

Antibody-Targeted Chemotherapy for the Treatment of Relapsed Acute Myeloid Leukemia

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Abstract

A promising new development in cancer treatment is antibody-targeted chemotherapy (ATC), a strategy that allows antineoplastic drugs to be delivered to malignant cells but not most normal ones, possibly resulting in fewer side effects. A new drug, gemtuzumab ozogamicin (Mylotarg™), employs the ATC strategy and has been approved by the Food and Drug Administration for the treatment of CD33+ acute myeloid leukemia (AML) in patients who are 60 years of age and older, are in their first relapse, and are not considered candidates for cytotoxic chemotherapy. AML is the second most frequent type of leukemia in adults and is associated with a poor prognosis. If untreated, death usually occurs within a few months of diagnosis. (Am J Manag Care 2000;6(suppl):S975-S985)

Acute myeloid leukemia (AML), a disease characterized by the proliferation of immature leukocytes known as blasts, interferes with normal hematopoiesis. The resulting anemia, thrombocytopenia, and neutropenia can lead to life-threatening conditions, including hemorrhage and infection.¹

Acute Myeloid Leukemia

AML is not common, representing less than 0.7% of all new cancers in the United States from 1992 to 1996.² Current projections indicate an expected 10,000 new cases of AML will be diagnosed in adults annually.³ Despite these seemingly low numbers, AML is the second most frequent type of leukemia in adults; for those who are diagnosed with this disease, the prognosis is usually poor.² Untreated, the disease is rapidly fatal, with death generally occurring within a few months of diagnosis. Although the 5-year survival rate for AML patients tripled from 1974 to 1995, it is still only 14.5%.²

Current treatment for AML involves 2 phases. The first, induction therapy, is an intensive chemotherapeutic regimen that attempts to eradicate the leukemia and normalize blood counts. The second phase of treatment, postremission therapy or consolidation, involves chemotherapy, hematopoietic stem-cell transplantation, or both.

Both phases of treatment are less likely to be successful in patients who are older than 60 years of age at first diagnosis or who have relapsed. As a result, the 5-year survival rates for relapsed patients and older patients—defined in this paper as older than 60 years of age at diagnosis—are less than 5% and 3%, respectively.^{2,4} Conventional chemotherapy is problematic because it is nonspecific, and traditional AML drugs have a high

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incidence of side effects such as alopecia, mucositis, and myelosuppression, the last of which can lead to infections. Because conventional therapy has such significant side effects, damaging healthy tissue as well as malignant cells, new treatment approaches are being actively pursued.

One of the most promising new developments in cancer treatment is antibody-targeted chemotherapy (ATC), a strategy that allows antineoplastic drugs to be delivered to malignant cells but not most normal ones, thus having the potential of fewer side effects.⁵ A new drug, gemtuzumab ozogamicin (MylotargTM), employs the ATC strategy and has been approved by the Food and Drug Administration for the treatment of CD33+ AML in patients who are 60 years of age and older, are in their first relapse, and are not considered candidates for cytotoxic chemotherapy.⁶

Compared with conventional chemotherapy, whose side effects are documented in the literature, treatment with gemtuzumab ozogamicin is

associated with a lower incidence of severe mucositis and infections and does not cause chemotherapy-related alopecia.⁷ However, patients receiving gemtuzumab ozogamicin can experience anemia, severe neutropenia, and severe thrombocytopenia similar to that among patients receiving other AML treatments.⁷ Unlike conventional treatments for AML, treatment with gemtuzumab ozogamicin can often be performed in the outpatient setting under the supervision of a physician experienced in the use of chemotherapy, resulting in fewer days of hospitalization.⁷ Gemtuzumab ozogamicin offers a promising alternative for the treatment of AML, providing oncologists and their patients with a novel opportunity for the management of the disease.

