Addressing Clinical Challenges in the Treatment of Leukemia

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INTRODUCTION

Leukemia is a malignant disease of the blood and bone marrow. It can be divided into 4 categories: myelogenous or lymphocytic, each of which can be acute or chronic. Acute leukemias, including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), progress rapidly and are characterized by ineffective, immature cells in the bone marrow that crowd out and prevent development of normal cells. Chronic leukemias, such as chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL), allow development of more normal cells and tend to progress more slowly.

Recently, the delineation and clarification of prognostic factors, advances in supportive care, and the implementation of more effective chemotherapeutic regimens have resulted in improved outcomes for patients with leukemia. In addition, a better understanding of the biology and molecular pathogenesis of various types of leukemia has led to the development of new, targeted agents that have the potential to be more effective and less toxic than standard therapies. At the 44th annual meeting of the American Society of Clinical Oncology (ASCO), held May 30-June 3, 2008, in Chicago, Illinois, researchers presented safety and efficacy data from clinical trials evaluating novel agents and treatment regimens for leukemia. Oncology nurses need to be aware of these recent findings so that they may be better equipped to educate patients about available treatment options and provide appropriate supportive care.
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OVERVIEW OF ACUTE MYELOID LEUKEMIA

AML is a form of cancer in which the bone marrow produces abnormal myeloblasts, red blood cells, or platelets. This year alone, an estimated 13,290 people will be diagnosed with AML and 8820 patients will die from the disease. More than one third of newly diagnosed patients are aged ≥75 years, and the median age at diagnosis is 67 years. The incidence of AML is expected to increase in coming years as a substantial proportion of the population will be classified as elderly.

Standard Treatment of AML

Induction therapy

Treatment induction for patients aged <60 years without antecedent hematologic disease (myelodysplastic syndrome [MDS]) typically involves 2 cycles of standard-dose cytarabine (100-200 mg/m² continuous infusion for 7 days) and an anthracycline (eg, idarubicin or daunorubicin) for 3 consecutive days. Another therapeutic option is high-dose cytarabine 2 to 3 g/m² and an anthracycline for 1 cycle. For patients aged 60 to 75 years, induction treatment is based on performance status (PS). Low-intensity therapy (ie, subcutaneous [SC] cytarabine or hydroxyurea) or best supportive care is recommended for patients with a PS ≥2.

Cytogenetic aberrations detected at diagnosis are important predictors of clinical outcome. In general, patients with ≥5 chromosomal abnormalities reap minimal benefits from standard treatments and are more suited for investigational therapy or supportive care. The National Comprehensive Cancer Network (NCCN) recommends cytogenetic studies to improve treatment selection. If complex chromosomal abnormalities are detected, a clinical trial is preferred. Other potential treatment options include standard-dose cytarabine with an anthracycline, or mitoxantrone for up to 2 cycles. A clinical trial or standard chemotherapy represents acceptable treatment options for patients without complex cytogenetics. Typically, patients aged >75 years with significant comorbidities do not benefit from conventional chemotherapy or clinical trials. For these patients, low-intensity therapy or best supportive care are recommended.

Consolidation therapy

A common consolidation therapy regimen for patients aged <60 years with good or intermediate cytogenetics is 3 to 4 cycles of high-dose cytarabine (3 g/m²). Alternately, 1 to 2 cycles of high-dose cytarabine-based consolidation therapy followed by autologous hematopoietic stem cell transplant (HSCT) or enrollment in a clinical trial may also be appropriate options. For patients with poor-risk cytogenetics, molecular abnormalities, or therapy-related AML or previous myelodysplasia, the NCCN recommends allogeneic HSCT, human leukocyte antigen (HLA)-matched unrelated donors, or enrollment in a clinical trial. For those with poor prognosis features, approaches to treatment include matched sibling HSCT, alternative donor HSCT, or inclusion in a clinical trial.

