Purpose/Objectives: To review the nursing implications of gemtuzumab ozogamicin (Mylotarg®, CMA-676, Wyeth Pharmaceuticals, Philadelphia, PA), a novel monoclonal antibody-targeted chemotherapy agent for relapsed acute myeloid leukemia (AML).

Data Sources: Published articles, abstracts, book chapters, manufacturer information, unpublished clinical trial data, and personal experiences with gemtuzumab ozogamicin.

Data Synthesis: Conventional chemotherapy for AML is associated with toxicities that often limit treatment options when AML relapses. Gemtuzumab ozogamicin is a humanized recombinant anti-CD33 monoclonal antibody linked to calicheamicin, a potent cytotoxic agent. The antibody targets the CD33 antigen found on the surface of leukemic blast cells and myeloid precursors. This targeting effect reduces the toxicity of gemtuzumab ozogamicin. The efficacy and tolerability of gemtuzumab ozogamicin have been documented in relapsed AML, particularly in patients 60 years of age or older, who often have no other treatment options. As with other monoclonal antibody therapies, an “infusion syndrome” (i.e., fever and chills) may occur but can be managed effectively when administration guidelines are used.

Conclusions: Gemtuzumab ozogamicin is the first of a new class of targeted therapies for the treatment of relapsed AML. A number of implications for nurses exist.

Implications for Nursing: Nurses must be knowledgeable about gemtuzumab ozogamicin preparation and administration, patient selection and monitoring, and intervention procedures. This knowledge is necessary to accurately inform patients and their families of the possible course of treatment and potential side effects.

Key Points . . .

- Acute myeloid leukemia (AML) is an aggressive disease; patients with AML have a median survival of about one year.
- Conventional chemotherapy for AML involves the use of cytotoxic drugs with significant side effects and possible hematopoietic stem cell transplantation.
- Gemtuzumab ozogamicin is efficacious and well tolerated. The infusion-related side effects are manageable with adherence to guidelines of administration, premedication, and strict patient monitoring.

Acute myeloid leukemia (AML) is a disease of the bone marrow and is manifested by fatigue, infections, and bleeding caused by crowding and suppression of normal marrow precursors by malignant clones. The etiology of AML is not known, but evidence suggests that AML is caused by acquired genetic defects occurring in hematopoietic precursor cells. These early, mutated precursor cells give rise to progeny that fail to differentiate and continue to proliferate. Inappropriate proliferation of myeloid blasts replaces normal bone marrow, which reduces the production of normal red blood cells and myeloid precursors. These early, mutated precursor cells give rise to progeny that fail to differentiate and continue to proliferate. Inappropriate proliferation of myeloid blasts replaces normal bone marrow, which reduces the production of normal red blood cells and myeloid precursors.
blood cells (RBCs), white blood cells (WBCs), and platelets. A reduction in the production of these cells leads to anemia, neutropenia, and thrombocytopenia.

**Epidemiology and Natural History**

AML constitutes about 80% of all acute leukemia cases in adults. The annual incidence of AML is 2.7 per 100,000 people (Ries et al., 2000). This rate increases dramatically to 14.1 per 100,000 people older than 65 (Ries et al.). AML occurs more commonly in adults than in children; the median age at diagnosis is 68 years. Because the incidence of AML increases with age, the number of new cases per year is projected to increase. The five-year survival rate for patients younger than 65 is about 25% but significantly lower—a rate of about 3%—for patients 65 or older (Ries et al.).

AML is an aggressive disease. If left untreated, leukemic myeloid cells will metastasize to the lymph nodes, spleen, and other vital organs. Most untreated or unresponsive patients will die within several months because of secondary infection or bleeding. Early symptoms of AML often resemble other conditions, making early diagnosis difficult.

