Implications of improved survival in patients with chronic myeloid leukemia: a nursing perspective

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With the introduction of tyrosine kinase inhibitor (TKI) therapy and the development of more sensitive monitoring techniques, the management of patients with chronic myeloid leukemia (CML) has evolved considerably over the last decade. In this review, we summarize the available literature evaluating the safety and efficacy of the TKIs imatinib, dasatinib, and nilotinib for information relevant to patient management to provide insight into long-term management of CML patients who receive TKI therapy. We suggest that these developments in treatment have expanded the role of oncology nurses, who can help address new issues that have arisen for patients learning to adapt to a chronic condition. The essential practice of monitoring, the critical importance of medication adherence, the safety profile of the three available TKIs, strategies for supportive care related to adverse events, drug-drug and drug-food interactions, and family planning are important aspects of long-term patient management.

Chronic myeloid leukemia (CML) is a rare hematologic cancer that originates in the bone marrow. It represents about 20% of all leukemias, and an estimated 5,000 new patients were diagnosed with the disease in the United States in 2010. The disease is slightly more common in men than it is in women, and it primarily affects older individuals. Although the median age at diagnosis is 65 years, it can occur across the life span: in the years 2004 to 2008, 20% of patients were diagnosed at age 44 years or younger, 30% between ages 45 and 64, and 50% at age 65 or older.[1]

Significant advances in the treatment of CML have increased the survival rate significantly. In 1975, the 5-year survival rate for a newly diagnosed patient was 19%; in 2002, it was 53%. With tyrosine kinase inhibitor (TKI) therapy, the most recent overall survival (OS) rate with 8 years of treatment was 85%.[2] With prolonged survival, CML can be managed in a manner similar to that used for a serious illness,[3] with an emphasis on ongoing patient education, support, and symptom management.

The oncology nurse's role

Oncology nurses are integral members of the multidisciplinary team and an invaluable resource for patients and their caregivers. The role of oncology nurses has expanded as new treatment options have become available, expectations for survival have increased, and monitoring has become more sophisticated. Understanding important aspects of CML (including treatment advances, required disease monitoring, long-term medication adherence, drug-drug interactions, and issues related to family planning) will help oncology nurses address the many questions and concerns patients may have as they learn to live with CML as a chronic condition.

Overview of CML

Pathophysiology

The cause of CML is a genetic abnormality known as the Philadelphia chromosome (Ph).[4] This chromosome is formed by a reciprocal translocation, or rearrangement, between chromosomes 9 and 22. Ph-positive (Ph$^+$) cells possess an abnormal gene, *BCR–ABL*, that produces an aberrant tyrosine kinase (TK) protein. The TKs normally help to regulate cell growth, division, and differentiation. The ab-

errant BCR-ABL TK, however, has elevated activity, which leads to dysregulated cell processes, malignant transformation, increased proliferation, and accumulation of immature myeloid cells in the blood and bone marrow. Confirmation, in 1990, that the BCR-ABL TK is the root cause of CML[5] led to the rapid development of targeted treatment with the ability to suppress the proliferation of cells that express the BCR-ABL TK.[6] The development of more potent agents soon followed, giving clinicians a powerful new armamentarium that has revolutionized the treatment of CML.

Clinical features

The diagnosis of CML is often an incidental finding during a routine check-up or blood test for an unrelated health problem; about 40% to 50% of patients are asymptomatic at diagnosis.[7] Objectively, the peripheral blood smear is typically characterized by leukocytosis.[4] Subjectively, symptoms may include weakness, fatigue, dyspnea, night sweats, weight loss, pallor, fever, joint or bone pain, abdominal fullness, and early satiety.[4,7] Most of these symptoms are related to anemia, thrombocytopenia, or neutropenia.[7]

