to postremission chemotherapy in patients who lack a suitable stem-cell donor.

A second meta-analysis published in 2010 evaluated autologous HSCT versus further chemotherapy or no further treatment for AML in CR1.[21] A total of 9 randomized trials involving 1,104 adults who underwent autologous HSCT and 1,118 who received additional chemotherapy or no additional treatment were identified. The analyses suggest that autologous HSCT in CR1 was associated with statistically significant reduction of relapse risk (RR=0.56, 95% CI 0.44 to 0.71, p=0.0004) and significant improvement in DFS (HR=0.89, 95% CI 0.80 to 0.98), but at the cost of significantly increased NRM (RR=1.90, 95% CI 0.72 to 0.87, p=0.0002). There were more deaths during the first remission among patients assigned to autologous HSCT than among the chemotherapy recipients or further untreated patients. As a consequence of increased NRM, no statistical difference in OS (HR = 1.05, 95% CI 0.91 to 1.21) was associated with the use of autologous HSCT compared to further chemotherapy or no further therapy. These results were concordant with those of the earlier meta-analysis cited above.

Randomized Controlled Trials

In 2020, Yegin published a randomized trial comparing autologous HCT versus cytarabine-based chemotherapy for AML patients in first complete remission who were not eligible for allogeneic HCT.[22] A total of 101 patients were included, 70 of whom received consolidation chemotherapy and 31 of whom received autologous HCT. Median follow-up was 915 days. The difference between groups in probability of leukemia-free survival was statistically significant, with 43% probably in the auto-HCT group and 4.8% in the chemotherapy group (p=0.008). Differences in five-year relapse incidence and probability of overall survival between groups were not statistically significant. Five-year relapse incidence was 65% and 46% in the chemotherapy and auto-HCT groups, respectively (p>0.05), and probability of overall survival at the last follow-up was 79.2% and 38.8% in the chemotherapy and auto-HCT groups, respectively (p=0.054). According to a multivariate analysis, there was a significant predictive impact of cytogenetic risk status on overall survival (p=0.002, HR 2.824; 95% CI 1.445 to 5.521).

Miyamoto (2018) reported results of a randomized, multicenter phase 3 trial conducted in 24 centers in Japan from 2003 to 2011 that compared autologous HCT versus high-dose cytarabine (HiDAC) consolidation as post-remission therapy in AML.[23] This trial enrolled 240 patients between 15 and 64 years of age with newly diagnosed favorable- and intermediate-risk AML, and Eastern Cooperative Oncology Group (ECOG) performance status of <3; 87 of those who achieved CR1 were randomized to autologous HCT or HiDAC. The study was powered to include 122 patients with five years of accrual and three years of post-accrual follow-up to detect a difference in DFS at three years of 40% versus 65%. Approximately one-third of the patients had favorable risk AML and the remaining two-thirds had intermediate-risk AML. The median age was 48 years. Median follow-up was approximately 4.5 to 5 years. Three-year DFS rate was 41% (95% CI, 27 to 55) in the HiDAC group and 55% (95% CI, 38 to 68) in the autologous HCT group (p=0.25). Three-year OS was 77% (95% CI, 61 to 87) versus 68% (95% CI, 52 to 80) (p=0.67). Cumulative incidence of relapse was 54% versus 41% (p=0.22). There were no differences between the HiDAC and autologous HCT groups in the incidence of liver or renal dysfunction. The incidence of life-threatening infectious complications (p=0.003) and mucositis/diarrhea (p=0.002) was significantly higher in the autologous HCT group.

A prospective, randomized phase III trial by Vellenga (2011) compared autologous HSCT with intensive consolidation chemotherapy among patients (16 to 60 years old) with newly diagnosed AML of similar risk profiles in complete remission (CR1).[24] Patients in CR1 after two cycles of intensive chemotherapy (etoposide and mitoxantrone), who were not candidates for allogeneic HSCT, were randomly allocated between a third consolidation cycle of the same chemotherapy (n=259) or autologous HSCT (n=258). The HSCT group showed a trend toward superior relapse-free survival, the primary outcome, compared to chemotherapy recipients (38% vs. 29%, respectively at five years, p=0.065, 95% CI 0.66 to 1.1). HSCT patients had a lower relapse rate at five years compared to chemotherapy recipients (58% vs. 70%, respectively, p=0.02). Overall survival did not differ between HSCT and chemotherapy recipients, respectively (44% vs. 41%, p=0.86). NRM was more frequent in the autologous HSCT group than in the chemotherapy consolidation group (4% vs. 1%, respectively, p=0.02). Despite this difference in NRM, the relative equality of OS rates was attributed by the investigators to a higher proportion of successful salvage treatments – second-line chemotherapy, autologous or allogeneic HSCT - in the chemotherapy consolidation recipients that were not available to the autologous HSCT patients. This large study shows an advantage

for post-remission autologous HSCT in reducing relapse, but similar OS rates secondary to better salvage of chemotherapy consolidated patients.