**Diagnosis and Treatment**

As a result of low RBC counts that are secondary to AML, patients with AML may present with fatigue and headaches. About one-third of these patients may have significant or near life-threatening infections, usually of bacterial origin. In addition, about one-third of patients have clinical signs of bleeding, usually in the form of petechiae, ecchymoses, or epistaxis. Bone marrow aspirates and biopsies are used to diagnose AML because the disease originates from hematopoietic precursor cells.

When AML is diagnosed, the aggressive nature of the disease mandates that treatment begin immediately. The first treatment goal is induction to obtain complete remission (CR). Once patients are stabilized (i.e., infections and hemorrhagic conditions are controlled), a combination of two drugs, daunorubicin and cytarabine, most often is administered (Masaoka, Ogawa, Yamada, Kimura, & Ohashi, 1996; Vogler et al., 1992). About 60%–80% of patients treated with daunorubicin and cytarabine achieve CR (Schiller et al., 1992). However, the majority of patients relapse, with only 24%–44% of those younger than 60 and less than 20% of those 60 or older achieving durable remissions with postremission therapy (Mayer et al., 1994). Early mortality during therapy is the result of drug resistance with failure to respond to chemotherapy or complications of myelosuppression.

Current options for postremission therapy include short-term, intensive treatment with cytarabine, dose-intensive cytarabine-based chemotherapy, and high-dose chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation (HSCT) (Löwenberg, Downing, & Burnett, 1999). The disease-free survival rate for patients treated with nontransplant postremission therapy is about 25%, with higher rates of disease-free survival observed in patients younger than 60 (Champlin et al., 1990; Mayer et al., 1994).

Advances in induction therapy have resulted in improved CR rates, with a majority of patients responding to initial chemotherapy. Despite postremission therapy, however, CR is maintained only for a median of about one year (Preisler et al., 1989; Preisler, 1995). In a study by Tallman et al. (2000), the lowest incidence of leukemic relapse was achieved with allogeneic HSCT during first CR; four- to five-year disease-free survival rates ranged from 50%–59%. However, many institutions place age limits for eligibility at 50–55 years because treatment-related mortality from HSCT increases with age.

The percentage of patients who achieved second remissions from chemotherapy regimens varied widely between studies, generally ranging from 30%–80%, depending largely on the prognostic characteristics of the patients enrolled (Bassan et al., 1998; Lee et al., 1998; Saito et al., 2000). However, these remissions tended to be brief. Several agents, including amsocurine, mitoxantrone, high-dose cytarabine, and idarubicin, have demonstrated activity in recurrent AML. These agents’ potential therapeutic results are limited by substantial levels of cardiac, central nervous system, gastrointestinal, and hematologic toxicities, as well as mucositis and alopecia. Therefore, treatment with these agents often is not an option for many AML patients 60 or older or those in poor medical condition.

A novel drug, gemtuzumab ozogamicin (Mylotarg®, CMA-676, Wyeth Pharmaceuticals, Philadelphia, PA), is an antibody-targeted chemotherapy agent that reduces potential toxicities by specifically targeting myeloid precursor cells. The targeted nature and greater tolerability of gemtuzumab ozogamicin provide a treatment opportunity for older patients with relapsed AML.

**Antibody-Targeted Chemotherapy**

**Clinical Rationale**

With current conventional cytotoxic chemotherapies, remission rates are variable and depend on patients’ ages, duration of the first CR, and response criteria, which vary by study. Recent developments in antibody-targeted chemotherapy suggest that an anti-CD33 antibody can target a therapeutic agent specifically to AML cells.

Technical problems burdened initial attempts to use monoclonal antibodies for targeted therapy. Patients’ immune systems recognized the murine monoclonal antibodies as foreign and developed human antimouse antibodies (HAMA) that reduced or eliminated the efficacy of the therapy (Schroff, Foon, Beatty, Oldham, & Morgan, 1985). New approaches to antibody-targeted therapy have overcome this limitation and have eliminated most of the HAMA response (Karius & Marriott, 1997).

