Current Treatments of Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is an aggressive blood cancer characterized by the rapid reproduction of immature myeloid blasts that disrupt the normal development of blood cells. Despite significant advances in treatment, AML continues to pose a major therapeutic challenge, particularly in older adults, due to the toxicity of the current treatments. This review examines the current therapeutic landscape of AML while also shedding light on emerging treatments. Chemotherapy is the cornerstone of induction therapy, most notably through the “7+3) regimen of cytarbine and anthracyclines, which targets rapidly dividing cells. For patients ineligible for intensive regimens, hypomethylating agents offer a less toxic alternative by reactivating tumor suppressor genes through DNA demethylation. Immunotherapy is an expanding treatment, with antibody-drug conjugates, immune checkpoint inhibitors, and CAR T-cell therapies showing promising results. Radiation therapy holds a supportive role, particularly in conditioning before stem cell transplants. Stem cell transplants remain the only curative strategy for many patients. Ongoing research increasingly focuses on integrating molecular profiling, epigenetic therapy, and immune-based approaches to enhance efficiency and minimize toxicity.

Intro

Acute myeloid leukemia (AML) is an aggressive cancer of the blood and bone marrow, characterized by the rapid accumulation of abnormal myeloid cells that interfere with normal hematopoiesis. It accounts for about 1% of all cancers and is the most common acute leukemia in adults. AML typically arises from mutations in hematopoietic stem cells, leading to an uncontrolled proliferation of immature white blood cells known as myeloblasts. These abnormal cells crowd out the healthy blood cells and manifest in symptoms like anemia, frequent infections, and excessive bleeding. Despite advances in therapy, the overall five-year survival rate remains low, particularly in older adults. This article will examine the current treatment landscape for AML, focusing on chemotherapy, hypomethylating agents, immunotherapy, radiation therapy, and stem cell transplantation.

Acute myeloid leukemia (AML) is a rapidly progressing cancer of the blood and bone marrow defined by the clonal expansion of immature myeloid blasts (Vakiti). Myeloid cells are a normal blood cell lineage that, under healthy conditions, give rise to red blood cells, platelets, and several types of white blood cells. In AML, genetic mutations disrupt the normal maturation of these myeloid cells, causing them to remain in an immature state and multiply uncontrollably. These blasts accumulate in the bone marrow and crowd out healthy blood cell production, resulting in bone marrow failure. AML develops abruptly and progresses quickly, making early recognition and intervention critical (Vakiti).

Chemotherapy

Chemotherapy is the standard first-line treatment for most patients diagnosed with AML. Chemotherapy is typically delivered intravenously in the hospital and is divided into two phases: induction and consolidation. Induction therapy is the aggressive initial phase designed to eliminate the bulk of leukemic cells and achieve remission, often using the “7+3” regimen (seven

days of cytarabine and three days of an anthracycline). Cytarabine inhibits DNA synthesis and disrupts replication with anthracyclines, intertwining the DNA and inhibiting topoisomerase II, shattering the genetic machinery of leukemic cells. This combination exploits the fact that cancer cells divide faster than most healthy cells, allowing for preferential destruction of leukemic blasts (American Cancer Society). Because chemotherapy damages all fast-dividing cells, it often causes broad side effects. Normal cells of the bone marrow, GI tract, hair, and mucous membranes are caught in the crossfire (American Cancer Society). Despite these challenges, chemotherapy remains a foundational component of AML treatment and often paves the way for curative strategies like stem cell transplantation.