For patients aged ≥60 years, consolidation therapy may consist of reduced-intensity HSCT, or standard-dose cytarabine with or without an anthracycline, or enrollment in a clinical trial. For patients with good PS, normal renal function, or good or normal karyotypes, 4 to 6 doses of cytarabine (1-1.5 g/m²/day) for 1 to 2 cycles is another option.

Treatment for relapsed disease

For patients aged <60 years with an early relapse (<6 months), enrollment in a clinical trial is recommended. If relapse occurs when tumor burden is low and the patient has a previously identified sibling or unrelated donor, allogeneic HSCT may be considered as primary therapy. If patients relapse after a long remission (≥6 months), retreatment with previously successful regimens or new therapies in a clinical trial setting are recommended. Viable treatment options for disease relapse in patients aged ≥60 years include the following:
- Clinical trial (strongly preferred)
- Treatment with gemtuzumab ozogamycin (a monoclonal antibody used in patients aged ≥60 years with relapsed AML who are not candidates for standard chemotherapy)
- Repeat initial induction therapy if a long initial remission was achieved
- Best supportive care for patients who do not wish to receive intensive therapy

Treatment Complexities: Disease Relapse and Older Patients

Disease relapse is a major cause of treatment failure, occurring in approximately 50% to 80% of patients who achieve complete remission. Relapse factors to consider include: duration of first complete remission, age, PS, other comorbidities, and the availability of an HLA-compatible donor. The likelihood of achieving a second complete remission is related to the duration of first complete remission, with cytogenetic

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<td>Characteristic</td>
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risk group becoming less important. Attaining a second complete remission with salvage chemotherapy is possible, but greater toxicity is experienced than during initial induction, and the second remission is usually shorter. AML is particularly challenging to treat in elderly patients. Standard chemotherapy is often mired by frequent or serious comorbid conditions. Older patients often have a more aggressive tumor biology with a greater incidence of unfavorable karyotypes (Table 1). In fact, AML biology varies by age, with elderly patients having a higher incidence of poor prognosis karyotypes, a higher frequency of previous MDS, and a greater expression of proteins resistant to chemotherapy. Older patients have a greater incidence of secondary leukemia and a limited capacity of hematopoietic recovery after chemotherapy. More intense induction regimens may not increase the likelihood of complete remission without increasing the number of serious adverse events (SAEs) and complications in this population. Thus, many older patients require investigational agents rather than standard induction therapy. Despite the need to provide effective, less toxic therapy for older patients with AML, this population remains underrepresented in clinical trials.

New Treatment Approaches for Patients with AML
Chemotherapy
Several new treatment options are being investigated for both younger and older patients with AML. Results from clinical trials evaluating novel therapies in older patients were presented at ASCO 2008. Among these new therapies is clofarabine, a next-generation nucleoside analogue. Erba and colleagues reported results from a phase 2 study of single-agent clofarabine in 116 patients with AML aged ≥60 years who were unlikely to benefit from standard induction chemotherapy. The induction dose was 30 mg/m² (1-hour infusion, days 1-5) and the reinduction/consolidation dose was 20 mg/m² (up to 6 cycles). Overall remission rate (ORR) in this study was 43%. Most treatment-related adverse events (AEs) were grade 1/2 in severity. The researchers concluded that clofarabine monotherapy was active and well tolerated in this population of patients.

Cloretazine, which belongs to the novel sulfonylhydrazine class of alkylating agents that damage DNA, represents another novel agent with the potential to improve outcomes. At ASCO 2008, Schiller and colleagues presented findings from a phase 2 trial evaluating cloretazine monotherapy in 85 older patients with de novo poor-risk AML. Induction therapy consisted of 600 mg/m² (60-minute infusion, day 1). In this trial, an ORR of 35% was observed with this regimen. Of the responders, 90% achieved remission after 1 induction cycle. The most common SAEs were myelosuppression or infection. Researchers concluded that cloretazine monotherapy provided antileukemia activity in this population, despite additional poor risk factors.