Overview of Leukemia

Most leukemia cases are represented by 4 types of cancer: chronic lymphocytic leukemia (CLL); acute lymphocytic leukemia (ALL); chronic myeloid leukemia (CML); and AML,

Table 1. The FAB AML Classification System

FAB Subtype	% of Cases*	Surface Protein Expression
M0: Minimally differentiated leukemia	2-3	CD13, 33
M1: Myeloblastic leukemia without maturation	20	CD13, 33, 34
M2: Myeloblastic leukemia with maturation	25-30	CD13, 15, 33, 34
M3: Hypergranular promyelocytic leukemia	8-15	CD13, 15, 33
M4: Myelomonocytic leukemia	20-25	CD11b, 13, 14, 15, 33
M5: Monocytic leukemia	20-25	CD11b, 13, 14, 15, 33
M6: Erythroleukemia (Di Guglielmo's Disease)	5	CD33
M7: Megakaryoblastic leukemia	1-2	CD33, 41

*Because ranges are given for each FAB subtype, percentages do not total 100%.
 AML = acute myeloid leukemia; FAB = French-American-British.
 Source: Reference 11.

also known as acute myelocytic or acute myelogenous leukemia. Although only AML is discussed in this paper, important points regarding the other 3 types of leukemia and their association with AML should be noted:

- Lymphocytic leukemias develop from B- and T-cell progenitors. Myeloid leukemias arise from neutrophil and monocyte progenitors.
- ALL occurs primarily in children. CLL, CML, and AML develop predominantly in adults.
- Survival may be extended with CLL and CML. AML and ALL are often rapidly fatal.
- In its later stages, CML may be almost indistinguishable from AML or ALL.⁸
- Despite their different lineages, AML and rarely ALL may express similar proteins, such as the cell-surface antigen CD33.⁹

Acute Myeloid Leukemia

AML is caused by the abnormal proliferation and rapid accumulation of myeloid progenitor cells, which ultimately leads to functional bone marrow failure. The result is severe anemia, thrombocytopenia, and neutropenia; these conditions are associated with fatigue, hemorrhage, and infection. A diagnosis of AML is established when leukemic cells compose more than 30% of the nucleated cells in the bone marrow.¹ In comparison, myeloblasts and promyelocytes compose less than 5% of the nucleated marrow cells in normal individuals.¹⁰

The French-American-British (FAB) classification system is widely used for the subdivision of AML into biologically distinct groups (Table 1).¹¹ AML has been associated with a variety of other medical conditions and toxic exposures. Individuals with chromosomal abnormalities, such as Down's syndrome, and those with inherited diseases of DNA fragility, such as Fanconi's anemia, have an

increased likelihood of developing AML.^{12,13} A correlation between AML and high-dose radiation has been identified.¹⁴ AML has also been linked to tobacco use, as well as exposure to benzene and pesticides.¹⁵⁻¹⁷

When patients develop AML following exposure to alkylating agents or topoisomerase II inhibitors for the treatment of a previous malignancy, the condition is referred to as secondary AML. Others consider secondary AML to include those cases that result from toxic exposure as well as cases of myelodysplastic syndrome (MDS) that transform into AML.^{18,19} MDS was first recognized in the late 1940s as a subacute form of AML, as AML frequently evolves from MDS over time.

The transformation of MDS to ADL is frequently accompanied by a significant degree of chromosomal alteration. For example, cytopenia is typically observed in patients with MDS, but blastic proliferation—and thus AML—usually only occurs after additional genetic mutations.²⁰ Like MDS, CML can also progress into a blast phase, which typically occurs 3 to 5 years after initial diagnosis.²¹ Depending on its definition, secondary AML probably accounts for between 10% and 30% of newly diagnosed AML cases.^{18,19}

Epidemiology. Representing only 0.7% of new cancer cases, AML is a relatively rare malignancy but a common leukemia.² Currently, 28,000 new cases of adult leukemia are projected to be diagnosed in the United States annually, with 35% of these expected to be AML.³ As shown in Figure 1, CLL is the only form of leukemia that occurs more frequently.² Most significantly, AML has the lowest 5-year survival rate of the 4 major leukemias, with only 14.5% of AML patients alive 5 years after diagnosis (Table 2).²