PRIMARY REFRACTORY AML

Conventional-dose induction chemotherapy will not produce remission in 20% to 40% of patients with AML, connoting refractory AML.[8] An allogeneic HCT using a matched related donor (MRD) or matched unrelated donor (MUD) represents the only potentially curative option for these individuals. In several retrospective studies OS rates have ranged from 13% at five years to 39% at three years, although this procedure is accompanied by NRM rates of 25% to 62% in this setting.[9, 25] For patients who lack a suitable donor (MRD or MUD), alternative treatments include salvage chemotherapy with high-dose cytarabine or etoposide-based regimens, monoclonal antibodies (e.g., gemtuzumab ozogamicin), multidrug resistance modulators, and other investigational agents such as *FLT3* antagonists.[26] Because it is likely that stem-cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, autologous HCT has no role in patients who fail induction therapy.

RELAPSED AML

Most patients with AML will experience disease relapse after attaining a first complete remission.[8] Conventional chemotherapy is not curative in most patients following disease relapse, even if a second complete remission (CR2) can be achieved. Retrospective data compiled from 667 of 1,540 patients entered in three phase III trials suggest allogeneic HSCT in CR2 can produce five-year OS rates of 26% to 88%, depending on cytogenetic risk stratification.[27] Because reinduction chemotherapy treatment may be associated with substantial morbidity and mortality, patients whose disease has relapsed and who have a suitable donor may proceed directly to allogeneic HCT.

In patients without an allogeneic donor, or those who are not candidates for allogeneic HSCT due to age or other factors, autologous HSCT may achieve prolonged DFS in 9% to 55% of patients in CR2 depending on risk category.[28, 29] However, because it is likely that stem-cell preparations will be contaminated with malignant cells in patients whose disease is not in remission, and it is often difficult to achieve CR2 in these patients, autologous HSCT in this setting is usually limited to individuals who have a sufficient stem-cell preparation remaining from collection in CR1.[28]

Allogeneic HSCT is often performed as salvage for patients who have relapsed after conventional chemotherapy or autologous HSCT.[28] The decision to attempt reinduction or proceed directly to allogeneic HSCT is based on the availability of a suitable stem-cell donor and the likelihood of achieving a remission, the latter being a function of cytogenetic risk group, duration of CR1, and the patient's health status. Registry data show DFS rates of 44% using sibling allografts and 30% with MUD allografts at five years for patients transplanted in CR2, and DFS of 35%–40% using sibling transplants and 10% with MUD transplants for patients with induction failure or in relapse following HSCT.[28]

REDUCED-INTENSITY ALLOGENEIC HCT

A growing body of evidence is accruing from clinical studies of RIC with allogeneic HSCT for AML.[30-37] Overall, these data suggest that long-term remissions (two to four years) can be achieved in patients with AML who because of age or underlying comorbidities would not be

candidates for myeloablative conditioning regimens. Meta-analyses, RCTs, and larger non-randomized studies are included below.

Systematic Reviews

Song (2021) evaluated the efficacy of RIC followed by allo-HCT in patients with AML and myelodysplastic syndrome via a meta-analysis of six RCTs (n=1413).[38] The RCTs compared RIC to MAC before first allo-HCT in patients with AML in complete remission or myelodysplastic syndrome. The primary endpoint was OS. Results revealed that OS was not significantly different between RIC and MAC (HR, 0.95; 95% CI 0.64 to 1.4; p=0.80). The cumulative incidence of relapse was also similar between the groups (HR, 1.18; 95% CI, 0.88 to 1.49; p=0.28). Nonrelapse mortality was significantly improved with RIC as compared to total body irradiation/busulfan-based MAC (HR, 0.53; 95% CI 0.36 to 0.8; p=0.002); however, treosulfan-based MAC significantly reduced nonrelapse mortality as compared to RIC (HR, 1.67; 95% CI 1.02 to 2.72; p=0.04). Reduced-intensity conditioning was associated with a trend of increasing graft failure (p=0.06); however, graft failure in both arms was rare. The authors concluded that RIC is recommended as an adequate option of preparative treatment before allo-HCT for patients with AML in complete remission or myelodysplastic syndrome. Limitations of the meta-analysis included the small number of included clinical trials, significant heterogeneity between included studies for some outcomes, and lack of blinding in some studies.