Efficacy and safety data on clore-tazine plus cytosine arabinoside in 210 patients with first relapse occurring after first complete remission of AML were reported by DeAngelo and colleagues. Patients received either cytosine arabinoside 1.5 g/m² (days 1-3) and cloretazine 600 mg/m² (treatment group) or cytosine arabinoside 1.5 g/m² (days 1-3) and placebo (control group). This trial was discontinued in 2007 because of disproportionate death rates between the treatment and control groups: 39% (55/140) and 8.6% (6/70), respectively. ORR for treatment and control groups was 37% versus 19%, respectively. P=.004. Grade 3/4 AEs in this trial included myelosuppression and infection.

FLT3 inhibitors
The FLT3 receptor, which is a member of the class III receptor tyrosine kinase family, plays an important regulatory role in hematopoiesis. FLT3 receptor mutations occur in a large percentage of patients with AML and are associated with adverse prognosis.

Midostaurin is a potent small-molecule inhibitor that targets both mutated and wild-type FLT3 and other molecular targets in AML. Stone and colleagues demonstrated the clinical activity of oral midostaurin (75 mg, 3 times daily) in 210 patients with mutant FLT3 relapsed/refractory AML. Following treatment, peripheral blast count decreased by 50% in 70% of patients.

At ASCO 2008, Yin and colleagues presented findings from a phase 1/2 pharmacology study of midostaurin in 115 patients with FLT3-mutated AML. Twenty patients with FLT3-mutated AML received midostaurin 75 mg 3 times daily (cohort 1); 95 patients with wild-type or FLT3-mutated AML were randomized to 50- or 100-mg twice-daily midostaurin (cohort 2). Midostaurin was biologically active in both mutations. In cohort 1, 80% of patients responded to treatment, and in cohort 2, 38% and 66% of patients with wild-type or FLT3-mutated AML, respectively, responded to treatment.

Another small-molecule tyrosine kinase inhibitor (TKI) targeting FLT3 is lestaurtinib. Knapper and colleagues evaluated this agent as monotherapy in a phase 2 multicenter, open-label trial involving untreated older patients (N=29) with AML who were unfit for intensive chemotherapy. Oral lestaurtinib (60 mg twice daily, increased to 80 mg twice daily) was administered for 8 weeks. Although lestaurtinib was
well tolerated, it achieved only relatively modest clinical responses: 60% of patients with FLT3-mutated AML and 23% of patients with wild-type FLT3 mutations.

Additional FLT3 inhibitors under investigation are semaxanib and sunitinib. Giles and colleagues showed that semaxanib 145 mg/m² twice weekly was active in 55 patients with refractory AML. Three patients achieved partial responses and 1 patient achieved hematologic improvement. Overall median survival was 12 weeks. Fiedler and colleagues demonstrated that oral sunitinib monotherapy (50 mg and 75 mg) induced partial remissions of short duration in patients with refractory AML. Patients with FLT3 mutations responded better than those with wild-type receptors.

Other novel approaches

Novel therapeutic approaches currently being studied include amonafide, tipifarnib, epigenetic therapy, and advances in transplantation. Amonafide is an adenosine triphosphate-independent topoisomerase II inhibitor developed for the treatment of secondary AML. At ASCO 2008, Rizzi and colleagues reported the durable complete remission of this agent plus cytosine arabinoside across poor-risk subsets of patients (N=88) with secondary AML, including older patients, and those with previous MDS or leukemogenic therapy. Patients with secondary AML received amonafide 600 mg/m² on days 1 to 5 and cytosine arabinoside 200 mg/m² continuous infusion on days 1 to 7. Complete remission was seen in 42% of patients, and was also consistent across poor-risk subgroups. The median duration of complete remission was >9 months for patients aged >60 years; median overall survival (OS) was 7 months, and for complete remission patients, >11 months.