The annual risk for developing AML increases progressively with age

from approximately 1 in 50,000 for a 50-year-old to 1 in 7000 for a 70-year-old.³ As the median age of diagnosis is 68, AML is largely a disease of older individuals.² Specifically, 56.8% of all new AML cases occur among people older than 65 years of age, with 63.6%

of the AML patients who die from their disease being in this age group.²

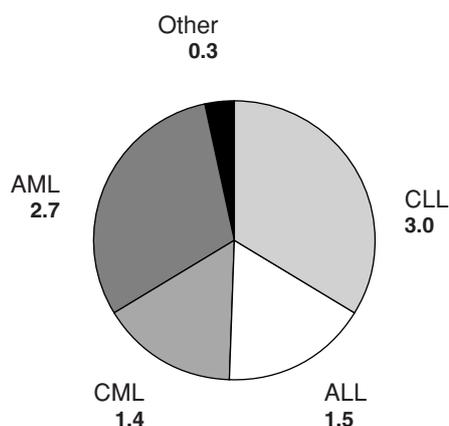
The seriousness of AML cannot be overstated, especially for the 75% of patients who relapse.²² They may be resistant to standard levels of treatment, requiring higher than normal chemotherapeutic doses, with significant side effects.²³ Although an initial complete remission is achieved in 60% to 80% of new AML patients, significantly fewer relapsed patients achieve a second complete remission.^{22,24} The median duration of first complete remission for new AML patients is 15 months, but for relapsed patients, the duration of second complete remission is only 4 to 8 months.²² Not surprisingly, the 5-year disease-free survival rate for relapsed patients who do not receive hematopoietic stem-cell transplantation is less than 5%.⁴

During the past 20 years, the 5-year survival rate for all AML patients has nearly tripled from 5.7% to 14.5%.² Unfortunately, that improvement has not significantly benefited patients older than 65 years of age. The most recent data show that the 5-year survival rate of patients in this age group is still only 2.8%, compared to 25.1% for patients younger than 65 years of age.² This difference can be explained by several possible reasons. Similar to relapsed patients, those older than 65 years of age are often less able than younger people to endure rigorous treatment regimens. Additionally, older patients are more likely to have AML resulting from MDS, which is associated with a poor prognosis, or AML with other poor risk characteristics, such as drug resistance.²⁵⁻²⁷

Treatment of AML

Treatment of AML is generally divided into 2 phases: remission induction and postremission therapy.¹ Remission is generally induced through a 1-week intensive treatment regimen that requires hospitalization.

Figure 1. Age-Adjusted SEER US Incidence Rates for Major Leukemias (Per 100,000 People)



SEER = Surveillance, Epidemiology, and End Results.
Source: Adapted from *SEER Cancer Statistics Review, 1973-1996* (National Cancer Institute).

Table 2. Age-Adjusted SEER US Mortality Rates (Per 100,000 People) and 5-Year Survival Rates for Major Leukemias

Leukemia	Five-Year Survival (%)
Acute myeloid leukemia (AML)	14.5
Chronic myeloid leukemia (CML)	31.9
Acute lymphocytic leukemia (ALL)	58.8
Chronic lymphocytic leukemia (CLL)	70.5

SEER = Surveillance, Epidemiology, and End Results.
Source: Adapted from *SEER Cancer Statistics Review, 1973-1996* (National Cancer Institute).

Two thirds of remissions are obtained with 1 induction course, and one third require 2 courses.¹¹

Conventional Chemotherapy. The most commonly used induction therapy is cytarabine (ARA-C) combined with an anthracycline antibiotic such as daunorubicin or idarubicin.¹ Cytarabine is usually administered by continuous intravenous infusion for 7 days, with 3 doses of anthracycline given intermittently during the week. This process is often referred to as the "7 + 3 regimen." Anthracyclines have cumulative cardiotoxicity and are usually contraindicated in patients with congestive heart failure, which includes a significant portion of patients older than 65 years of age.^{10,28} An alternative treatment for these patients is high-dose cytarabine (HIDAC), which has an extreme marrow-suppressive effect. HIDAC may have comparable efficacy to the 7 + 3 regimen but has higher toxicity, particularly cerebellar toxicity, especially in the elderly.²⁹

The factors listed in Table 3 have been associated with failure of remission induction. This group can be divided into factors that are disease-specific (1,2,3,4,5,6) and treatment-specific (6,7).

When complete remission is achieved, postremission therapy is given to the patient to extend remission and to prevent relapse. Several postremission treatment approaches exist, including allogeneic or autologous hematopoietic stem-cell transplantation (HSCT), further chemotherapy, or a combination of HSCT and chemotherapy.

