CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- List drug names, mechanisms of action, and pharmacologic properties for three new oncology agents
- Identify contraindications and precautions that may preclude or condition the drug's use
- Outline potential adverse drug reactions, drug interactions, and necessary monitoring parameters
- State route of administration, dosing schedule, and dosing formulations

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Name of Faculty or Presenter	Reported Financial Relationship
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CE INFORMATION

The following information pertains to the CE-certified article entitled **New cancer therapies in 2009: A review for the oncology nurse**. Those wishing to apply for CE can do so by visiting www.mycme.com.

Release date: May 1, 2010

Expiration date: May 1, 2011

Estimated time to complete this activity: 45 minutes

Co-provided by the Postgraduate Institute for Medicine and Haymarket Media, Inc.

Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

Statement of need/program overview: Registered nurses and nurse practitioners working in oncology should be informed and stay current about new therapies and new indications for drugs used in everyday practice.

Faculty: James Alexander, PharmD, PhD, Director, Institute for Pharmaceutical Industry Fellowships, Rutgers University School of Pharmacy, Piscataway, NJ

Media: Journal article

Credit Designation: This educational activity for 0.75 contact hours is provided by Postgraduate Institute for Medicine.

Accreditation Statement: Postgraduate Institute for Medicine is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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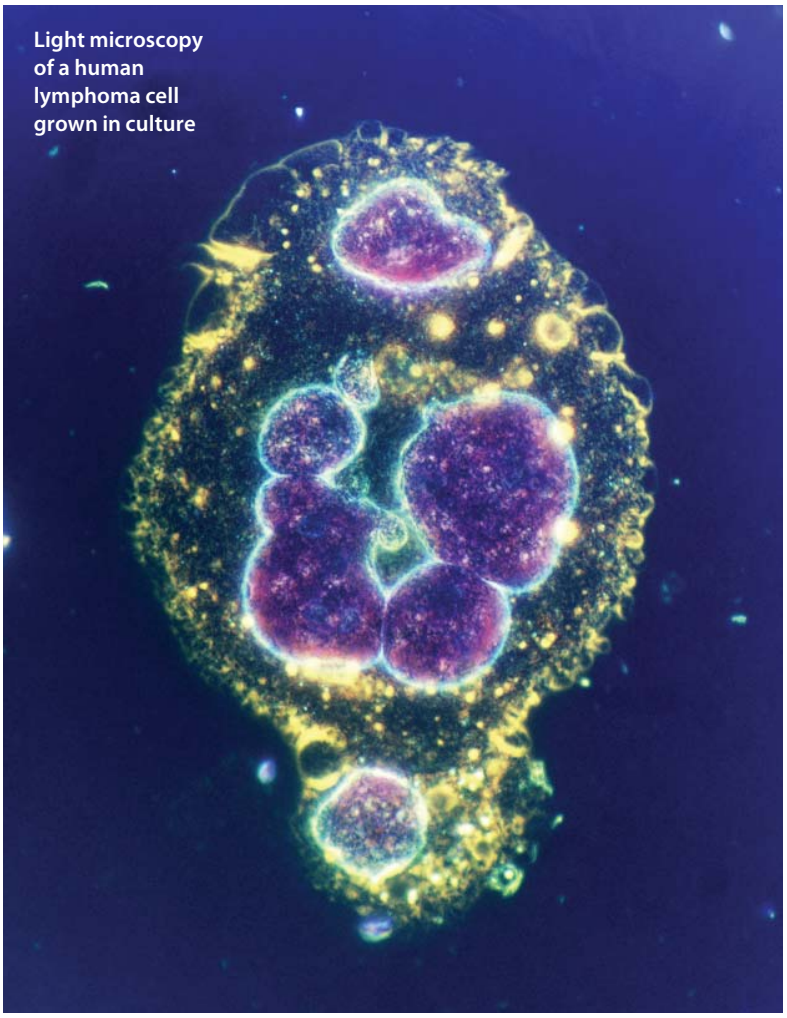
New cancer therapies in 2009: A review for the oncology nurse

Plerixafor for stem cell transplantation, transdermal granisetron to prevent nausea and vomiting, and everolimus for kidney cancer are profiled.