Phases of disease

The disease progresses through three successive phases: chronic phase (CP), accelerated phase (AP), and blast crisis (BC).[8] Eighty-five percent of patients are diagnosed in CP.[7] Without treatment, CP-CML could last 4 to 6 years.[4] The next phase, AP, is characterized by rapid growth of leukemic cells as blasts make up an increasing percentage of cells in the bone marrow or peripheral blood. This phase could last 3 to 18 months, although progression to BC might occur within a few weeks or months.[4] The final and fatal phase, BC, is characterized by increased numbers of blasts in the blood or bone marrow. It is defined as ≥ 20% blasts in blood or bone marrow, a value specified by the World Health Organization, or ≥ 30% blasts in blood, marrow, or both, as specified by the International Bone Marrow Transplant Registry. National Comprehensive Cancer Network (NCCN) Guidelines have included both these definitions for BC.[9] Historically, the median survival for patients in BC has been 3 to 6 months.[8]

Treatment Options

Past treatments for CML incorporated approaches that had been developed for other indications.[10] Many of those treatments, such as radiation and chemotherapy with busulfan or hydroxyurea, had no impact on disease progression and did little to prolong survival. Indeed, the median survival of patients receiving radiation or chemotherapy was 3 to 5 years.[11] In the early 1980s, researchers began the clinical development of interferon alfa (IFN-α) for CML. It was the first treatment for CML that was shown to improve survival and slow the rate of disease progression.[12,13] The 5-year survival rate in one randomized, comparative study was 52% for patients who received IFN-α compared with 34% for those who received standard chemotherapy.[12] However, IFN-α was often poorly tolerated by the patients and associated with high discontinuation rates. Common adverse events (AEs) have included flu-like symptoms (experienced by almost all patients), gastrointestinal tract disorders (≤ 60% of patients), psychiatric symptoms (including depression/anxiety, ≤ 18%), dermatologic effects (≤ 33%), and chronic autoimmune-related toxicity (≤ 70%).[14] Poor tolerability was noted to be the major problem with IFN-α treatment.[13]

Allogeneic stem cell transplantation (SCT) offers a subset of patients, especially those who are younger and who have human leukocyte antigen (HLA)–matched donors, the prospect of a cure. Most CML patients (> 70%), however, are ineligible for SCT.[15] Further, this approach carries substantial risks. One long-term study in 102 patients with CP-CML who received transplants from HLA-identical sibling donors found that the 15-year OS was 53%. Infection was a common cause of mortality: 17 patients died from chronic graft-versus-host disease (GVHD) with superimposed infection, 8 died from infection without GVHD, and 1 died from hematologic relapse. Long-term morbidities included invasive cancer, cardiac or respiratory failure, cataracts, osteonecrosis, and endocrinopathies.[16]

The current era of treatment began in 2001, with the Food and Drug Administration's (FDA's) approval of the first TKI, imatinib. It quickly replaced IFN-α as the standard of care after a randomized comparative study of imatinib and IFN-α plus low-dose cytarabine demonstrated significantly higher response rates with imatinib.[17] Not only was imatinib highly superior but most of the patients receiving IFN-α crossed over to the imatinib arm. The rates of complete cytogenetic response (CCyR) after a median follow-up of 19 months were 76.2% in the imatinib arm compared with 14.5% in the IFN-α plus low-dose cytarabine arm ($P < .001$). Imatinib was also better tolerated. An 8-year analysis of this study demonstrated the durability of responses: the estimated event-free survival rate was 81%, the rate of freedom from transformation to AP/BC was 92%, and OS was 85%; OS was 93% when only CML-related deaths and those before SCT were analyzed.[2]

The development and approval of second-generation TKIs soon followed. Dasatinib (approved by the FDA in 2006) and nilotinib (approved in 2007) are both more

TABLE 1 Features of the tyrosine kinase inhibitors approved in the United States for treatment of CML

	Imatinib	Dasatinib	Nilotinib
Approved indications and dosages for CML	• Patients with CML-CP newly diagnosed or after IFN-α therapy, 400 mg once daily • Patients with CML-BC or CML-AP, 600 mg once daily[61]	• CML-CP in newly diagnosed or patients resistant or intolerant to imatinib, 100 mg once daily • CML-AP, myeloid or lymphoid CML-BC, 140 mg once daily[56]	• CML-CP in newly diagnosed patients, 300 mg twice daily • CML-CP in patients resistant or intolerant to imatinib and CML-AP, 400 mg twice daily[59]
Mechanism of action	Inhibits *BCR-ABL*, PDGFR[66]	Multikinase inhibitor; inhibits *BCR-ABL*, Src family (Src, Lck, Yes, Fyn), c-KIT, EphA2, and PDGFRB[66]	Inhibits *BCR-ABL*, PDGFR, c-KIT[18,66]
Disorders that may be exacerbated	Superficial edema[61]	Pleural effusion, bleeding, cardiopulmonary disease[21,56]	Hepatic or pancreatic disorders[20,59]

