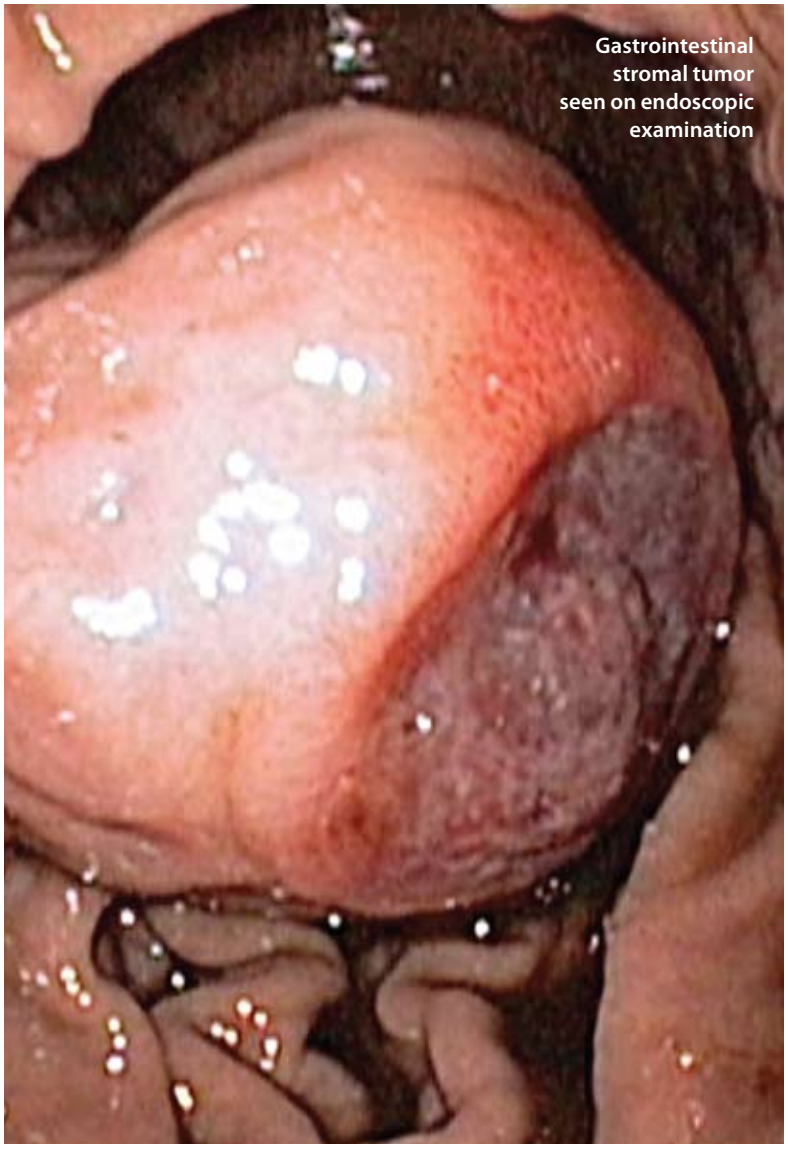
Oral therapy: Managing side effects can aid adherence

Diligent patient education that addresses adherence and persistence issues can optimize outcomes in patients with gastrointestinal stromal tumors.



Gastrointestinal stromal tumor seen on endoscopic examination

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Anticancer therapy has increasingly shifted away from traditional intravenous chemotherapy toward greater use of oral cancer therapies, significantly increasing convenience and independence for patients. As a result, patients need to commute to the clinic for treatment less frequently and avoid potential complications associated with IV injections, hence experiencing improved quality of life. However, oral therapy has made monitoring side effects, and adherence and persistence with therapy, more problematic.[1,2] These are critical issues, especially with targeted therapies, because patients often need to continue treatment for years. The potential for nonadherence and nonpersistence is increased over a longer term.

One oral targeted therapy that has changed clinical outcomes for patients with chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) is imatinib (Gleevec).[3,4] The agent is administered as a daily regimen and has a generally manageable toxicity profile, yet adherence is not ideal.[5] This article discusses GIST treatment with imatinib and how nurses can improve treatment adherence, persistence, and clinical outcomes of oral anticancer therapy by promoting patient education and timely reporting and management of adverse effects.