A 2014 meta-analysis compared reduced-intensity and myeloablative conditioning regimens for allogeneic HSCT in patients with AML.[39] The analysis included 23 clinical trials that were reported between 1990 and 2013, with approximately 15,000 adult patients. Eleven studies included AML and myelodysplastic syndrome (MDS) and five included AML only. A subanalysis from 13 trials in patients with AML or MDS showed that OS was comparable in patients who received either reduced-intensity or myeloablative transplants, and the two-year or less and two-year or greater OS rates were equivalent between the two groups. The two- to six-year PFS, non-relapse mortality, and acute and chronic graft-versus-host disease (GVHD) rates were reduced after RIC-HCT, but relapse rate was increased. Similar outcomes were observed regardless of disease status at transplantation. Among the RIC-HSCT recipients, survival rates were superior if patients were in complete remission at transplantation.

Randomized Controlled Trials

Lubbert (2023) conducted a randomized controlled phase III trial comparing reduced intensity therapy using decitabine monotherapy to standard intensive chemotherapy (daunorubicin and cytarabine) prior to allogeneic HCT.[40] The study included 606 patients from 54 European hospitals. All subjects were aged 60 years and older and were newly diagnosed with AML. Of 302 patients who were randomized to decitabine, 122 (40%) had HCT. In the standard chemotherapy group, 298 subjects received induction therapy, and 118 (39%) had HCT. After a median follow-up of four years, the OS was 26% in the decitabine group and 30% in the standard chemotherapy group (p=0.68). OS was not significantly different despite a lower rate of CR in the decitabine group compared to the standard chemotherapy group (75% vs. 91%). Grade 3-5 adverse events were fewer in the decitabine group (84%) compared to the standard chemotherapy group (94%). The authors concluded that reduced intensity conditioning with decitabine did not affect OS and was better tolerated.

Beelen (2022) published a randomized control trial designed to compare event-free survival (EFS) after treosulfan-based conditioning with a widely applied reduced-intensity conditioning

(RIC) busulfan regimen in older or comorbid patients with AML or myelodysplastic syndrome (MDS) undergoing allogeneic hematopoietic cell transplantation (HCT).[41] Patients presenting HCT-specific comorbidity index >2 or aged ≥50 years were randomly assigned (1:1) to intravenous (IV) fludarabine with either treosulfan (30 g/m2 IV) or busulfan (6.4 mg/kg IV) after stratification by disease risk group, donor type, and participating institution. The primary endpoint was EFS with disease recurrence, graft failure, or death from any cause as events. EFS of patients (median age 60 years) was superior after treosulfan compared to RIC busulfan: 36-months-EFS rate 59.5% (95% CI, 52.2-66.1) vs. 49.7% (95% CI, 43.3-55.7) with a hazard ratio (HR) of 0.64 (95% CI, 0.49-0.84), p = 0.0006. Likewise, overall survival (OS) with treosulfan was superior compared to busulfan: 36-month-OS rate 66.8% vs. 56.3%; HR 0.64 (95% CI, 0.48-0.87), p = 0.0037. Overall, this study indicates that the treosulfan regimen appears particularly suitable for older AML and MDS patients.

A randomized comparative trial (Bornhauser 2012) in matched patient groups compared the net health benefit of allogeneic HSCT with reduced-intensity conditioning (RIC) versus myeloablative conditioning.[42] In this study, patients (age 18-60 years) were randomly assigned to receive either RIC (n=99) of four doses of 2 Gy of total-body irradiation and 150 mg/m^2 fludarabine or standard conditioning (n = 96) of six doses of 2 Gy of total-body irradiation and 120 mg/kg cyclophosphamide. All patients received cyclosporin and methotrexate as prophylaxis against graft-versus-host disease. The primary endpoint was the incidence of non-relapse mortality (NRM) analyzed in the intention-to-treat population. This unblinded trial was stopped early because of slow accrual of patients. The incidence of NRM did not differ between the RIC and standard conditioning groups (cumulative incidence at three years 13% [95% CI 6 to 21] versus 18% [10 to 26]; HR 0.62 [95% CI 0.30 to 1.31], respectively). Relapse cumulative incidence at three years was 28% [95% CI 19 to 38] in the RIC group and 26% [17 to 36]; HR 1.10 [95% CI 0.63 to 1.90]) in the standard conditioning group. Disease-free survival at three years was 58% (95% CI 49 to 70) in the RIC group and 56% (HR 0.85, 95% CI 0.55 to 1.32) in the standard conditioning group. Overall survival at three years was 61% (95% CI 50 to 74) and 58% (47 to 70); HR 0.77 (95% CI 0.48 to 1.25) in the RIC and standard conditioning groups, respectively. No outcomes differed significantly between groups. Grade 3 to 4 of oral mucositis was less common in the RIC group than in the standard conditioning group (50 patients in the reduced-intensity conditioning group vs. 73 patients in the standard conditioning group); the frequency of other side-effects such as GVHD and increased concentrations of bilirubin and creatinine did not differ significantly between groups.