Tipifarnib is a farnesyltransferase inhibitor that inhibits cell growth, induces apoptosis, and inhibits angiogenesis. At ASCO 2008, Feldman and colleagues presented final results of a phase 1, dose-finding, multicenter, open-label trial of tipifarnib (200 mg twice daily for 21 days) plus low-dose cytosine arabinoside (10 mg SC twice daily for 10 days) in 26 patients with untreated AML (aged ≥65 years) or relapsed/refractory AML (aged >18 years). Five patients with MDS were also included. Complete response was seen in 13% of all participants and 16% of patients in the maximum tolerated dose (MTD) group. MTD for tipifarnib and cytosine arabinoside was 300 mg and 15 mg, respectively, and common grade 3/4 events included neutropenia, thrombocytopenia, and anemia.

Another factor affecting adult outcomes is a greater incidence of the Philadelphia chromosome.

Epigenetic therapy with agents such as decitabine, 5-azacytidine, and histone deacetylase inhibitors is another promising strategy for the treatment of AML. In addition, advances in stem cell transplant technology, such as reduced-intensity conditioning regimens and alternative stem cell sources, have improved outcomes and established allogeneic transplantation as a main strategy in both younger and older patients.

Conclusion

The incidence of AML among elderly patients is high and treatment remains especially challenging because of age, poor PS, comorbidities, poor prognosis karyotypes, and AEs associated with standard chemotherapy regimens. Novel therapies have shown promising results and may positively affect treatment paradigms and outcomes among elderly patients.

OVERVIEW OF ACUTE LYMPHOBLASTIC LEUKEMIA

ALL is a form of cancer in which the bone marrow produces too many lymphocytes. In 2008, 5,430 new cases of ALL and 1,460 deaths from ALL are expected. Age represents an important factor in ALL; prognosis has been shown to be better in patients aged <35 years. Factors contributing to poor outcomes in adults include greater frequency of high-risk leukemia with greater drug resistance, poor tolerability and compliance with therapy, and less effective treatment regimens.

Another factor affecting adult outcomes is a greater incidence of the Philadelphia chromosome, a specific chromosomal abnormality that results from reciprocal t(9;22) (q34;q11) chromosome rearrangements that fuse coding regions of the BCR gene, located on chromosome 22, with the ABL receptor independent tyrosine kinase gene on chromosome 9. BCR/ABL t(9;22) translocations are associated with poor prognosis and are present in approximately 20% to 50% of adult patients with ALL, compared with 2% to 10% of pediatric ALL patients. Patients with Philadelpia-positive (Ph+) ALL are rarely cured with chemotherapy alone.

Previous studies have shown that adolescents with ALL benefit more from pediatric rather than adult chemotherapy regimens. This may be partly explained by the greater amount of steroids, vincristine, and L-asparaginase given to children with ALL. Recently, Huget and colleagues tested the use of pediatric regimens in adults aged 15 to 60 years with Philadelphia-negative ALL. Results showed that regimens consisting of a 5-drug induction, high dose-intensity consolidation blocks, delayed intensification, and 2-year maintenance substantially improved outcomes in adult patients aged up to 45 years. Complete remission was achieved in 93.5% of patients.
Standard Treatment of ALL

**Induction therapy**

Induction regimens frequently used to treat adult ALL include prednisone, vincristine, and an anthracycline. In some instances, other drugs are added, such as asparaginase or cyclophosphamide. Combination therapy induction regimens typically produce complete response rates in the range of 60% to 90%. For patients with Ph+ ALL, imatinib should be added to maintenance regimens.21

**Consolidation therapy**

Patients with ALL are candidates for consolidation therapy once normal hematopoiesis is achieved. For adults, treatment entails short-term, intensive chemotherapy followed by longer term therapy at lower doses, high-dose marrow-ablative chemotherapy or chemoradiation with allogeneic stem cell rescue, and high-dose therapy with autologous stem cell rescue. For patients with Ph+ ALL, imatinib should be added to maintenance regimens.21 In children, commonly used consolidation regimens include high-dose methotrexate with mercaptopurine, high-dose asparaginase for long duration, and reinduction treatment. Using one regimen does not prohibit the use of others, and for patients with high-risk ALL, use of all treatments may be beneficial.

**Hyper-CVAD**

Hyper-CVAD indicates hypofractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine therapy.