CML-AP = CML in accelerated phase; CML-BC = CML in blast crisis; CML-CP = CML in chronic phase; IFN-α = interferon alfa; PDGFR = platelet-derived growth factor receptor

potent in vitro than is imatinib, nilotinib is more selective for the BCR-ABL TK than is imatinib,[18] and dasatinib is a dual kinase inhibitor of SRC kinase plus BCR-ABL.[19] Both received initial indications for second-line treatment in patients with CML who had failed first-line therapy with imatinib. Characteristics of the three TKIs approved in the United States for treatment of CML are summarized in Table 1.

The findings from two recently published randomized controlled trials in newly diagnosed patients with CP-CML, one comparing nilotinib 300 mg/day or 400 mg/day and imatinib and the other comparing dasatinib and imatinib, have demonstrated that each of the newer agents is associated with significantly higher rates of cytogenetic and molecular responses than is imatinib.[20,21] In the study comparing nilotinib and imatinib, the rates of major molecular response (MMR) at 12 months were significantly higher in the nilotinib 300-mg and 400-mg arms (44% and 43%, respectively) than in the imatinib arm (22%, $P < .001$, both comparisons).[20] CCyR rates by 12 months were also higher with nilotinib 300 mg and 400 mg (80% and 78%, respectively) than with imatinib (65%, $P < .001$, both comparisons). Time to transformation to AP or BC was significantly longer in both nilotinib arms compared with the imatinib arm ($P = .01$ and $P = .004$, respectively). Two-year follow-up data have recently been reported and demonstrate sustained response, reduced progression to advanced disease, and no new safety issues for patients treated with nilotinib.[22]

In the dasatinib versus imatinib trial, by 12 months, the rates of confirmed CCyR were significantly higher with dasatinib than with imatinib (77% vs 66%, respectively; $P = .007$), as were the rates of confirmed MMR (46% vs 28%, $P < .0001$).[21] Transformation to AP or BC occurred in 1.9% and 3.5% of patients in the dasatinib and imatinib arms, respectively (not significant). Extended follow-up data for up to 2 years are now available to support these findings.[23] Both nilotinib and dasatinib have recently received approval for the treatment of newly diagnosed patients with CML. The NCCN Guidelines now recommend imatinib, nilotinib, or dasatinib for first-line therapy and dasatinib or nilotinib for second-line therapy.[9]

Treatment during advanced phases

Although the current overall prognosis for CML has improved with TKI therapy, the advanced disease phases are more difficult to treat.[24,25] Several studies have examined the rates of response in patients in AP. In a study with imatinib, 34% of patients attained complete hematologic response (CHR) and 24% achieved major cytogenetic response (MCyR); 59% had 12-month progression-free survival and 74% survived 12 months.[26] In a study of nilotinib use in patients in AP who were resistant or intolerant to imatinib, 30% achieved CHR, 32% MCyR, and 20% CCyR. The estimated OS at 24 months was 67%.[27] Dasatinib has also been shown to be effective in AP patients who failed initial treatment with imatinib.[28]

Patients in BC are less likely to respond to TKI therapy. In one study, imatinib was able to induce CHR in 8% of patients in BC, MCyR in 16%, and CCyR in 7%. The estimated median survival time was 6.9 months.[29] Dasatinib has been studied in patients in BC who were either intolerant or resistant to imatinib. With a minimum of 8 months' follow-up, 26% of patients with myeloid BC achieved CHR, 31% achieved MCyR, and 87% of MCyRs were complete. Similar results were seen in patients with lymphoid BC. Among patients able to achieve a major hematologic response, 74% remained free of disease progression at the 8-month follow-up.[30]