Light microscopy of a human lymphoma cell grown in culture

JAMES ALEXANDER, PHARMD, PHD

This article reviews three therapeutic options that recently became available for the treatment of cancer or conditions related to cancer:

- The hematopoietic stem cell mobilizer *plerixafor* (Mozobil), for use in combination with granulocyte-colony stimulating factor to mobilize hematopoietic stem cells to the peripheral blood for collection and autologous transplantation in patients with non-Hodgkin's lymphoma or multiple myeloma;
- A transdermal form of the selective 5–hydroxytryptamine type 3 receptor antagonist *granisetron* (Sancuso), used to prevent nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy regimens of up to 5 consecutive days' duration; and
- The mTOR kinase inhibitor *everolimus* (Afinitor), for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

Plerixafor was approved by the FDA in December 2008; granisetron was approved in September 2008; and everolimus was approved in March 2009.

PLERIXAFOR (MOZOBIL)

Indication: Plerixafor, a small-molecule CXCR4 chemokine receptor antagonist, is indicated for

use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and autologous transplantation in patients with non-Hodgkin's lymphoma or multiple myeloma.

Pharmacology: Plerixafor is a chemokine CXC receptor 4 (CXCR4) antagonist that is designed to mobilize hematopoietic stem cells from the bone marrow to the bloodstream for harvest, enabling certain patients to proceed to transplant.[1] It blocks the binding of stromal cell-derived factor-1α, which, with CXCR4, plays a role in the homing and trafficking of stem cells in the bone marrow. Treatment with plerixafor causes increases in circulating leukocytes and stem cells.

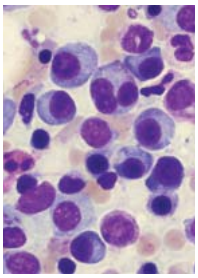
Patients with non-Hodgkin's lymphoma or multiple myeloma may be candidates for autologous hematopoietic stem cell transplantation as part of their treatment. Before the transplant can take place, a minimum number of stem cells, generally about 2 million/kg, must be collected. For some patients, this may be a lengthy process or may not occur satisfactorily.

Clinical trials: Two placebo-controlled studies were conducted to evaluate the safety and efficacy of plerixafor in combination with G-CSF for stem-cell mobilization.[1] In the first study, conducted in patients with non-Hodgkin's lymphoma, 59% of 150 patients given plerixafor + G-CSF collected ≥ 5×10^6 CD34+ cells/kg in four or fewer apheresis sessions, compared to 20% of 148 patients given placebo + G-CSF. In the second study, conducted in patients with multiple myeloma, 72% of 148 patients who were treated with plerixafor + G-CSF collected ≥ 6×10^6 CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34% of 154 patients given placebo + G-CSF. The target numbers of stem cells in the studies were selected based on literature that suggests that reaching these targets can help to facilitate engraftment. Updated 12-month follow-up findings showed that graft durability rates for patients in the plerixafor + G-CSF and placebo + G-CSF arms were comparable.[2]

In the literature: Researchers investigating the efficacy and toxicity of combining G-CSF at standard doses with plerixafor to mobilize stem cells in patients with non-Hodgkin's lymphoma and multiple myeloma found that the combination increased circulating CD34 cells/μL and led to the adequate collection of stem cells for autotransplant in 96% of 49 patients studied, 28 of whom were classified as heavily pretreated. They concluded that this combination may have particular value in heavily pretreated patients.[3]

Precautions: Prescribing physicians, nurses caring for patients receiving plerixafor, and patients should be aware of the potential for tumor cell mobilization in leukemia patients, increased circulating leukocyte and decreased platelet counts, and splenic enlargement. It is important to monitor blood and platelet counts (especially neutrophils) and be alert to the potential for splenic rupture (eg, left upper quadrant/scapular or shoulder pain). The drug has been assigned a pregnancy category D rating and is not recommended for nursing mothers.