**New Treatment Approaches for Patients with ALL**

TKIs such as imatinib, dasatinib, nilotinib, bosutinib, and INNO-406 dominate the new treatment investigations for ALL. Disease recurrence with hyper-CVAD (hypofractionated cyclophosphamide vincristine, doxorubicin, dexamethasone + high doses of methotrexate and cytarabine therapy) remains problematic. Thus, Thomas and colleagues evaluated the addition of imatinib (600 mg days 1-14; 600 mg continuously for courses 2-8; 800 mg maintenance) to this regimen for de novo or minimally treated patients with Ph+ ALL (N=54). A total of 93% of patients with active disease and all 6 patients with refractory disease attained complete remission with treatment. Moreover, the addition of imatinib improved outcomes compared with hyper-CVAD alone (Figure).25 In another trial, the TKI dasatinib 50 mg twice daily added to hyper-CVAD demonstrated a high complete remission (90% after cycle 1) and complete molecular remission rates (47%) in patients with newly diagnosed Ph+ disease.26

Kantarjian and colleagues conducted a phase 1 trial to evaluate nilotinib (50-700 mg once daily and 400 and 600 mg twice daily) in patients (N=119) with imatinib-resistant CML or Ph+ ALL. Researchers found that 1 of 10 patients with Ph+ ALL had a partial hematologic response and 1 of 3
patients with persistent molecular signs of ALL had a complete molecular remission. Another TKI, bosutinib, was shown to be active in Ph+ ALL and CML. At ASCO 2008, Gambacorti-Passerini and colleagues presented data on its use in 72 patients who failed or were intolerant to imatinib and other TKIs. In this open-label trial, patients received bosutinib 500 mg daily; treatment was well tolerated and gastrointestinal symptoms were the main AE. Efficacy and safety data for INNO-406 (30 mg once daily to 480 mg twice daily) for treatment of 46 patients with advanced Ph+ ALL resistant or intolerant to imatinib or other TKIs were also presented at the meeting. Complete cytogenetic responses were seen in 3 patients. Grade 3/4 drug-related AEs included increased liver enzymes, thrombocytopenia, and acute renal failure.

Conclusion

Patient age is an important predictor of outcomes in ALL. Poor outcomes in adults have been attributed to a greater incidence of high-risk leukemia with greater drug resistance, poor tolerability and compliance with therapy, less effective treatment regimens, and Ph+ disease status. Several trials involving TKIs have yielded positive results, and these agents may improve the cure rates in adults with ALL.

OVERVIEW OF CHRONIC LYMPHOCYTIC LEUKEMIA

CLL is a disorder of morphologically mature but immunologically less mature lymphocytes. CLL manifests as increased accumulation of lymphocytes in the blood, bone marrow, and lymphatic tissues. In 2008, 15,110 new cases and 4390 deaths from the disease are expected in the United States. This form of leukemia occurs mainly in middle-aged and elderly persons and its incidence increases in later decades of life. The clinical course of CLL is heterogeneous; some patients have a normal life expectancy whereas others have drug-resistant disease and die within 2 years of diagnosis. In recent years, prognostic markers such as chromosomal abnormalities have been used to stratify patients in clinical trials and to individualize treatment. As shown in Table 2, 13q abnormalities have a favorable prognosis, whereas trisomy 12q and 11q abnormalities have less favorable outcomes. Chromosomal abnormality 17p is associated with mutated p53 and with poor response rates and shorter response to standard treatments. In addition, zeta-chain-associated protein kinase (ZAP)-70 is a potential surrogate marker for mutational status; ZAP-70 positivity in previously untreated and asymptomatic patients has a more unfavorable median survival compared with ZAP-70 negativity.