Allogeneic HSCT involves the introduction of stem cells from a human leukocyte antigen-compatible donor to provide support for bone marrow reconstitution. Only 25% to 30% of patients will have suitable donors, and the treatment carries the risk of graft-versus-host disease.¹⁰ In contrast, autologous HSCT may

involve the reintroduction of stem cells isolated from the patient's own blood or bone marrow during remission, resulting in a higher relapse rate.

Postremission chemotherapy may be given as high dose (intensification therapy), standard dose (consolidation therapy), or low dose (maintenance therapy), depending on the patient's clinical situation.¹⁰ HIDAL is the most common postremission treatment and is generally given during 5 days in 2 or 4 cycles. Strong evidence exists for a dose-response effect of ARA-L during AML postremission treatment in younger patients, even in high-risk groups.³² Younger patients may better tolerate the therapy, which may be associated with particularly severe side effects, discussed below.³³

Several factors are correlated with AML relapse. For example, female patients, patients who are 50 years of age or older at diagnosis, and those who had a delayed response to induction are more likely to relapse than their counterparts.³⁴ AML patients with unfavorable chromosomal

Table 3. Factors Correlated with Poor Patient Response Rates to Induction Therapy

1. Unfavorable chromosomal abnormalities (eg, the loss or deletion of chromosomes 5 and 7) ³⁰
2. Secondary AML
3. Leukocyte count >20,000/mm ³
4. Unfavorable immunophenotype (eg, CD11b) ³¹
5. Presence of the multidrug resistance protein—MDR1
6. Age >60 years
7. Poor physical condition

AML = acute myeloid leukemia.

Source: References 30, 31.

abnormalities and a leukocyte count of more than 20,000 are also more likely to relapse.³⁴ AML patients who have few high-risk factors at diagnosis are often recommended to receive high-dose chemotherapy followed by HSCT because they often do not respond to further standard-dose chemotherapy alone.²² Some are treated solely with HIDAL, which often causes severe side effects.²⁹

Therapy is also problematic for older patients with AML. A recent study indicates that these patients are more likely than younger ones to have AML with unfavorable chromosomal abnormalities and multidrug resistance.³⁵ This suggests that the poor prognosis of older AML patients may be both treatment specific (they can't tolerate chemotherapy) and disease specific. Older patients are often discouraged from HSCT by clinicians who consider it too toxic.³⁶

In addition, older patients often cannot tolerate intensive chemotherapy because of comorbid conditions such as heart disease.^{10,28} Not surprisingly, some clinicians may discourage older patients from any therapy at all, even though several studies show a

clear benefit to chemotherapy, and even intensive chemotherapy may benefit the older patient with favorable cytogenetics and no other contraindications.^{37,38} However, the inability to tolerate a treatment regimen is a clear contraindication. For these reasons, older AML patients, as well as relapsed patients, need a new therapy that is both effective and tolerable.

Shortcoming of Conventional Chemotherapy. Because traditional chemotherapeutic agents are non-specific in that they cannot discriminate between healthy and malignant cells, they often cause potentially severe side effects (shown in Table 4), including nausea, vomiting, mucositis (including stomatitis), and myelosuppression, which can lead to severe infections.^{32,39-44}

Similar side effects are seen in older patients, who may be less able to tolerate them than younger AML patients. One approach to decreasing the likelihood of severe bacterial or fungal infection related to the myelosuppressive effect of chemotherapy has been the use of recombinant hematopoietic growth factors, such as granulocyte-colony stimulating factor (G-CSF) and macrophage-colony stimulating factor (M-CSF). Patients treated with these factors may have higher remission rates because of decreased toxicity, but no firm evidence of increased survival has been found.⁴⁵

Antibody-Targeted Chemotherapy

The need is great for a new AML drug that is as effective as traditional chemotherapy but with fewer serious side effects. One possibility may be antibody-targeted chemotherapy (ATC). In brief, ATC targets malignant cells while sparing most normal ones. This gives the drug the potential to be as effective as conventional chemotherapy but better tolerated and with an improved safety profile.