Adverse reactions: The most common adverse reactions (≥ 10%) reported in patients who received plerixafor and G-CSF that were more frequent than in patients who received placebo were diarrhea, nausea, fatigue, injection site reactions, headache, arthralgia, dizziness, and vomiting.



A bone marrow aspirate obtained in multiple myeloma demonstrates variable plasmocytosis.

Interactions: May be potentiated by drugs that reduce renal function or compete for active tubular secretion.

Dosage, administration, and availability: Plerixafor, which must be given in combination with G-CSF, can commence after 4 days' treatment with G-CSF. Plerixafor, administered subcutaneously beginning at 0.24 mg/kg/day for up to 4 days (max, 40 mg/day) should be given each evening or approximately 11 hours before starting morning apheresis. For patients with moderate to severe renal impairment (creatinine clearance <50 mL/min), plerixafor dosing should start at 0.16 mg/kg/day, up to a maximum of 27 mg/day. The agent is available as a preservative-free 20 mg/mL solution in 1.2-mL single-use vials.

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GRANISETRON TRANSDERMAL PATCH (SANCUSO)

Indication: Granisetron transdermal system is indicated for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days' duration. A single application may be administered over a multiday chemotherapeutic regimen and may serve as an alternative to daily oral or intravenous administration.

Pharmacology: The granisetron transdermal patch is a selective 5–hydroxytryptamine type 3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors. Receptor sites for 5-HT3 are located on vagal nerve terminals and in the chemoreceptor trigger zone in the brain. During emetogenic chemotherapy, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT3 receptors, inducing vomiting. By blocking these 5-HT3 receptors, granisetron reduces emesis due to chemotherapy regimens.

The most common reported side effects are constipation, headache, and local patch irritation.

The transdermal patch system delivers the antiemetic granisetron to the systemic circulation via passive diffusion. The absorption of drug from the patch is variable from patient to patient. An analysis of daily applications of granisetron transdermal system in healthy subjects at 1 week suggests a high intersubject variability in systemic exposure. Maximal concentration is reached at approximately 48 hours after patch application.

Clinical trials: A phase 3, randomized, parallel group, double-blind, double-dummy study involving 641 patients was conducted to evaluate the effectiveness of granisetron transdermal in the prevention of chemotherapy-induced nausea and vomiting (CINV). The efficacy of granisetron transdermal was compared to that of oral granisetron 2 mg once daily for the prevention of nausea and vomiting in patients receiving multiple-day chemotherapy.[1] The primary end point was the proportion of patients with no vomiting and/or retching, no more than mild nausea and no rescue medication from the first dose until 24 hours after the start of the last day's chemotherapy dose.

Transdermal granisetron was applied 24 to 48 hours before the first dose of chemotherapy and left on for 7 days; oral granisetron was administered daily 1 hour before each dose of chemotherapy. The patch formulation was effective in 60.2% of patients, and the oral administration of granisetron was effective in 64.8% of patients.[1]

In the literature: Researchers seeking to determine the pharmacokinetic profile of granisetron transdermal formulation and examine its possible relationship with age, gender, and renal function found that the drug's clearance was not affected by these variables, and they concluded that no dose adjustment would have to be made based on age or renal function.[2]

Precautions: The granisetron transdermal system is not recommended for patients younger than 18 years. Use may mask progressive ileus and/or gastric distention. Patients should be instructed to avoid direct sun or UV light (cover patch with clothing during use and for 10 days after removing patch). This drug has been assigned a pregnancy category B rating, and caution should be exercised in nursing mothers. Transdermal granisetron has not been evaluated in children, the elderly, or patients with hepatic or renal impairment; however, in intravenous administration of the agent, elderly subjects have exhibited lower drug clearance and a longer half-life compared with a young, healthy population.