Table 2. Chromosomal Abnormalities and Associated Prognosis in Patients with CLL

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<th>Chromosomal Abnormality</th>
<th>Median Survival (months)</th>
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<tr>
<td>Normal karyotype</td>
<td>Favorable outcome</td>
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<tr>
<td>Trisomy 12q</td>
<td>Atypical morphology; intermediate outcome</td>
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<tr>
<td>13q abnormality</td>
<td>Favorable outcome if isolated abnormality</td>
</tr>
<tr>
<td>11q abnormality</td>
<td>Extensive lymphadenopathy; shorter treatment-free interval; shorter survival time</td>
</tr>
<tr>
<td>17p abnormality</td>
<td>Shorter treatment-free interval; shorter survival time; resistance to fludarabine</td>
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CLL manifests as increased accumulation of lymphocytes in the blood, bone marrow, and lymphatic tissues.

New Treatment Approaches for Patients with CLL

At ASCO 2008, several research groups presented data on the use of novel therapies for CLL, including alemtuzumab, rituximab, lumiliximab, oblimersen, and imatinib. Elter and colleagues demonstrated that combination fludarabine (25 mg/m²), cyclophosphamide (200 mg/m²), and the monoclonal antibody alemtuzumab (300 mg SC) was safe and effective in 20 patients with relapsed/refractory
CLL. Overall response rate was 70% and the most serious side effects were thrombocytopenia and neutropenia.\(^{32}\)

In another trial, first-line use of alemtuzumab 10 mg SC 3 times daily for 18 weeks appeared to be as effective as standard chemotherapy and was well tolerated in elderly patients (N=48) with B-CLL. Seven percent of patients had a complete response and 33% had a partial response. In treatment responders, median progression-free survival (PFS) was 11.8 months and OS was 30 months.\(^{33}\)

In a separate study, Woyach and colleagues evaluated combined use of rituximab (375 mg/m\(^2\) infused 3 times weekly) and etanercept (25 mg SC twice weekly) in 34 patients with relapsed CLL/small lymphocytic lymphoma. The overall response rate was 29%, median response duration was 12.3 months, and median PFS was 6.5 months. AEs were mild and included infusion reactions, cytopenias, and infections.\(^{34}\)

In a phase 1/2 multicenter trial, Byrd and colleagues found that the monoclonal antibody lumiliximab plus fludarabine, cyclophosphamide, and rituximab (375 mg/m\(^2\) or 500 mg/m\(^2\)) for up to 6 cycles was effective and safe for patients with relapsed B-CLL. Overall, complete, and partial response rates were 65%, 52%, and 13%, respectively. Median PFS for all responders and complete responders was 23.4 and 30.4 months, respectively. Furthermore, no additional toxicity was seen with the addition of lumiliximab.\(^{35}\)

Rai and colleagues evaluated the long-term effects of adding the antisense oligonucleotide, oblimersen (3 mg/kg/day for 7 days, 4 days before chemotherapy) to fludarabine and cyclophosphamide in relapsed/refractory CLL. The addition of oblimersen to chemotherapy significantly increased complete response rate compared with chemotherapy alone: 17% versus 7%, respectively (\(P=0.025\)). Duration of response was also significantly greater with the addition of oblimersen: approximately 36 months versus 22 months, respectively (\(P=0.031\)).\(^{36}\)

Data from a phase 1 trial demonstrated that the TKI imatinib (300-600 mg/day) plus chlorambucil (8 mg/m\(^2\)) for up to 6 cycles was effective and safe in 11 previously treated patients with CLL. Overall response in this trial was 40%. One dose-limiting toxicity (grade 3 thrombocytopenia) and 2 severe AEs (pneumonia and herpes) were documented.\(^{37}\)

**Conclusion**

CLL mainly affects middle-aged and elderly persons. Relatively recent identification of prognostic markers, particularly chromosomal abnormalities, has been used to stratify patients in clinical trials and select treatment. Standard treatment of CLL includes chemotherapy, steroids, monoclonal antibodies, radiation, and transplantation. Novel monoclonal antibody and antisense oligonucleotide agents have yielded promising efficacy and safety data in trial settings, and these therapies may hold value in clinical practice settings.