AN OVERVIEW OF GIST

Gastrointestinal stromal tumors are rare, compared with other cancers, but are nonetheless the most common mesenchymal tumors in the GI

tract.[6] A Swedish study approximated prevalence at 129 cases per million population in western Sweden; in the United States, new cases are estimated at 6,000 or fewer per year.[7,8]

Approximately 85% to 90% of GIST contain activating mutations in the tyrosine kinases (KIT) or platelet-derived growth factor receptor alpha (PDGFRA), thus contributing to the pathophysiology of the tumor.[4] The remaining 10% to 15% of tumors do not have mutations in KIT or PDGFRA and are called *wild-type*. Other cellular pathways are deregulated, however, causing GIST.

TREATMENT

Localized, resectable primary GIST Surgery is recommended for all primary tumors 2 cm or larger.[4] However, even with complete resection, approximately 50% of patients experience recurrence.[9] Imatinib is a tyrosine kinase inhibitor (TKI) that targets KIT and PDGFRA. It is indicated as first-line adjuvant therapy for the treatment of GIST following surgical resection of the primary tumors.[5] In a phase III clinical trial, adjuvant imatinib (400 mg/day) significantly improved recurrence-free survival (RFS) in patients who underwent surgical resection of gastrointestinal stromal tumors 3 cm or larger compared with placebo (1-year RFS, 98% vs. 83%, respectively).[10]

Adjuvant imatinib was particularly effective in high-risk patients (those with tumors 10 cm or greater), showing an overall survival benefit with 3 years of treatment compared with 1 year (92% vs. 82%, respectively).[10,11] Therefore, even though the optimal duration of treatment with imatinib for nonprogressing GIST has not yet been defined, the National Comprehensive Cancer Network (NCCN) guidelines recommend considering 3 years of adjuvant therapy for patients with intermediate- to high-risk GIST to reduce the risk of recurrence.[12] An ongoing clinical trial (PERSIST) is investigating the benefits of 5 years of adjuvant therapy in high-risk patients (NCT00867113).[13]

Advanced/metastatic GIST Imatinib is also indicated for unresectable or advanced/metastatic GIST, starting with 400 mg/day until disease progression.[4,5] This recommendation is based on results from the B2222 trial, which showed a 5-year overall survival rate of 68.1% in patients treated with imatinib, regardless of the dose they received (400 vs. 600 mg/day).[14] A subsequent trial (the BFR14 trial) showed that patients with advanced GIST who discontinued imatinib therapy after 3 years had a much lower progression-free survival rate (16%) than those who continued therapy (80%), pointing to the importance of adherence and persistence with treatment.[15] A meta-analysis of two phase III clinical trials of imatinib at 400 and 800 mg/day in patients with unresectable/metastatic GIST showed that patients with KIT exon 9 mutations benefited from the higher dose, whereas patients without exon 9 mutations did not.[16] Based on these data, the NCCN Task Force recommends that patients who are responding or experiencing stable disease continue therapy.[4] If disease progression occurs while the patient is taking 400 mg/day, treatment can continue with the same dose, the dose can be increased to 800 mg/day, or treatment can be switched to sunitinib (Sutent).[4]

Neoadjuvant treatment Although not FDA-approved for this usage, imatinib may be administered as neoadjuvant therapy to downstage GIST and facilitate resection or to reduce surgical morbidity of resectable GIST.[4] The RTOG 0132/ACRIN 6665 clinical trial investigated the efficacy and safety of neoadjuvant therapy with imatinib (600 mg/day for 8 weeks) in patients with potentially resectable primary or recurrent/metastatic disease.[17] In this setting, estimated 2-year progression-free survival and overall survival were 82.7% and 93.3%, respectively, in patients with primary disease vs 77.3% and 90.9%, respectively, in patients with advanced disease.[17] These results compare advantageously to the historical median progression-free survival of 7 to 20 months and demonstrate the potential benefits of imatinib as a neoadjuvant agent.[4]

ADHERENCE AND PERSISTENCE

Medication adherence and persistence are different issues.[18] Adherence refers to compliance with a prescribed or recommended treatment, with respect to timing and dosing. In that regard, under- and over-medication both result in nonadherence. Persistence, on the other hand, refers to continuing treatment over time from start to end of therapy.