TABLE 2 CML testing and milestones[a]

Test	Test Frequency (Pre-/Postmilestone)[b]	Milestone Time (mo)	Milestone Target Response	Definition[7]
Hematologic	Every 2 weeks until milestone is achieved; every 3 months thereafter	3	CHR	Complete normalization of peripheral blood counts (leukocyte $<10 \times 10^9$/L) Platelet count $<450 \times 10^9$/L No immature cells (eg, myelocytes, promyelocytes, or blasts) in peripheral blood No signs or symptoms of disease; no palpable splenomegaly
Cytogenetic	At 3 and 6 months, then every 6 months until milestone is achieved; every 12 months thereafter	6	CCyR or PCyR	CCyR: 0% Ph$^+$ metaphase cells in a bone marrow sample[c] PCyR: 1%-35% Ph$^+$ metaphase cells in a bone marrow sample[c]
		12,18	CCyR	0% Ph$^+$ metaphase cells in a bone marrow sample[c]
Molecular[d]	If continuing in CCyR, every 3 months for 2 years, then every 6 months for 3 years			

CCyR = complete cytogenetic response; CHR = complete hematologic response; IS = International Scale; MMR = major molecular response; NCCN = National Comprehensive Cancer Network; PCyR = partial cytogenetic response; Ph$^+$ = Philadelphia chromosome–positive

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[a] Milestones adapted with permission from the NCCN Guidelines;[9] please refer to those guidelines for more thorough recommendations for management of adverse events.[9] Definitions adapted from Faderl et al,[7] with permission from *Annals of Internal Medicine*; [b] Recommended testing frequency before and after attainment of milestone target response; [c] A minimum of 20 metaphases should be examined; [d] Although molecular monitoring is recommended, a milestone response of MMR (≥ 3-log reduction in International Scale of BCR-ABL mRNA) is not currently indicated in the NCCN Guidelines. The European LeukemiaNet guidelines recommend MMR at 18 months[31]

Monitoring CML

Most patients are in CP at diagnosis, and TKI therapy is associated with very low rates of progression to the advanced phases. Because treatment is most successful in CP, it is essential to ensure that milestone responses occur within expected time frames in newly diagnosed patients and that relapse, if it occurs, is detected early. This is accomplished through monitoring. Monitoring is frequent during the initial 12 to 18 months of treatment. In fact, patients are seen every 2 weeks for the first 3 months or so until the first treatment milestone is reached (Table 2).[9,31] The frequency of these tests can overwhelm some patients. It is helpful to educate patients on the required tests, their purpose, and expected results. Further, the patient should be introduced early on to the concept of CML as a chronic disease requiring lifelong treatment and periodic monitoring, and that message should be reiterated at every visit.

There are three levels of response to treatment: hematologic, cytogenetic, and molecular.[9] Testing for a hematologic response involves examination of white blood cells and platelets, cytogenetic testing involves evaluation of chromosomes within cells (specifically, the Ph chromosome), and evaluation of a molecular response involves detection of cells that are producing the BCR-ABL TK. Each reflects a deeper response, or a successive decrease in leukemic cells. The NCCN[9] and

European LeukemiaNet[31] recommendations for monitoring CML are summarized in Table 2.

The first milestone response is a CHR—defined as white blood cell count $< 1 \times 10^9$/L with a normal differential and platelet count of $< 450 \times 10^9$/L. This response generally occurs 3 months after initiating therapy.[9,32,33] Monitoring is done regularly through a complete blood count until CHR is achieved, then at 3-month intervals.[9]

The second milestone response expected is CCyR, defined as 0% Ph$^+$ metaphases in a minimum of 20 metaphases. This response generally occurs between 6 and 18 months after initiation of therapy.[9,32,33] Cytogenetic assessments are performed by standard karyotyping or fluorescence in situ hybridization (FISH)[34] and repeated at 6 and 12 months from the initiation of therapy. Although FISH may be more sensitive than conventional cytogenetics, few studies have monitored the response to treatment and NCCN Guidelines do not recommend FISH for monitoring response. If CCyR is achieved at 6 months after treatment initiation, then cytogenetic testing does not necessarily have to be repeated at 12 months. For patients who have not achieved CCyR at 12 months after treatment initiation, bone marrow cytogenetics should be assessed at 18 months. Once CCyR is achieved, bone marrow cytogenetics are necessary only if clinically indicated.[9]