**Gemtuzumab Ozogamicin**

Gemtuzumab ozogamicin is a targeted chemotherapy agent composed of humanized anti-CD33 antibody linked to calicheamicin, an antitumor antibiotic that binds to DNA and produces double-strand DNA breaks. Humanizing the antibody was crucial to ensuring that the risk of HAMA formation was minimized. Thus, 98.3% of the antibody was derived from a human immunoglobulin gamma, and the remaining variable region was derived from a murine antibody (hp 67.6, chemical compound) that binds CD33 (Wyeth Laboratories, 2000).

**Proposed mechanism of action:** The CD33 antigen is a cell marker that is expressed on the surfaces of normal and leukemic myeloid colony-forming cells but is not expressed on pluripotent hematopoietic stem cells or nonhematopoietic cells. In addition, CD33 is expressed on the surfaces of leukemic blasts in more than 90% of patients with AML (Legrand et al., 2000). Binding the antibody portion of gemtuzumab
ozogamicin to CD33 results in the formation of an antibody/protein complex that is internalized and directed to the lysosomes. The acidic pH in the lysosomes leads to the release of calicheamicin, which then binds to DNA, resulting in DNA breaks and cell death by apoptosis.

**Pharmacokinetics:** At the dose level of 9 mg/m², detectable plasma concentrations of medication are present immediately after IV administration. The maximum plasma concentration, achieved shortly after the start of infusion, is $2.86 \pm 1.35$ mg/L (Korth-Bradley, Dowell, Berger, Liu, & King, 1999). The medication has a long half-life of 72 ± 42 hours. Plasma levels decrease with time, with an area under the curve of $123 \pm 105$ mg.hour/L. Results using flow microfluorometry indicate that in patients who receive 9 mg/m² gemtuzumab ozogamicin, 92% of CD33 binding sites on peripheral blast cells are occupied within 30 minutes (Sievers, Appelbaum, et al., 1999).

**Clinical experience:** Phase I and II clinical trials have evaluated the ability of people with relapsed AML to tolerate gemtuzumab ozogamicin. A phase I, ascending-dose study of 40 patients with relapsed and refractory AML examined the safety of gemtuzumab ozogamicin, using a regimen of as many as three doses of gemtuzumab ozogamicin (0.25–9 mg/m²) 14 days apart (Sievers, Appelbaum, et al., 1999). The study found that two doses of 9 mg/m² given 14 days apart was the most appropriate regimen for phase II trials.

Three international, phase II, open-label, single-arm, multidose studies were conducted to assess the efficacy and tolerability of gemtuzumab ozogamicin in patients with relapsed AML (Sievers, Larson, et al., 1999). These studies included 142 patients diagnosed with CD33⁺ AML with relapse confirmed by bone marrow biopsy or aspiration. All patients had CD33⁺ AML in first relapse following first CR of at least three months (for patients 60 and older) or six months (for patients younger than 60). Gemtuzumab ozogamicin (9 mg/m²) was administered by IV infusion over a two-hour period, with the two doses given 14 days apart. Patients were evaluated for 28 days after the second dose to evaluate for potential toxicities and disease response to treatment.

The median age of patients treated with gemtuzumab ozogamicin was 53 years (Sievers, Larson, et al., 1999). Patients had a median remission duration of 11 months prior to gemtuzumab ozogamicin treatment, and 94% had received prior postremission therapy. After one dose of gemtuzumab ozogamicin, 43% of patients had 5% or less blasts in bone marrow. The overall remission rate for patients treated with two doses of gemtuzumab ozogamicin was 30%.