Ringden (2013) published a phase II single-center, randomized toxicity study that compared MAC and RIC in allogeneic HSCT to treat AML.[43] Adult patients 60 years of age or younger with AML were randomly assigned (1:1) to treatment with RIC (n=18) or MAC (n=19) for allogeneic HSCT. A maximum median mucositis grade of 1 was observed in the RIC group compared with 4 in the MAC group (p<0.001). Hemorrhagic cystitis occurred in eight (42%) of the patients in the MAC group and none (0%) in the RIC group (p<0.01). Results of renal and hepatic tests did not differ significantly between the two groups. RIC-treated patients had faster platelet engraftment (p<0.01) and required fewer erythrocyte and platelet transfusions (p<0.001) and less total parenteral nutrition than those treated with MAC (p<0.01). Cytomegalovirus infection was more common in the MAC group (14/19) than in the RIC group (6/18) (p=0.02). Donor chimerism was similar in the two groups with regard to CD19 and CD33, but was delayed for CD3 in the RIC group. Five-year treatment- related morbidity was approximately 11% in both groups, and rates of relapse and survival were not significantly

different. Patients in the MAC group with intermediate cytogenetic AML had a three-year survival of 73%, compared with 90% among those in the RIC group.

Nonrandomized Studies

Solomon (2019) performed a retrospective cohort analysis to compare myeloablative and reduced intensity conditioning for AML (n=818), ALL (n=286), and MDS (n=221).[44] The primary end point was disease-free survival. Data from patients aged 18 to 70 treated at the Center for International Blood and Marrow Transplant Research (over 400 transplant centers worldwide) years received T-cell-replete bone marrow or peripheral blood from a haploidentical relative. An analysis that adjusted for comorbidity score, graft type, and disease risk index found that for younger patients (between the ages of 18 and 54 years), disease-free survival was lower with reduced-intensity regimens in. In older patients (between the ages of 55 and 70), disease-free survival did not differ between conditioning groups. In the younger patients, but not older patients, relapse was higher with reduced-intensity regiments in the adjusted analysis. Non-relapse mortality was not different based on conditioning regimen intensity in younger patients but was lower with reduced-intensity regimens in older patients. Overall survival was not different based on conditioning regimen intensity after adjusting for disease, comorbidity score, CMV seropositivity, and disease risk index. The authors concluded that myeloablative regimens are preferred and reduced-intensity regimens should be reserved for those unable to tolerate myeloablation.

In a 2014 study, Bitan compared outcomes in children with AML who underwent allogeneic HSCT using RIC regimens or myeloablative conditioning regimens.[45] A total of 180 patients were evaluated, 39 who underwent RIC and 141 who received myeloablative regimens. Univariate and multivariate analyses showed no significant differences in the rates of acute and chronic GVHD, leukemia-free survival, and OS between treatment groups. The five-year probabilities of OS with RIC and myeloablative regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were not higher with RIC compared with myeloablative conditioning (MAC) regimens (39% vs 39%; p=0.95), and recipients of MAC regimens were not at higher risk for transplant-related mortality compared with recipients of RIC regimens (16% vs 16%; p=0.73).