**References**


NURSING MANAGEMENT OF PATIENTS WITH LEUKEMIA: TREATMENT-RELATED SIDE EFFECTS

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In 2008, an estimated 44,000 individuals (children and adults) will be diagnosed with some form of leukemia. This disease is not limited to one specific age group; therefore, it is imperative that both pediatric and adult oncology nurses are apprised of the latest advances in treatment. Nurses must also be aware of the common side effects related to leukemia therapy and appropriate management strategies.

The most common side effect associated with leukemia therapy is myelosuppression (Table). Traditional chemotherapeutic agents exert their cytotoxic action through the destruction of actively dividing cells, with an inability to distinguish between normal cellular function and malignant cellular function. These cytotoxic effects can cause destructive changes to bone marrow function, leading to a disruption in the formation and development of blood cells (hematopoiesis). The result is myelosuppression, which can manifest as:

- decreased production of white blood cells and increased risk of neutropenia and infection;
- decreased production of red blood cells and increased risk of anemia;
- decreased platelet production and increased risk of thrombocytopenia and bleeding.

Neutropenia

For the oncology patient receiving cytotoxic therapy, neutropenia has long been identified as a major risk factor in the development of infection. The signs and symptoms of infection may be absent or very discreet due to neutropenia, the absence of neutrophils, or the inability to mount an inflammatory response. Therefore, fever that develops in a neutropenic patient must be promptly evaluated as a possible sign of infection. The use of corticosteroids, which are pivotal in the treatment of both ALL and CLL, may also mask the inflammatory response of infection, thereby delaying the onset of fever and the prompt treatment of infection.

In addition, monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs), which have recently been added to the therapeutic armamentarium for leukemia, may increase the risk of opportunistic infections, as well as other treatment-related toxicities (Table).

The most common side effect associated with leukemia therapy is myelosuppression.

According to the National Comprehensive Cancer Network (NCCN) guidelines, neutropenic patients should receive empiric broad spectrum antibiotics at the first indication of infection. This intervention is necessary to prevent a delay in treatment for patients who may have bacteremia or other serious infections.

Nurses need to be aware that the neutropenic patient is not only at risk for bacterial infections, but other opportunistic infections, including parasitic, fungal, and viral. Patients with long periods of neutropenia may be prescribed prophylactic trimethoprim/sulfamethoxazole to prevent the parasitic infection of Pneumocystis jirovecii (previously Pneumocystis carinii). Prophylactic antifungal and antiviral agents are also used during neutropenic periods to prevent fungal and viral infections.

The prophylactic use of antibiotics and antiviral therapy has been shown to reduce morbidity in high-risk pediatric AML patients. Over a 4-year study, prophylactic administration of intravenous cefepime or vancomycin and voriconazole was reported to decrease the incidence of septicemia, as well as the number of days of hospitalization. Although the use of prophylactic antibiotics raises concerns over the development of resistant enterococcal and fungal infections, only 3 of the 78 patients developed vancomycin-resistant Enterococcus colonization or bacteremia. Furthermore, patients receiving prophylactic antibiotics in this study experienced a decrease in fungal infections compared with those in previous studies.

Oncology nurses play a key role in educating patients and their caregivers on the importance of prompt recognition and reporting of fever or other signs of infection, including chills, diaphoresis, edema, tenderness or erythema, or drainage from any site. Changes in mental status, respiration, and urine or stools (including burning and diarrhea) should also be reported.

Anemia

Another side effect of leukemia and its treatment is anemia, which presents in 20% to 60% of all cancer patients at the time of diagnosis. Unfortunately, this condition is frequently undertreated, in spite of its high incidence. Anemia is an imbalance between the production and destruction (or loss) of red blood cells, resulting in decreased red blood cell count, hemoglobin content, and oxygen-carrying capacity of the blood.
Anemia may also be related to preexisting comorbidities resulting from bleeding, hemolysis, renal insufficiency, malnutrition, and/or other chronic illnesses. The use of cytotoxic agents may cause nutritional deficiencies, which further contribute to anemia.