Treatment-emergent adverse events associated with gemtuzumab ozogamicin were observed during the treatment period (i.e., the day of infusion to 28 days after the final dose). Chills, fever, and occasional hypotension and dyspnea, which were observed during infusion, are typical of antibody-based therapies (Winkler et al., 1999). Tumor lysis syndrome was reported occasionally. Thrombocytopenia and neutropenia are expected with gemtuzumab ozogamicin treatment because the CD33 antigen is present on hematopoietic precursor cells. Grade 3 or 4 thrombocytopenia was observed in 99% of the patients; 97% experienced grade 3 or 4 neutropenia (Wyeth Laboratories, 2000). Grade 3 or 4 bleeding was observed in 15% of the patients, including epistaxis (3%) and intracranial hemorrhage (4%). Only 4% of the patients had grade 3 or 4 mucositis. In addition, 28% of the patients experienced grade 3 or 4 infections, including opportunistic infections. The most frequent infections were sepsis (16%) and pneumonia (7%). Treatment-related cardiotoxicity, cerebellar toxicity, and alopecia were not observed.

All responding patients recovered from neutropenia to an absolute neutrophil count of 500/µL by a median of 41 days from the first dose of gemtuzumab ozogamicin (E.L. Sievers, personal communication, May 14, 1999). Patients who received the second dose of gemtuzumab ozogamicin less than 18 days after the first dose experienced a shorter duration of neutropenia.

About 30% of the patients had a moderate incidence of generally transient grade 3 or 4 elevations of hepatic transaminases or bilirubin. Clinically serious hepatic veno-occlusive disease occurred rarely (i.e., 2% of patients) after gemtuzumab ozogamicin therapy. A history of previous HSCT appeared to predispose patients to veno-occlusive disease after gemtuzumab ozogamicin therapy.

Phase I and II trials have demonstrated the efficacy and safety of gemtuzumab ozogamicin. Given the fact that treatment with gemtuzumab ozogamicin has a low incidence of severe mucositis or alopecia, gemtuzumab ozogamicin is a rational choice for the treatment of older patients with AML. No important clinical differences were observed in these safety endpoints between patients younger than 60 and those 60 and older. Gemtuzumab ozogamicin is a new treatment option for patients with relapsed AML and is approved for patients 60 and older who are not candidates for conventional chemotherapy.

**Nursing Implications**

Because gemtuzumab ozogamicin treatment is a new therapy, nurses should familiarize themselves with the issues and concerns specific to the use of antibody-targeted chemotherapy, especially because some of these issues differ from those of conventional chemotherapy. Nurses should be aware of the proper method of administering the drug, be conscious of potential side effects, and design a plan to anticipate and manage side effects. In addition, nurses should educate patients and their families about the course of treatment, possible side effects, planned interventions for those side effects, and potential disease response.

**Patient Selection**

Gemtuzumab ozogamicin is indicated for the treatment of patients with CD33⁺ AML in first relapse who are 60 or older and are not considered candidates for conventional cytotoxic chemotherapy. Therefore, it must be determined, usually by flow cytometry evaluation of the immunophenotype, that the AML is CD33⁺. Patients’ WBC counts must be less than 30,000 cells/µL at the time of administration because higher WBC counts can result in severe acute respiratory distress syndrome (Wyeth Laboratories, 2000). Baseline complete blood counts, routine chemistry tests, and liver function tests, including levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, also should be determined. Finally, gemtuzumab ozogamicin has not been studied in patients with bilirubin greater than 2 mg/dL, and caution should be exercised when administering gemtuzumab ozogamicin to patients with hepatic impairment.