Adherence and persistence are complex; they depend on factors that can be disease- or patient-related, such as depression, forgetfulness, asymptomatic disease, adverse effects, infrequent follow-up, complexity of treatment, medication cost, age, polypharmacy, and lack of knowledge.[2,4,19] In general, studies on oral cancer therapies report adherence rates ranging from 17% to 100%.[20-28] Information on adherence to imatinib therapy in GIST is limited; however, one study showed an overall adherence rate of 73% (defined as the apparent mg taken:mg prescribed ratio), but only 50% of patients were 100% adherent, taking the correct dose at the correct time.[29] In the same study, persistence (measured as time on prescription without significant gaps between refills) only averaged 255 days over 24 months.[29]

Continued on page 26

Suboptimal adherence and persistence are a concern as they may lead to reduced therapeutic effectiveness. Indeed, interruption of imatinib treatment has been shown to result in rapid progression of GIST (within 6 to 12 months).[10,30] Another study found that patients with suboptimal clinical response had significantly higher amounts of untaken drug.[31] Under-medication may limit the effectiveness of imatinib, as its elimination half-life is 10 to 20 hours.[32,33] In contrast, over-medication (eg, taking multiple doses to compensate for a missed dose) could increase toxicity and adverse effects.[2]

MANAGING ADVERSE EFFECTS TO IMPROVE ADHERENCE

Adverse effects from imatinib treatment are most prevalent in the first 8 weeks of treatment, generally mild to moderate, and manageable without treatment interruption or dose reduction.[34,35] In addition, they tend to improve over time and resolve after discontinuation.[4,34] Adverse effects are similar at both 400 and 800 mg/day and, except for edema, the incidence of grade 3 or greater adverse effects is similar. Moreover, many of the adverse effects reported in clinical trials of long-term therapy at 400 mg/day are similar in grade and occurrence to those reported with placebo, indicating that the adverse effects may be related to the underlying disease.[10,34]

The most commonly reported adverse effects are edema, diarrhea, nausea, fatigue, anemia, muscle cramps, abdominal pain, and rash[4,5] (Table 1). Fatalities from imatinib therapy, although rare, were related to GI perforation. Serious side effects, such as cardiac dysfunction, abnormal liver function tests, lung toxicity, low blood count, and GI bleeding are rare with imatinib therapy for GIST.[5,34] A brief interruption of therapy followed by reintroduction of the agent may be used to manage some adverse effects for some patients. These short interruptions (1-2 weeks) were not shown to affect clinical outcomes; however, patients should consult their oncology clinicians before making any change in their treatment regimen.[4]

Patients with GIST may remain on imatinib therapy for years; therefore, adverse effect management is pivotal to adherence and persistance.

Patients with GIST may remain on imatinib therapy for years; therefore, adverse effect management is pivotal to treatment adherence, persistence, and, ultimately, clinical outcomes. Patients should keep a diary of their medication administration and adverse effects.[1] In addition, vigilance in asking patients how well they are tolerating their prescribed treatment, and whether they are experiencing any adverse effects is essential in order to manage side effects in a timely fashion.[2]

Dermatologic Skin rash often occurs in the first weeks of treatment, but may occur at any time during therapy and may be pruritic.[34] It often resolves over time, but can be treated with topical or oral diphenhydramine hydrochloride, other antihistamines, or corticosteroids.[4,34] Antibiotics may be needed for secondary skin infections. In rare cases, skin rash can lead to erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson syndrome. Imatinib therapy should be interrupted and prednisone administered (1 mg/kg, tapering to 20 mg/day over several weeks), before reintroducing imatinib.[34] Skin may tan unevenly, so patients should be instructed to use sunscreen.[34] With long-term therapy, skin may become thin and tear or bruise easily. Blood blisters may occur and resolve spontaneously. Other steps to minimize skin damage are to keep skin well moisturized, avoid hot showers or baths as well as strong detergents or soaps, and wear sun protection. Some patients also report decreased bruising after taking omega-3 fatty acids. Hair thinning and lack of texture have also been reported with long-term use. These effects do not pose dangerous problems, are reversible upon treatment interruption, and do not require specific treatment.[36]