Hypomethylating Agents (HMAs)

For older patients or those unfit for intensive chemotherapy, hypomethylating agents (HMAs) like azacitidine and decitabine are widely used. These methyl groups inhibit other enzymes from producing the protein they code, essentially “turning off” the gene. HMAs inhibit DNA methyltransferases, enzymes responsible for adding methyl groups to cytosine residues in DNA. HMAs, such as azacitidine and decitabine, were originally developed in the 1960s as nucleoside analogs designed to interfere with DNA replication. However, they gained importance in oncology when researchers discovered their ability to inhibit DNA methyltransferases. Excessive DNA methylation silences tumor suppressor genes in AML, locking cells in an undifferentiated state. By incorporating into DNA, HMAs reduce this abnormal methylation, allowing for genes to be reactivated (Maurillo). These drugs were first approved for myelodysplastic syndrome (a group of disorders that affect the bone marrow) and later extended to AML, specifically for older.

HMAs are given in cycles, often administered subcutaneously or intravenously over several days each month. Unlike chemotherapy, their effects accumulate gradually over weeks to months. This makes them better tolerated in frail or elderly patients, but less effective at achieving rapid remission. Only about half of patients respond to HMAs (Maurillo). Side effects include bone marrow suppression, fatigue, gastrointestinal upset, fever, and injection-site irritation. HMAs are increasingly combined with venetoclax, yielding higher response rates and improved survival compared to HMAs alone (Guerra). This approach is now a frontline standard for many elderly or high-risk patients.

Immunotherapy

Immunotherapy seeks to exploit the body’s natural defenses against AML. Several approaches are currently in clinical use or trials.

Antibody Drug Conjugate

Antibody-drug conjugates (ADCs) are a type of cancer treatment that deliver strong chemotherapy drugs directly to cancer cells while protecting healthy cells. In acute myeloid leukemia (AML), ADCs target proteins found mostly on leukemia cells, such as CD33. The antibody part of the ADC attaches to the cancer cell, allowing the drug to enter the cell and cause damage, usually by breaking its DNA, which kills the cell. Gemtuzumab ozogamicin (GO) is an ADC used in AML that links an anti-CD33 antibody to the chemotherapy drug

calicheamicin. GO was first approved by the FDA in 2000 for older patients with relapsed AML, withdrawn in 2010 because of safety concerns, and then reapproved in 2017 with a new dosing plan that made it safer but still effective. Today, it is often used with standard chemotherapy, and researchers are developing other ADCs to improve AML treatment even further (FDA)

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors work by disrupting inhibitory pathways that AML cells exploit to suppress immune responses. In AML, leukemic blasts and their environment can increase the level of molecules like PD-L1 and CTLA-4 ligands, which bind to receptors on T cells and deactivate them. This allows the leukemia to evade the immune system. By blocking these pathways with monoclonal antibodies, checkpoint inhibitors aim to reenergize T-cell responses against AML. Although these therapies have been very promising in melanoma and lung cancer, results in AML have been more modest. Clinical trials so far have shown limited single-agent activity (a measurable anti-leukemic response), but are showing promise when combined with other treatments like HMAs. (Tang)

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy represents one of the most advanced forms of immunotherapy and has revolutionized the treatment of lymphoid cancers. T cells are a type of white blood cell that serve as central players in the adaptive immune system, capable of identifying and destroying abnormal or infected cells. They are specifically chosen for CAR engineering because of their natural ability to recognize antigens and orchestrate immune responses, including directly killing target cells and recruiting other immune cells. In most CAR T-cell approaches, cytotoxic $CD8^+$ T cells are emphasized because they are specialized in inducing apoptosis in abnormal cells, while helper $CD4^+$ T cells are often included to provide cytokine support that sustains and amplifies the anti-leukemic response. The therapy involves extracting a patient's T cells, genetically engineering them to express synthetic receptors that recognize tumor cells, expanding them in a laboratory, and reintroducing them into the patient to target cancer cells. The first major breakthrough came when CAR T therapy was used to treat B-cell acute lymphoblastic 3 leukemia, a cancer arising from the B-cell lineage. Researchers engineered T cells to express a CAR targeting a protein found only on B cells, resulting in dramatic remissions and, in many cases, eradication of the malignancy. While this approach has shown durable remissions in lymphoid cancers, its application in AML is much more difficult. The biggest challenge lies in selecting the target antigen: most antigens present on AML blasts are also found on normal hematopoietic stem cells, raising the risk of prolonged bone marrow destruction and life-threatening cytopenias. Current clinical trials are investigating strategies to improve safety and efficacy. These include dual-targeted CARs, which require recognition of two AML antigens before activation, as well as CAR T cells engineered with "suicide switches" that allow clinicians to eliminate the modified T cells with a specific drug if severe toxicity occurs.