Table 4. Incidence of Severe Physical Side Effects of Conventional Chemotherapy Among Patients with AML in First Relapse

Side Effects*	Incidence Range, % [†]
Grade 3 or 4 infections	45-83
Grade 3 or 4 mucositis	5-50
Grade 3 or 4 nausea or vomiting	4-29
Grade 3 or 4 bleeding	3-25

*Grade 1 or 2 side effects are considered easily manageable; grade 3 or 4 side effects are considered to be severe.

[†]These ranges include studies of refractory patients.

AML = acute myeloid leukemia.

Source: References 32, 29-44.

The first step of ATC therapy is to create a monoclonal antibody that binds to an antigen expressed on the surface of malignant but not most normal cells. This antibody is attached to a chemotherapeutic agent; together, they represent the ATC drug. The drug is injected into a patient. It then binds to malignant cells (as well as some normal cells that express the antigen) via the targeted antigen-antibody interaction and is internalized. Inside the cells, the chemotherapeutic agent is released from the antibody and does its work.

AML is ideally suited for ATC because an antibody has been developed specific to CD33, an antigen that is expressed on the surface of AML cells in more than 80% of patients and on some normal myeloid precursors.⁴⁶ It is not, however, expressed on pluripotent hematopoietic progenitor cells, which are critical to the patient's return to health after successful AML therapy, or most other non-hematopoietic cell types.⁵ A member of the sialoadhesin molecular family, CD33 is a developmental myeloid protein, which means that it is typically expressed on immature or leukemic leukocytes but not on normal, mature ones or pluripotent hematopoietic progenitor cells.^{5,47} In addition, the myeloid leukemic cells are widely accessible in the blood and bone marrow. As a result, ATC can offer targeted treatment to many AML patients.

The potential of CD33-specific ATC may extend beyond AML. More specifically, cells of other blood cancers and cancer-like disorders—such as ALL, MDS, multiple myeloma, and CML in its blast crisis phase—are also known to sometimes express CD33.⁴⁸⁻⁵¹

In theory, these diseases may be amenable to CD33-specific ATC if they express the CD33 antigen.

A New Therapy for AML

Gemtuzumab ozogamicin has become the first ATC drug to be

approved for the treatment of AML. It has been approved for the treatment of patients who are 60 years of age and older, are in first relapse, and are not considered candidates for cytotoxic chemotherapy. Gemtuzumab ozogamicin has been granted orphan drug status because of the small number of cases of relapsed AML. It can be distinguished from many conventional AML treatments by its single-day dosing regimen and its ability to have at least some doses administered in an outpatient setting.⁷

Gemtuzumab ozogamicin is a humanized recombinant antibody linked with the novel, potent antitumor antibiotic ozogamicin, isolated from a bacterium in caliche clay, a type of soil found in Texas. The antibody portion of gemtuzumab ozogamicin is specific to the CD33 antigen, which, as noted above, is a glycoprotein commonly expressed on the external surface of AML cells but not on most normal hematopoietic stem cells or non-hematopoietic cells.