**Guidelines for Dosing and Administration**

Figure 1 offers nursing guidelines for the preparation and administration of gemtuzumab ozogamicin. Because gemtuzumab ozogamicin is sensitive to light, it must be protected from direct and indirect sunlight and fluorescent light during
preparation and administration of the infusion. Before administration, patients should receive oral prophylactic medications including 650–1,000 mg acetaminophen and 50 mg diphenhydramine. Acetaminophen may be repeated every four hours throughout the infusion day. Treatment should be initiated by and remain under the supervision of primary care providers who are experienced in the use of cytotoxic chemotherapeutic agents. Gemtuzumab ozogamicin may be administered on an outpatient basis, but patients should be monitored for clinically significant symptoms (e.g., fever, chills, rigor, nausea, vomiting, hypotension) during the 4–6 hours immediately following the infusion. The recommended dose is a two-hour IV infusion of 9 mg/m². Shorter infusion schedules have not been tested. A second dose of gemtuzumab ozogamicin may be given 14 days after the first infusion regardless of hematopoietic recovery but may be postponed if patients have severe, life-threatening infection or elevated liver function tests (i.e., total bilirubin at least three times the upper limit of normal).

**Patient Monitoring and Intervention**

Patients should be monitored carefully throughout treatment with gemtuzumab ozogamicin. Table 1 reviews common side effects and appropriate nursing interventions. Vital signs (i.e., temperature, pulse, respiration, and blood pressure) should be taken at baseline, before infusion, as needed during infusion, and immediately at the end of infusion. These measurements should be repeated as needed for as long as four hours after treatment. Table 2 summarizes the acute infusion-related adverse events associated with gemtuzumab ozogamicin treatment (Wyeth Laboratories, 2000). Infusion-related symptoms generally occur shortly after the two-hour infusion and are resolved within 2–4 hours with supportive therapy. Patients often experience severe chills and spiking fevers within four hours of infusion. Other common acute infusion-related adverse events include nausea, vomiting, and headache. As a precaution, most patients should receive prophylactic medications including diphenhydramine, acetaminophen, and IV fluids. Blood cultures and septic work-up should be taken according to institutional policy. Patients experiencing chills should receive warm blankets and be treated with 50 mg IV diphenhydramine. If severe rigors persist, patients should be treated with IV meperidine. If fever and chills persist, patients should be admitted to an inpatient unit for continued observation and possible further intervention. Hypotension can occur several hours after the end of the infusion period, so an observation period is required to prevent this from occurring away from clinical supervision. Grade 3 or 4 nonhematologic infusion-related adverse events generally are rare but can include chills, fever, hypotension, hypertension, hyperglycemia, hypoxia, and dyspnea. Fewer infusion-related events, particularly those of grade 3 or 4 severity, are observed after the second dose.

Separating drug-related effects from known leukemia complications is difficult. Table 3 lists common treatment-emergent adverse events (Sievers, Larson, et al., 1999). Within 4–8 days after infusion, patients may experience elevated total bilirubin, AST, and ALT levels. Abnormalities in liver function generally are transient and reversible without intervention. Patients must be observed for elevated liver function. Total bilirubin, AST, and ALT levels should be monitored twice per week. Although some patients have reported anorexia and low-grade nausea, these side effects generally have not required antiemetic treatment.

### Table 1. Nursing Interventions

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Nursing Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion syndrome (i.e., fever and chills during and immediately after infusion)</td>
<td>Administer oral acetaminophen and diphenhydramine prior to infusion. Monitor vital signs • At baseline and during infusion • Before infusion • Immediately after infusion • Every hour for four hours. Admit patient if fever persists.</td>
</tr>
<tr>
<td>Chills and rigor</td>
<td>Instruct patient to wear warm clothes for infusion. Administer IV diphenhydramine and meperidine as ordered as needed. Wrap patient in warm blankets. Increase ambient air temperature. Admit patient if chills persist.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Administer antiemetics as ordered. Assess dehydration and electrolyte levels preinfusion and during course of treatment. Monitor nutritional status preinfusion and during course of treatment.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Monitor vital signs. Check for orthostatic tolerance every four hours. Monitor for tachycardia, dizziness, and shortness of breath. Administer fluids.</td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>Monitor aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels twice a week.</td>
</tr>
</tbody>
</table>
therapy. Nonetheless, patients should be counseled regarding the importance of maintaining adequate hydration and nutrition.