Radiation Therapy

Radiation therapy plays a more limited but still important role in the treatment of AML. Unlike solid tumors, leukemia does not usually form a discrete mass that can be easily targeted by radiation. Instead, radiation is used in specific clinical scenarios: to eradicate leukemic cells hiding in sanctuary sites (such as the central nervous system or testes), to reduce the size of

localized leukemia-related tumors (chloromas), or as part of conditioning regimens before hematopoietic stem cell transplantation. Modern radiation therapy works by using high-energy X-rays or gamma rays generated by a linear accelerator to damage the DNA of cancer cells. Because AML cells are highly proliferative and have weaker DNA repair mechanisms compared to normal cells, they are more vulnerable to radiation-induced injury. Healthy tissues nearby are better able to repair sublethal DNA damage, which provides a therapeutic window.

Historically, total body irradiation (TBI) emerged in the 1970s as a way to suppress the patient's immune system before allogeneic stem cell transplantation, reducing the risk of graft rejection while eliminating residual leukemia. Today, TBI is often combined with chemotherapy as part of conditioning regimens. Advances in radiation delivery, such as intensity-modulated radiation therapy, have reduced collateral damage to healthy tissues, but side effects remain a concern. Acute toxicities include skin irritation, fatigue, nausea, and mucositis, while long-term risks include endocrine dysfunction, infertility, tissue fibrosis, and secondary malignancies. Despite these risks, radiation remains a valuable adjunctive therapy, particularly in patients undergoing transplantation or in those with extramedullary AML lesions (Paiz).

Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is the only potentially curative therapy for many patients with AML, particularly those at high risk of relapse or who have already relapsed after chemotherapy. The principle behind HSCT is twofold: first, high-dose chemotherapy (often combined with radiation) eradicates residual leukemia and ablates the patient's diseased marrow; second, infusion of healthy hematopoietic stem cells restores normal blood cell production. Over time, it was discovered that donor immune cells also exert a powerful graft-versus-leukemia (GVL) effect, in which transplanted T cells recognize and attack residual AML cells, providing an additional layer of disease control (Loke).

Stem cell transplantation was first attempted in the 1950s and gained traction in the 1970s with the development of matched sibling donor protocols. Early outcomes were hampered by graft rejection and treatment-related mortality, but advances in HLA typing, supportive care, and immunosuppressive therapy have dramatically improved safety. Today, two major forms of HSCT are used: autologous (where the patient's own stem cells are collected, stored, and reinfused) and allogeneic (where stem cells come from a donor). In AML, allogeneic transplantation is favored because of the GVL effect, though it carries higher risks such as graft-versus-host disease (GVHD), in which donor immune cells attack healthy tissues. The GVL effect is an immune response in which the donor's immune cells recognize and destroy the recipient's leukemic cells.

Allogeneic transplantation is now considered the standard of care for younger patients with poor-risk AML or those who relapse after initial therapy. Nevertheless, it remains associated with significant complications, including infections, organ toxicity, GVHD, and long-term immunosuppression. Recent advances, such as haploidentical transplantation (using half-matched family donors) and post-transplant maintenance therapies, are expanding access and improving survival. Overall, HSCT represents the most powerful curative option for AML, though patient selection and timing are critical to balance benefits against risks (Loke).