The third milestone response is molecular response, defined as ≥ 3-log reduction in International Scale of BCR-ABL mRNA.[9] Molecular testing, performed by monitoring the level of BCR-ABL mRNA with quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), is currently the most sensitive method for detecting low levels of disease. The NCCN Guidelines recommend assessing BCR-ABL transcript levels every 3 months once the patient appears to be responding to treatment. If continuing in CCyR, BCR-ABL transcript levels should be measured every 3 months for 2 years, then every 6 months for 3 years (Table 2). If the BCR-ABL transcript levels increase after MMR has been achieved, qRT-PCR analysis should be repeated within 1 to 3 months.[9]

If patients do not achieve the milestone responses described in the Table 2, then the treatment strategy should be reevaluated. Some patients are resistant to front-line treatment. Resistance is most often caused by the development of mutations in the BCR-ABL kinase gene that can prevent the TKI from binding to, and preventing the activity of, the BCR-ABL TK. Dasatinib and nilotinib have been shown to be active against many of the imatinib-resistant BCR-ABL kinase domain mutations, except T315I.[35,36] Other disease-related factors, such as BCR-ABL gene amplification or insensitivity of leukemic stem cells to TKIs, can also cause resistance. Patient-related factors, including poor medication adherence and drug-drug interactions, which decrease the blood levels or bioavailability of the TKI, may also play a role.[37] The treatment options for patients who fail first-line therapy include changing to an alternative TKI, evaluation for SCT, or enrollment in a clinical trial.[9] Patients should be counseled regarding the benefits and risks of the available options and expected outcomes. Although attending and/or clinical study physicians determine clinical trial eligibility, nurses can educate patients about trial processes and discuss what they should expect by participating in them. For example, oncology nurses can talk to patients about the general purpose of a clinical trial; the differences between phase I, II, and III trials; the fact that, in the case of a blinded study, patients will not necessarily be receiving the experimental treatment; and that patients will be monitored more closely than they would be during standard treatment. Even in patients who have highly resistant disease, treatment is still possible, using agents that act on different cell processes that are also implicated in CML. New trials are ongoing. Clinical trials are recommended for patients who have failed one or more treatments.[9]

Emerging issues with longer survival

With the increase in survival among CML patients come new challenges similar to those of patients with other chronic conditions. These include the need for long-term medication adherence, effective early management of AEs, ongoing assessment of drug-drug interactions (particularly in elderly patients who may be more vulnerable to side effects or may have comorbid conditions that require complex medication regimens), and family planning. In addition to the education and support received during clinic visits, patients may appreciate the resources available to them through advocacy networks such as the National CML Society (www.nationalcmlsociety.org) and the Leukemia & Lymphoma Society (LLS, www.lls.org). For example, the LLS Web site provides disease information, the opportunity to chat online with other CML patients and ask questions of experts, links to support groups, information about clinical trials, and tools (such as a tool to track appointments, medications, side effects, and results of monitoring).

Adherence

Assessing patient adherence to lifelong treatment during follow-up visits is critical for optimizing outcomes in chronic diseases.[38] Poor adherence to imatinib treatment in patients with CML appears to be prevalent; in some studies, up to one-third of patients were found to be nonadherent.[39-41] Patients who are responding favorably may be tempted to discontinue treatment because of general complacency or a belief that continuous treatment is no longer necessary. Treatment-related toxicity is an important component in poor medication adherence.[39,42] Additional factors that fuel nonadherence include patient forgetfulness, disease complexity, having to take concomitant medications, higher initial doses, sociocultural issues, higher copayments, male gender, living alone, and unemployment.[40,43,44] Identifying patients with factors associated with poor adherence allows nurses to focus educational efforts on those most at risk of nonadherence.