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2020, the American Society for Transplantation and Cellular Therapy published expert panel recommendations on the role of hematopoietic cell transplant (HCT) in newly-diagnosed adult acute myeloid leukemia.[46] Recommendations were generated based on findings from a systematic review and graded based on prespecified criteria. Expert panel recommendations regarding allogeneic HCT (allo-HCT) and autologous HCT and the grades of the recommendations are as follows:

- Patients with unfavorable-risk in first remission (CR1) should undergo allo-HCT. (Grade A)
- Patients with intermediate-risk in CR1 should undergo allo-HCT. (Grade B)
- Patients with favorable-risk in CR1 should not undergo allo-HCT. (Grade C)
- The role of secondary mutational abnormalities in selecting a patient for allo-HCT is unclear. (Grade N/A)

- The presence of measurable residual disease at the end of induction therapy should be considered an indication to offer allo-HCT. (Grade C)
- The role of allo-HCT is unclear in patients with induction failure. (Grade N/A)
- Patients with secondary acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)
- Patients with therapy-related acute myeloid leukemia in CR1 should undergo allo-HCT. (Grade D)
- Patients ≥ 60 years in CR1 should undergo allo-HCT. (Grade B).
- Autologous HCT is a good alternative to chemotherapy consolidation in patients who are not eligible for allo-HCT. (Grade B)
- Myeloablative conditioning should be the preferred type of conditioning in patients who are fit for myeloablative conditioning, but reduced-intensity conditioning is an acceptable alternative in unfit patients. (Grade D)

In 2020, the American Society for Transplantation and Cellular Therapy (formerly The American Society for Blood and Marrow Transplantation) published guidelines on indications for autologous HCT and allo-HCT.[47] Although a formal systematic review was not conducted, evidence was partly used as the basis for the recommendations. The publication reported that none of the authors had any relevant financial conflicts of interest to declare. Table 2 summarizes recommendations for HCT in acute myeloid leukemia.

Table 2. Recommendations for the Use of Hematopoietic Cell Transplantation to Treat Acute Myeloid Leukemia

Indication	Allo-HCT[a]	Autologous HCT[a]
AML, age <18 years		
First CR, low risk	N	N
First CR, intermediate risk	C	N
First CR, high risk	S	N
Second or greater CR	S	N
Not in remission	S	N
Acute promyelocytic leukemia, relapse	R	R
AML, age ≥18 years		
First CR, low risk	N	C
First CR, intermediate risk	S	C
First CR, high risk	S	C
Second CR	S	C
Third or greater CR	C	C
Not in remission	C	N

[a] Recommendations were classified as follows: S, standard of care (well-defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies); C, standard of care, clinical evidence available (large clinical trials are not available; however, sufficiently large cohort studies have shown efficacy with acceptable risk of morbidity and mortality); N, not generally recommended
allo-HCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; CR: complete response; HCT: hematopoietic cell transplantation

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network clinical guidelines (v.6.2023), for acute myeloid leukemia state that allo-HCT is recommended for patients aged <60 years after standard-dose cytarabine induction with induction failure or significant residual disease without a hypocellular marrow.[1] It is also recommended after high-dose cytarabine induction with induction failure, or

as post-remission therapy in those with intermediate-risk or poor-risk cytogenetics. Allo-HCT is identified as a "reasonable option" for patients aged ≥60 years after standard-dose cytarabine induction with residual disease or induction failure or following complete response (preferably in a clinical trial). In addition, allo-HCT is recommended for relapsed or refractory disease.

According to the guidelines, the role of autologous HCT in the intermediate-risk group is diminishing due to improvements in allo-HCT that have expanded the pool of potential donors outside the family setting. For patients with intermediate-risk cytogenetics and/or molecular abnormalities including MRD positive, autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial.

For the AML subtype acute promyelocytic leukemia (APL), the NCCN guidelines recommend autologous HCT for people who are transplant candidates with APL, age ≥18 years as additional therapy for relapse if polymerase chain reaction (PCR) negative and in second remission (after consideration of central nervous system (CNS) prophylaxis).

The NCCN guidelines recommend allogeneic HCT for transplant candidates with APL, age ≥18 years as additional therapy for relapse if PCR positive and in second remission (after consideration of CNS prophylaxis), or if no remission after arsenic trioxide therapy.

For blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare myeloid malignancy, the NCCN guidelines recommend consideration of either allogeneic or autologous HCT (or Tagraxofusp-erzs) if CR after induction therapy.

SUMMARY

There is enough research to show that allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen, or a reduced-intensity conditioning regimen may be medically necessary for people with acute myeloid leukemia (AML) when policy criteria are met. Additionally, autologous HCT may be considered medically necessary to treat AML for any indication other than as first line treatment.

Due to a lack of evidence and guidelines, autologous and allogeneic hematopoietic cell transplantation with any regimen is considered investigational when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
	38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

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