Gastrointestinal GI events are common during treatment and may be due to local irritation.[34] Instruct patients to take imatinib with food and a large glass of water, and to remain upright for 1 hour after ingestion to minimize nausea and vomiting.[5] Splitting the dose and taking it with meals at separate times of the day or taking prochloroperazine (Procomp, generics) or ondansetron (Zofran, Zuplenz, generics) may also help.[34] Patients can manage abdominal pain and cramping by increasing their fluid intake, consuming electrolyte replacement beverages in particular, or by taking calcium supplements.[4,34] The FDA cautions against the off-label use of quinine (Qualaquin, generic) and tonic water.[4,37] Other medications that can help patients manage GI events include simethicone (Imodium, generics), to control flatulence; loperamide hydrochloride (Imodium, generics) or atropine sulfate/diphenoxylate hydrochloride (Lomotil, Lonox, generics), to treat diarrhea; and antacids or proton pump inhibitors, to manage dyspepsia.[4,34] Patients may occasionally experience taste disturbances; in addition, patients should avoid spicy or acidic foods, carbonated drinks, and alcoholic beverages.[5]

Hematologic Anemia is common in patients with GIST; therefore, serum iron, ferritin, and transferrin levels should be monitored.[34] Patients with iron-deficient anemia should

TABLE 1. Frequency of adverse events reported by 10% or more of participants in phase III clinical trials

	Adjuvant 400 mg/day[a]		Unresectable/ metastatic GIST[b]	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Dermatologic				
Alopecia	9.5-11.3	0-0	11.9-14.8	3.2-4.3
Pruritus	11.0-12.9	0-0.9	15.4-18.9	4.3-5.4
Rash (dermatitis)	26.1-29.4	2.1-2.7	38.1-49.8	7.6-8.9
Other skin toxicity	—	—	17.6-20.1	5.7-5.9
Gastrointestinal				
Abdominal distension	7.4-11.9	0.3-0.5	—	—
Abdominal pain/ cramping	21.1-26	0-3.0	55.2-57.2	11.8-13.8
Constipation	8.8-12.8	0-0	14.4-14.8	4.1-5.1
Diarrhea	43.8-59.3	0.5-3.0	56.2-58.2	8.1-8.6
Dyspepsia	17.2-17.5	0.5-0.9	10.9-11.5	0.5-0.6
Flatulence	8.9-19.1	0-1.0	10.0-10.1	0.1-0.2
Nausea	44.8-53.1	1.5-2.4	58.1-64.5	7.8-9.0
Other GI toxicity	—	—	25.2-28.1	6.6-8.1
Vomiting	10.8-25.5	0.5-2.4	37.4-40.6	7.5-9.2
Hematologic				
Anemia (hemoglobin decreased)	46.9-72.2	0.5-0.6	32.0-34.8	4.9-6.4
Blood creatinine increased	11.6-30.4	0-0	10.1-10.8	0.4-0.6
Hemorrhage/other hemorrhage	3.1	0	12.3-13.3	6.1-6.7
Leukopenia	5.0	0.3	17.0-19.6	0.7-1.6
Neutropenia/ granulocytopenia	16.0-24.2	3.3-4.6	11.5-16.1	3.1-4.1
Platelet count decreased	5.0-11.3	0-0	—	—
White blood cell count decreased	14.5-34.5	0.6-2.1	—	—
Muscular				
Myalgia	9.3-12.2	0-0	30.2-32.2	3.8-5.6
Spasms	16.3-30.9	0-0.5	—	—
Respiratory				
Cough	11.0	0	14.5-16.1	3.2-4.5
Dyspnea	—	—	13.6-14.2	5.6-6.8
Other				
Anorexia	16.9	0.3	31.1-35.5	4.7-6.6
Arthralgia	8.8-15.1	0-0	12.3-13.6	3.0-4.8
Dizziness	4.6-12.5	0-0.5	10.0-11.0	2.8-4.8
Edema	10.8	0	76.7-86.1	9.0-13.1
Periorbital	47.2-59.3	0.5-1.2	—	—
Peripheral	26.7-33.0	0.3-0.5	—	—
Fatigue	48.5-57.0	1.0-2.1	69.3-74.9	11.7-12.2
Fever (absence of neutropenia)	6.2	0	12.9-13.2	3.4-4.9
Headache	8.2-19.3	0-0.6	19.7-22.0	3.6-5.7
Infection	13.9	1.5	—	—
Infection (without neutropenia)	—	—	15.5-16.5	5.6-6.6
Lacrimation increased	9.8-18.0	0-0	—	—
Liver enzymes (alanine transaminase) increased	16.6-28.9	2.1-2.7	—	—
Liver enzymes (amino-transferase) increased	12.2	2.1	—	—
Other constitutional symptoms	—	—	15.2-16.7	4.4-6.4
Other neurological toxicity	—	—	15.0-15.2	4.9-6.4
Other renal/genitourinary toxicity	—	—	13.6-14.2	5.2-6.5
Pain	25.8	1.0	—	—
Other pain (not tumor-related)	—	—	20.4-20.8	5.0-5.9
Rigors/chills	—	—	10.2-11.0	3.0-4.6
Sweating	—	—	8.5-12.7	2.8-4.6
Weight gain	16.9	0.3	10.6-12.0	0.6-1.0