Poor adherence increases the risk for disease relapse, even in patients who have previously achieved a complete response.[45] Conversely, good treatment adherence is associated with greater probability of achieving milestone molecular responses.[39] The NCCN Guidelines recommend assessing adherence in patients not meeting milestone responses.[9]

Poor adherence also increases overall health-care utilization and medical costs.[39,41,46] Patients with low adherence (measured by medication possession ratio [MPR], the fraction of days that patients filled their prescription) had significantly more inpatient visits and days hospitalized ($P < .0001$) and a 283% increase in

nondrug costs than did patients who were more adherent.[46] Another analysis based on US claims data showed that every 10% reduction in adherence (as measured by MPR) was associated with a concomitant 14% increase in non-imatinib health-care costs and a 15% increase in overall medical costs.[41]

Knowledge of CML and the role of ongoing treatment in managing it can improve adherence.[40] Oncology nurses can incorporate an ongoing dialogue and regular contact with patients, patient education, involvement of family members, and adherence monitoring. Involvement of health-care practitioners, family, and even community support are additional resources that assist patients' adherence to prescribed treatments.

Collectively, these findings underscore the need to convey the importance of lifelong treatment to patients and their caregivers. Evidence to date does not support discontinuation of TKI therapy, even in patients with a complete molecular response (CMR, or undetectable *BCR–ABL*).[47,48] Discontinuation of imatinib treatment is associated with poorer therapeutic response, relapse, increased drug resistance, and disease progression.[40,42,49] Furthermore, evidence of minimal residual disease is found in patients in CMR,[48] and fewer than half of patients maintain CMR after discontinuation of imatinib.[47] The nature of minimal residual disease, that is, the remaining leukemic stem cells, and their sensitivity to TKIs and alternative therapies are focuses in current research efforts to eradicate disease in CML patients.

Adverse event management

Accurate assessment and management of symptoms early in the course of treatment is critical to ensure optimal treatment, outcomes, and quality of life.[50] In a recent survey concerning practice patterns, 160 health-care participants were asked "Which treatment-related symptoms do you find most challenging in patients with CML?" Common answers were fatigue (21%), myelosuppression (20%), skin rash (11%), nausea or vomiting (10%), diarrhea (10%), headaches (6%), the effects of liver function (6%), edema (6%), muscle cramps (4%), and electrocardiographic changes (2%).[51] Patients who experience treatment-related side effects, even low-grade effects, may be inclined to interrupt or discontinue treatment or decrease dosages,[52] placing them at risk for acquiring drug resistance, suboptimal response, loss of milestone responses, or progression of disease.[45,53]

The three available TKIs have safety profiles that are similar in some aspects and unique in others. It is important that oncology nurses be aware of key differences. Further, the intensity and frequency of these AEs may differ in the first- and second-line settings. Most of the

clinical experience is with imatinib. The most common AEs reported in a study with 5 years of follow-up were edema (60%), muscle cramps (49%), diarrhea (45%), nausea (50%), musculoskeletal pain (47%), rash or other skin problems (40%), abdominal pain (37%), fatigue (39%), joint pain (31%), and headache (37%).[3] The more severe AEs included neutropenia (17%), thrombocytopenia (9%), anemia (4%), and elevated liver enzymes (5%), which were seen early in the course and occurred less frequently with continuing treatment.[3]

A study comparing nilotinib and imatinib in a front-line setting found that rates of common AEs, including nausea, diarrhea, vomiting, muscle spasm, and edema, were higher with imatinib. Rates of rash, headache, pruritus, and alopecia, conversely, were higher with nilotinib. Hematologic abnormalities (neutropenia, thrombocytopenia, and anemia) occurred more frequently with imatinib.[20] Oncology nurses also should be aware that patients who receive nilotinib require periodic electrocardiogram monitoring for QTc prolongation (see Table 1) and laboratory monitoring for potential biochemical abnormalities. In a comparison of dasatinib and imatinib in a front-line setting, nausea, vomiting, muscle inflammation, rash, and superficial edema were more frequent with imatinib than with dasatinib, whereas headache was more frequent with dasatinib. Among the types of fluid retention, pleural effusion was seen only with dasatinib.[54] Pleural effusions are a particular concern with dasatinib.[55] Further, the rates of hematologic abnormalities were higher with dasatinib than with imatinib.[54]