During the treatment phase, myelosuppression is the major toxicity. Figure 2 suggests guidelines for managing thrombocytopenia and infections in patients after gemtuzumab ozogamicin treatment. Because of disease- and treatment-induced thrombocytopenia and infections, supportive care during gemtuzumab ozogamicin treatment may include platelet transfusions and prophylactic broad-spectrum antibiotics, especially in febrile patients (Rebulla et al., 1997; Rubin, Hathorn, & Pizzo, 1988).

Education

To minimize treatment-associated anxiety, patients and their families need a fundamental understanding of antibody-targeted chemotherapy. Understanding infusion-related side effects, particularly fever, is key for patients preparing for treatment. Healthcare professionals should stress the frequent monitoring of body temperature during the period after the infusion as an aid in early detection of infections. Patients must plan to spend the entire day at the hospital or infusion clinic and make arrangements to have others drive them home. Nurses should suggest that patients bring warm clothes and any medications that may be needed over the course of the day. Patients should be assured that drug-related cardiac or cerebellar toxicities have not been reported with gemtuzumab ozogamicin treatment. The frequency of severe mucositis and infections is lower with gemtuzumab ozogamicin compared with conventional chemotherapy. Also, gemtuzumab ozogamicin is not associated with hair loss, a common side effect of conventional chemotherapy. During the recovery period, patients may require blood product support and, therefore, need frequent monitoring of their complete blood cell counts.

Summary and Conclusions

AML is an aggressive disease of the bone marrow that occurs more commonly in older adults. Patients present with life-threatening infections and bleeding and are diagnosed with AML when bone marrow biopsies reveal abnormal myeloid production. Conventional chemotherapy treatment will result in CR in 60%–80% of patients. However, even with postremission therapy, 75% of patients eventually will relapse. The lowest incidence of relapse is obtained when HSCT is used as postremission therapy. However, few older patients can tolerate transplantation procedures. Gemtuzumab ozogamicin is a novel antibody-targeted chemotherapy agent that delivers a potent cytotoxic antitumor antibiotic specifically to CD33+ myeloid cells. Phase I and II clinical trials have established the safety and efficacy of gemtuzumab ozogamicin, and the drug has been approved for treatment of patients 60 and older in first relapse with CD33+ AML. The peripheral WBC counts should be reduced to less than 30,000 cells/µL prior to the initiation of gemtuzumab ozogamicin therapy.

The most common infusion-related side effects are fever, chills, and, less commonly, hypotension and dyspnea. These

Table 2. Acute Infusion-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Severity (% of Patients)</th>
<th>Grade 3 or 4 (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>62</td>
<td>11</td>
</tr>
<tr>
<td>Fever</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Note. Based on information from Mylotarg® prescribing information (Wyeth Laboratories, 2000).

Table 3. Incidence of Grade 3 or 4 Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>99</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>97</td>
</tr>
<tr>
<td>Infections of any type</td>
<td>28</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>23</td>
</tr>
<tr>
<td>Elevated liver function</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16</td>
</tr>
<tr>
<td>Fever</td>
<td>15</td>
</tr>
<tr>
<td>Bleeding</td>
<td>15</td>
</tr>
<tr>
<td>Chills</td>
<td>13</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>11</td>
</tr>
</tbody>
</table>

Note. Based on information from Sievers, Larson, et al. (1999).
can be managed with appropriate nursing care, including the administration of antipyretic and antiemetic medications. As expected with this type of therapy, major adverse events with gemtuzumab ozogamicin are thrombocytopenia and neutropenia. These can be managed with platelet infusions and broad-spectrum antibiotics. Generally, transient elevations of hepatic transaminases and bilirubin may occur. Treatment with gemtuzumab ozogamicin provides patients 60 and older, who otherwise may not have an acceptable treatment option, with an opportunity for remission of relapsed AML. With further research, gemtuzumab ozogamicin also holds promise for other populations of people with AML.

References


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