Transfusions of packed red blood cells are the standard treatment for anemia in this patient population. Erythropoiesis-stimulating agents (ESAs) have been used in conjunction with cytotoxic agents in the prevention of anemia. However, a recently released statement by the US Food and Drug Administration set restrictions on the use of ESAs for patients receiving myelosuppressive chemotherapy without curative intent, due to an increased risk of disease progression and shortened survival in patients with lymphoid cancers.7

Anemia is commonly associated with symptoms of fatigue. Cancer-related fatigue is defined as “a distressing persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”8 Of 419 oncology patients asked to assess their treatment-related symptoms, 60% cited fatigue as the most distressing side effect of therapy.9,10 Beyond the physically distressing symptoms of fatigue, cancer patients may worry that this condition is indicative of disease progression or recurrence.

A balance of rest and exercise is important to maintain functional homeostasis. Garcia and colleagues reported the results of a 6-week interventional exercise program for leukemia patients during the induction phase of therapy. The program was conducted by an exercise physiologist and was modified weekly based on patient tolerance. An initial battery of fitness and psychological assessments were completed within the first 3 days of induction, with exercise interventions prescribed 3 to 4 times per week. Evaluations at designated intervals during and at the completion of induction therapy were conducted using the Revised Piper Fatigue Scale and Depression questionnaire. Patient evaluations demonstrated a 62.5% decrease in overall fatigue and a 35.3% decrease in depression symptoms.11

Thrombocytopenia

Treatment-induced thrombocytopenia, defined as a platelet count <100,000/mcL, is the most common cause of bleeding in oncology patients. The risk of bleeding increases when the platelet count is <50,000/mcL, with counts <20,000 increasing the risk of spontaneous bleeding.12 The most common sites of bleeding include the mucous membranes, skin, gastrointestinal system, genitourinary system, and respiratory tract.

Oncology nurses play an integral role in providing education and supportive care to patients who are at an increased risk of bleeding. They should advise patients to use soft bris-
tle toothbrushes and electric razors and avoid the use of rectal thermometers and suppositories. Soft foods, increased fluids, and stool softeners are preventive measures that can minimize trauma to the gastrointestinal tract. Patients and family members should be advised to remove environmental hazards that may contribute to falls or other trauma. Nurses should also routinely monitor for nosebleeds, melanotic stools, and hematuria, as well as for occult bleeding in emesis, urine, and stool.

Although platelet transfusion remains the most common intervention in the management of thrombocytopenia, alloimmunization and transmission of viral and bacterial infections may occur, and patients must be advised of these possible complications.

New Therapies and Side Effect Considerations

A better understanding of the heterogeneity of leukemia has led to the development of new targeted therapies, including monoclonal antibodies and small-molecule TKIs. Gemtuzumab ozogamicin is a monoclonal antibody used in the treatment of AML. Its side effects include hepatotoxicity and myelosuppression (Table). Infusion-related toxicities may include low-grade chills, fever, nausea, vomiting, and anaphylaxis.

Imatinib is a potent TKI used in the treatment of Philadelphia-positive (Ph+) CML and ALL. Nilotinib has received approval for the treatment of CML and is showing promise in clinical trials for Ph+ ALL. Besides being effective, these agents may also have better safety profiles than imatinib.

The presence of the FLT3 mutation in AML patients has been shown to correlate with an increased relapse risk and reduced overall survival, making it an attractive therapeutic target. Sorafenib and lestaurtinib are agents currently in clinical trials to determine their clinical effect on FLT3 mutations. Their side effects include cardiac failure, hypertension, bleeding, and gastrointestinal toxicity.

Nursing Management

Oncology nurses play a key role in the education and support of leukemia patients and their families. This should include an emphasis on proper nutrition, a balance of rest and exercise, prevention of infection, and the prompt reporting of side effects. Prior to the initiation of therapy, a comprehensive assessment of the patient’s physical and emotional status should be performed. This will establish a baseline against which any adverse reactions to therapy can be compared. As integral members of the cancer care team, nurses understand that toxicities are not just numbers on a patient’s chart. Observing how their patients respond after each round of therapy and evaluating trends over time are essential for providing prompt and appropriate interventions.

References