As clinical experience with nilotinib and dasatinib in the front-line setting grows, their safety profiles will become better defined. For example, the revised prescribing information for dasatinib, reflecting its approval in the front-line setting, suggests heightened concern for bleeding-related events and cardiac events (QTc prolongation, congestive heart failure, left ventricular dysfunction, and myocardial infarction). In addition, the new prescribing information notes an increased rate of toxicities in geriatric patients.[56] Some of the patient disorders that may be exacerbated by treatment with TKIs are summarized in Table 1. The NCCN Guidelines provide recommendations for managing various treatment-related toxicities, including treatment interruption, dose reduction, and supportive-care measures.[9]

Drug-drug and drug-food interactions

Routine review of patients' over-the-counter and dietary agents minimizes the risk of drug-drug interactions. These interactions can increase the risk of some AEs and reduce or enhance the therapeutic effect of the administered agents. Special consideration should be given to

elderly patients, who may be receiving medications for comorbid conditions.

TKI inhibitors are primarily metabolized by the cytochrome P-450 3A4 (CYP3A4) pathway.[57] When TKIs are administered with other agents metabolized by the CYP3A4 pathway, there is the potential for drug-drug interactions. A recent review article provides a comprehensive list of drugs and their potential interactions with imatinib, nilotinib, and dasatinib.[58] Patients should be aware that the use of even common medications can be problematic. For example, use of aspirin in patients receiving dasatinib can increase the risk of bleeding events. Exposure to acetaminophen is increased in patients taking imatinib, and the herbal supplement St John's Wort decreases exposure to all three TKIs.[58] If the administration of a particular agent cannot be avoided, dose adjustments per prescribing information and vigilant monitoring are recommended.

Similarly, food-drug interactions can occur by inhibition of the CYP3A4 enzymes; grapefruit is the most notable example and should be avoided in patients receiving TKIs.[58] The bioavailability of nilotinib is increased when it is taken with a meal. Nilotinib should be taken twice daily at about 12-hour intervals and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken, and no food should be consumed for at least 1 hour after the dose is taken.[59] Nurses can help patients with scheduling by suggesting, for example, that they take nilotinib at 10:00 AM and 10:00 PM.

Family planning

Nurses can provide valuable information to patients considering family planning. Pregnancy does not appear to affect overall prognosis in patients with CML, but disease response and teratogenicity must be considered.[60] Teratogenic effects have been observed in animal models, so women are advised to avoid pregnancy while receiving TKI therapy.[56,59,61] There is a paucity of conclusive data on teratogenicity in humans. Severe fetal abnormalities have been observed in 6.4% of live births in women receiving imatinib.[62] However, cases of imatinib use during pregnancy without complications or congenital defects also have been reported.[60]

There is insufficient evidence to recommend continuation of TKI therapy during pregnancy.[9] The NCCN Guidelines recommend performing a risk–benefit evaluation on the mother and fetus, with a CML management strategy to be decided on a case-by-case basis. Male patients are advised to consider sperm cryopreservation before TKI therapy is started.[9] Breastfeeding is strongly discouraged,[58,61,63] due to substantial levels of imatinib or its metabolite in breast milk, creating a risk of adverse reactions in the nursing infant.[63]

Conclusion

The TKIs have revolutionized CML management, resulting in prolonged survival, so that CML is now managed like other chronic illnesses. As CML patients live longer with an incurable illness, oncology nurses play an increasingly important role in educating and supporting patients over the long term. Patients and clinicians are now faced with new issues, such as lifelong treatment, long-term monitoring, adherence, and family planning. Treatment-related responsibilities, monitoring treatment adherence, and patient education are important aspects of nursing care that substantially contribute to positive outcomes.[64,65] Proactive inquiries on disease- and treatment-related symptoms and their impact on quality of life allow for early identification of issues that may necessitate a dosing modification or change in treatment. The field of CML is rapidly evolving with advances in treatment and monitoring; these advances have translated into improved long-term survival for patients. As new therapies and monitoring techniques are evaluated, education and support continue to be important aspects of optimizing patient care.

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