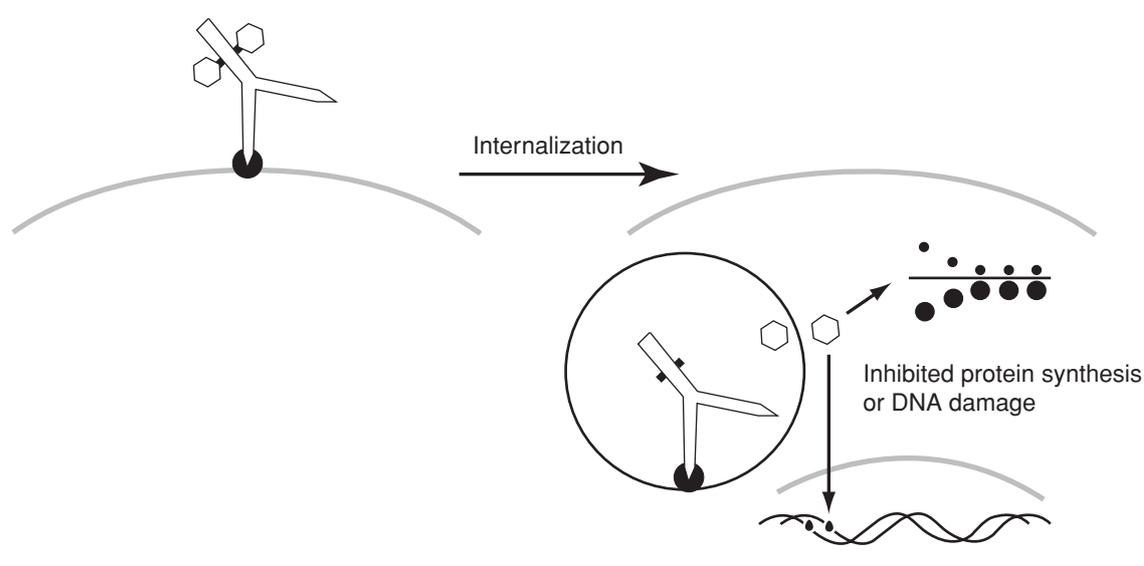
The mechanism of action of gemtuzumab ozogamicin involves the drug binding to the CD33 antigen on the AML cell membrane, then being internalized (Figure 2). At this point, ozogamicin is released from the antibody inside the lysosomes of cells then migrates to the cell nucleus and binds to DNA, causing breaks in the double helix and resulting in cell death.⁵²

Three factors distinguish gemtuzumab ozogamicin from conventional therapy. First, gemtuzumab ozogamicin is the only treatment indicated specifically for relapsed AML. Second, the FDA concluded that gemtuzumab ozogamicin has an adequate safety profile, although it can cause severe myelosuppression when used at recommended doses because it targets some normal myeloid precursors. In addition, gemtuzumab ozogamicin has not been associated with alopecia.⁷ Third, because of its safety profile and potential for outpatient

administration, gemtuzumab ozogamicin may be associated with fewer days of patient hospitalization than traditional chemotherapy. Research shows that patients treated with gemtuzumab ozogamicin had a median of 24 days of hospitalization compared to 31 and 38 days for AML patients treated with conventional chemother-

apy.^{7,53,54} Further, some patients undergoing gemtuzumab ozogamicin therapy did not require hospitalization at all, although careful monitoring is required because gemtuzumab ozogamicin can produce a postinfusion syndrome of fever, chills, and rarely, hypotension and dyspnea.⁷ In contrast, the literature suggests that

Figure 2. Mechanism of Action: Antibody-Targeted Chemotherapy



Source: Reference 52.

Table 5. Incidence of Severe Physical Side Effects of Gemtuzumab Ozogamicin Compared with Conventional Chemotherapy Among Patients with AML in First Relapse

Side Effect	Gemtuzumab Ozogamicin, %	Conventional Chemotherapy, %
Grade 3 or 4 infections	28	45-83
Grade 3 or 4 mucositis	4	5-50

Source: Reference 7, 32, 39-44.

all patients undergoing conventional chemotherapy regimens require at least some hospitalization.^{55,56}

Thus, for patients with AML who are 60 years of age and older and in first relapse, gemtuzumab ozogamicin therapy offers remission and survival rates that are comparable to those of conventional chemotherapy, may result in fewer and shorter hospitalizations, and causes fewer severe side effects than conventional therapy (Table 5).

Conclusion

Despite the remarkable medical progress that has been made over the past 25 years, AML remains a deadly disease. Five years after diagnosis, patients have only a 14.5% chance of survival. If a patient has relapsed AML, 5-year survival is less than 5%, and if the patient is 60 years of age or older, it is less than 3%. The current therapies used to treat the disease cause side effects ranging from alopecia to life-threatening infections. For these reasons, new therapeutic approaches are needed for AML.

The biotechnology revolution may transform AML treatment. One strategy—ATC—offers the potential to treat AML as effectively as current drugs but with fewer serious side effects. One ATC drug, gemtuzumab ozogamicin, has been approved by the FDA for the treatment of CD33+ AML in patients 60 years of age and older who are in first relapse and are not considered candidates for cytotoxic chemotherapy. This drug has been shown to have fewer severe side effects, possibly resulting in fewer and shorter hospitalizations, and both of these factors may translate to higher patient satisfaction.

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