Adverse reactions: The most common side effects reported with the granisetron transdermal patch are constipation, headache, and local patch irritation. Arrhythmias and electrocardiographic abnormalities may be associated with use of oral 5-HT3 receptor antagonists. No arrhythmias have been identified in studies of the transdermal form.

Interactions: Patients should not use the patch with other granisetron products.

Dosage, administration, and availability: The granisetron patch should be applied to clean, dry, and intact healthy skin on the upper outer arm 24 to 48 hours before chemotherapy and removed no sooner than 24 hours after chemotherapy is completed. The patch may be worn for up to 7 days. The granisetron transdermal system is available as a 34.3-mg (52 cm^2) patch.

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EVEROLIMUS (AFINITOR)

Indication: Everolimus (Afinitor), an mTOR kinase inhibitor, has been approved for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.[1]

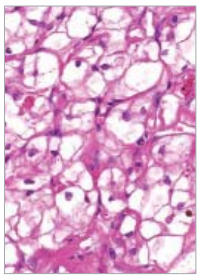
Pharmacology: The mammalian target of rapamycin, mTOR, is a serine-threonine kinase involved in a cellular process that has been shown to be deregulated in several human cancers. Everolimus is a rapamycin derivative that binds to an intracellular protein, forming a complex that inhibits mTOR kinase activity. It also reduces the activity of S6 ribosomal protein kinase and eukaryotic elongation factor 4E-binding protein, which are two other factors involved in protein synthesis in the mTOR pathway. In addition, it reduces the expression of both vascular endothelial growth factor and hypoxia-inducible factor. The inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake.

Clinical trials: An international, multicenter, randomized, double-blind trial was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Patients were randomly assigned 2:1 to receive everolimus or placebo (along with best supportive care), and their progression-free survival was assessed via a blinded, independent, central radiologic review. The median progression-free survival for everolimus was 4.9 months compared to 1.9 months with placebo. However, the overall survival results were not mature, and 32% of patients had died by the time of cut-off.[1]

In the literature: Although everolimus was first used in the prevention of allograft rejection and vasculopathy in cardiac transplant patients, it has been proven effective for an entirely different purpose in combating renal cell carcinomas.[2] As the second line of defense, everolimus has been effective in prolonging progression-free survival. It has been found recently that outcomes of initial treatment with sunitinib or sorafenib (or both) should not deter the use of second-line targeted therapy, because the first-line use of targeted agents does not appear to be predictive of outcomes with second-line therapy such as everolimus.[3]

Precautions: Everolimus is not recommended in patients with pre-existing invasive fungal infections, as the agent has certain immunosuppressive properties. Renal function, blood glucose, lipids, and complete blood count should be monitored before initiation of treatment with everolimus and periodically thereafter. Everolimus should not be used in patients with severe hepatic impairment. This agent has been assigned a pregnancy category D rating and is not recommended for nursing mothers or for women who are pregnant. If everolimus is used during pregnancy or if the patient becomes pregnant while taking the drug, she should be apprised of the potential hazard to the fetus.

Adverse effects: The most common adverse reactions in the clinical study (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine level. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during everolimus treatment were for infections, anemia, and stomatitis. For a complete list of adverse effects, see the prescribing information.[1]



Grade 1 renal cell tumors have round, uniform nuclei with absent or inconspicuous nucleoli.

Drug interactions: Moderate to strong cytochrome P-450 3A4 (CYP3A4) inhibitors (eg, ketoconazole, erythromycin, fluconazole, verapamil, or grapefruit) and P-glycoprotein inhibitors should not be used concomitantly because they may increase everolimus blood concentrations. Strong CYP3A4 inducers may decrease everolimus blood concentrations; if another treatment cannot be administered, an increase in the everolimus dosage is suggested.

Dosage and availability: The recommended dosage is 10 mg daily with water. Continue as long as benefit is observed or until unacceptable toxicity occurs. Everolimus tablets are available in 5- and 10-mg strengths in packages of 28. ■

James Alexander is Director, Institute for Pharmaceutical Industry Fellowships, Rutgers University School of Pharmacy, Piscataway, New Jersey.

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