Conclusion

Acute myeloid leukemia remains one of the most formidable challenges in hematologic oncology, characterized by rapid progression and high relapse rates. While traditional chemotherapy continues to serve as the foundation of treatment, it is increasingly being complemented and, in some cases, replaced by more targeted and personalized strategies. Hypomethylating agents have provided a lifeline for older and medically fragile patients, offering meaningful disease control with manageable toxicity. Immunotherapies, including antibody-drug conjugates, checkpoint inhibitors, and CAR T-cell therapies, represent a rapidly evolving frontier that harnesses the immune system to selectively eliminate leukemic cells. Radiation therapy, though limited in scope, continues to play a critical supportive role, particularly in transplantation conditioning and extramedullary disease control. Finally, stem cell transplantation remains the most potent curative option, capitalizing on both myeloablation and the graft-versus-leukemia effect to achieve long-term remission.

Despite these advances, AML treatment remains hindered by drug resistance, relapse, and treatment-related morbidity. Ongoing research is increasingly focused on integrating molecular profiling, epigenetic modulation, and immunologic precision to optimize outcomes and minimize toxicity. As understanding of AML biology deepens, the future of treatment will likely involve highly individualized regimens that combine targeted therapy, immune modulation, and transplantation tailored to each patient's genetic and clinical profile. The convergence of cytotoxic, molecular, and immunologic therapies offers a path toward transforming AML from a highly lethal malignancy into a disease with durable remission and meaningful long-term survival.

Works Cited

ACS. “Chemotherapy for Acute Myeloid Leukemia (AML).” *American Cancer Society*, 4 March 2025, https://www.cancer.org/cancer/types/acute-myeloid-leukemia/treating/chemotherapy.html.

Bleakly, Marie, et al. “Naive T-Cell Depletion to Prevent Chronic Graft-Versus-Host Disease.” *National Library of Medicine*, 10 January 2022, https://pubmed.ncbi.nlm.nih.gov/35007144/.

Blood Cancer United. “Acute myeloid leukemia (AML).” *Blood Cancer United*, https://bloodcancerunited.org/blood-cancer/leukemia/acute-myeloid-leukemia-aml.

Döhner, Hartmut, et al. “Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN.” *Ash Publications*, 22 September 2022, https://ashpublications.org/blood/article/140/12/1345/485817/Diagnosis-and-management-of-AML-in-adults-2022.

FDA. “FDA Approves Gemtuzumab Ozogamicin for CD33-positive AML.” https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml.

Gill, Saar, and Sherly Mardiana. “CAR T Cells for Acute Myeloid Leukemia: State of the Art and Future Directions.” *National Library of Medicine*, 5 May 2020, https://pmc.ncbi.nlm.nih.gov/articles/PMC7218049/.

Guerra, Veronica A., et al. “Venetoclax-based Therapies for Acute Myeloid Leukemia.” *National Library of Medicine*, June 2019, https://pmc.ncbi.nlm.nih.gov/articles/PMC6581210/.

Lu, Tianyu, and Ruolin Wang. “Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia: Who, When, and How?” *Frontiers*, 2 May 2021, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2021.659595/full.

Maurillo, Luca, et al. “Azacitidine for the treatment of patients with acute myeloid leukemia: report of 82 patients enrolled in an Italian Compassionate Program.” *National Library of Medicine*, 15 February 2012, https://pubmed.ncbi.nlm.nih.gov/21761399/.

NIH. “Acute Myeloid Leukemia Treatment (PDQ®) - NCI.” *National Cancer Institute*, 14 March 2025, https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq.

Paiz, Adrien. “Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: A review.” *ScienceDirect*, March 2018, https://www.sciencedirect.com/science/article/abs/pii/S1040842817303268.

Tang, Lu, et al. “Immunotherapy in hematologic malignancies: achievements, challenges and future prospects.” *National Library of Medicine*, 18 August 2023, https://pubmed.ncbi.nlm.nih.gov/37591844/.

Vakiti, Anusha, and Samuel B. Reynolds. “Acute Myeloid Leukemia.” *STATPEARLS*, 27 April 2024, https://www.statpearls.com/point-of-care/25443.