[a]Trial 1, n=337; trial 2, n=194 [b]400 mg/day, n=818; 800 mg/day, n=822

receive oral ferrous sulfate. In cases of poor absorption or intolerable adverse effects, administer IV iron.[34] An acute drop in hemoglobin levels of more than 2 g/dL may require treatment interruption until levels stabilize; patients should be evaluated for GI tract hemorrhage.[4,34] If absolute neutrophil counts are 1,000 cells/mm^3 or less, withhold imatinib until recovery, then restart the drug, with (if symptoms recur) or without dose reduction.[4,34] Patients with repeated events or severe neutropenia may benefit from administering granulocyte colony stimulating factor.[4,34]

Other adverse effects Periorbital or peripheral edema, the most common adverse effect in this patient group, is typically mild but worse in the morning, and should first be addressed by reducing dietary salt intake, especially if the patient has a weight gain of 5 lb or more in a week.[4,34,38] Accordingly, monitoring patients' weight and educating them about signs of fluid retention are essential. If needed, a diuretic such as furosemide (Lasix, generics) may be given.[4,34] If severe fluid retention occurs, administer a diuretic and withhold imatinib until the event resolves. Nutritional consultations, exercise, and sleep therapy can be used to manage fatigue caused by anemia.[39] Myalgia and spasms occur most frequently in the hands, feet, and legs. Increasing daily fluid intake; avoiding cold temperatures; and taking calcium and magnesium supplements,

electrolyte replacements, or muscle relaxants (eg, carisoprodol [Soma, generics], meprobamate) are steps patients can take to manage these adverse effects.[4,34] Patients with grade 2 increased liver enzymes (alanine transaminase or aminotransferase) should undergo a complete assessment to determine the cause of the liver dysfunction.[34] Substances known to cause liver damage, such as alcohol, should be avoided.[34]

Patients should be advised to consult their oncology clinicians before taking any OTC medications, including NSAIDs and herbal supplements, while they are taking imatinib.[5] In patients with grade 3 hepatotoxicity, imatinib therapy should be interrupted, then reintroduced at a lower dose when liver function falls below 2.5 ULN. With close monitoring, reescalation of the dose may then be considered.[34] Oral corticosteroids may be prescribed for patients with severe hepatotoxicity.[34] Asymptomatic spontaneous subconjunctival hemorrhages have been reported; however, these appear to resolve spontaneously.[40]

Disease progression In patients with advanced/metastatic disease, progression during therapy can be treated by increasing the dose to 600 to 800 mg/day.[4] However, nonadherence could lead clinicians to unnecessarily increase the dose, or switch to sunitinib, the only other medication approved for treatment of GIST.[4] Therefore, nurses should be diligent in confirming patients' adherence to the regimen before assuming treatment failure to avoid exhausting treatment options.[4]

ADDITIONAL STRATEGIES FOR IMPROVING TREATMENT ADHERENCE

Educating patients about their treatment can help them manage their expectations and promote adherence, safety, and optimal dosing.[41] Patient education should focus on appropriate dosing and timing of medication for optimal efficacy, potential consequences of nonadherence, and the drug's toxicity profile. In addition, nurses need to be diligent about stressing the importance of reporting adverse effects and informing health care providers about all medications and supplements he or she takes.[1]

Patients also need to know about potential food-drug or drug-drug interactions with imatinib, which helps promote adherence/persistence as well (Table 2). Because the liver enzyme cytochrome 3A4 (CYP3A4) metabolizes imatinib,

TABLE 2. Potential interactions with imatinib[4,14,42]

DRUGS THAT AFFECT IMATINIB		DRUGS AFFECTED BY IMATINIB	
May increase plasma levels of or exposure to imatinib		**Plasma levels of or exposure may be increased**	
• Atazanavir (Reyataz) • Clarithromycin (Biaxin, generics) • Cyclosporine (Gengraf, Neoral, Sandimmune, generics) • Erythromycin • Fluconazole (Diflucan, generics) • Grapefruit, grapefruit juice • Indinavir (Crixivan) • Itraconazole (Onmel, Sporanox, generics) • Ketoconazole (Nizoral, generics) • Levothyroxine	• Nefazodone • Nelfinavir (Viracept) • Pomegranate juice • Quinine (Qualaquin, generic) • Ritonavir (Kaletra, Norvir) • Seville oranges • Star fruit • Telithromycin (Ketek) • Verapamil (Covera-HS, Calan, Verelan, generics) • Voriconazole (Vfend, generics)	• Acetaminophen/paracetamol • Amlodipine (Norvasc, generics) • Atorvastatin (Caduet, Lipitor, generics) • Bisoprolol (Zebeta, generics) • Cyclosporine (Gengraf, Neoral, Sandimmune, generics) • Digoxin (Lanoxin, generics) • Dihydropyridine calcium channel blockers • Diltiazem • Glyburide (Diabeta, Glynase, generics) • HMG-CoA reductase inhibitors (eg, statins)	• Levothyroxine • Metoprolol (Lopressor, Toprol, generics) • Midazolam • Nifedipine (Adalat, Afeditab, Procardia, generics) • Quinidine • Simvastatin (Zocor, generics) • Tamoxifen (Soltamox, generics) • Triazolobenzodiazepines • Warfarin[a] (Coumadin, Jantoven, generics)
May decrease plasma levels of imatinib		**May cause these drugs to miss their therapeutic window**	
• Carbamazepine • Dexamethasone • Fosphenytoin • Oxcarbazepine (Trileptal, generics) • Phenobarbital	• Phenytoin (Dilantin, Phenytek, generics) • Primidone (Mysoline, generics) • Rifampin (Rifadin, generics) • St. John's wort	• Alfentanil (Alfenta, generic) • Cyclosporine • Dihydroergotamine (D.H.E. 45, Migranal, generics) • Ergotamine (Ergomar)	• Fentanyl • Pimozide (Orap) • Quinidine • Sirolimus (Rapamune) • Tacrolimus (Prograf, generics)
May decrease imatinib intracellular exposure			
• Cimetidine (Tagamet, generics)	• Ranitidine (Zantac, generics)		

Note: For complete and updated information, a pharmacist or appropriate drug information references should be consulted.

[a] Patients taking warfarin should be switched to heparin.

drug interactions may occur with other substrates or modulators of CYP3A4.[4] CYP3A4 inhibitors, such as grapefruit or grapefruit juice, star fruit, pomegranates, and Seville oranges (in marmalades), should be avoided.[4,5,43,44] Patients should be encouraged to read food labels carefully. They may assume they are not consuming these foods when, in fact, they are. For example, some orange juice brands contain grapefruit juice.

Drugs or herbal substances that induce imatinib metabolism may reduce serum levels of the drug and affect its efficacy. Patients should be asked specific questions about the use of herbs and supplements, and advised to talk to their pharmacist about potential interactions between imatinib and the other drugs, supplements, and herbs they take. Lastly, imatinib may also affect the metabolism of other CYP3A4 substrates, such as warfarin (Coumadin, Jantoven, generics) and midazolam, potentially increasing their toxicity; dosing may need to be adjusted accordingly.[4] Patient education about the potential risks of these interactions is critical.

Patient advocacy groups are also reliable sources of information for patients and caregivers. In addition to information about the disease, approved therapies, and potential side effects and their management, some advocacy groups provide information on clinical trials and fundraising efforts for cancer research.

Proactive follow-up with patients promotes treatment adherence. Telephone calls to review treatment adherence, inquire about adverse effects, and recommend strategies for management are effective patient care tools.[1] If medication cost is an issue, patients can be directed to the various financial assistance programs available.

CONCLUSION

The transition from IV to oral oncology treatments has shifted the onus of adherence from the health care providers to the patients. Consequently, adherence and persistence have become increasingly challenging, especially with long-term targeted therapy. Nurses are uniquely positioned to foster adherence. By taking a proactive approach to promoting adherence and persistence, and to understanding the causes of nonadherence and nonpersistence, nurses have an opportunity to help maximize the benefits of oral therapy and, therefore, patients' clinical outcomes. ■

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Continued on page 34

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