



COMMUNITY ONCOLOGY

— CLINICAL ISSUES IN COMMUNITY PRACTICE —

REVIEWS

Denosumab in cancer patients with **bone metastases**: a new advance or more of the same?

Adam Brufsky

Pictured above: bone resorption by osteoclasts

First-line treatment of **chronic myeloid leukemia**: imatinib versus nilotinib and dasatinib

Nicholas J. DiBella

Ixabepilone in **advanced breast cancer**: clinical, treatment, and cost-related studies

Adam Brufsky

REVIEWS

Management of capecitabine-related **gastrointestinal toxicities** in women with breast cancer

Soley Bayraktar and Stefan Glück

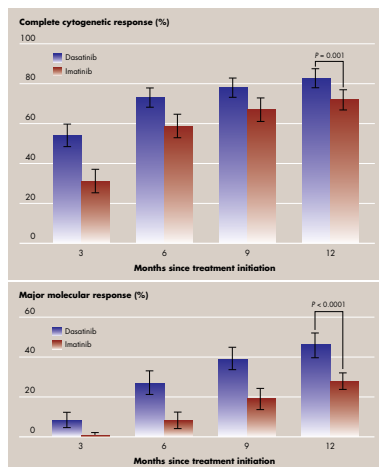
ADVERSE EVENTS ALERT

Radiation overexposure following brain perfusion CT scans in California, Florida, and Alabama (2008–2009)

Zaina P. Qureshi, Oliver Sartor, and Charles L. Bennett

WASHINGTON UPDATE

One **transition** at a time, please



Treatment of chronic myeloid leukemia (CML) with dasatinib (Sprycel) significantly improves the percentage of patients achieving a complete cytogenetic response and major molecular response, compared with CML patients treated with imatinib (Gleevec). A similar advantage over imatinib was observed in CML patients treated with nilotinib (Tasigna; see page 65).

Washington Update

92 One transition at a time, please

Susan London and Mary Ellen Schneider

State and specialty societies have written to Health and Human Services Secretary Kathleen Sebelius to ask that she urge the Centers for Medicare & Medicaid Services (CMS) to reverse a "last-minute" decision requiring physicians to use e-prescribing during the first 6 months of 2011 or face penalties in 2012 and 2013. The signatories argue it is unfair to impose the additional requirement as physicians work to adopt a certified product for participation in the Medicare electronic health records incentive program and that the CMS should minimize the financial and logistic challenges of the various incentive and penalty programs by expanding the number of exemption categories.

LETTER FROM THE EDITOR

57 The FDA's Avastin decision flies in the face of science-based medicine

Lee S. Schwartzberg, MD, FACP, *The West Clinic, Memphis, TN*

Bevacizumab (Avastin) in 2011 does not look like the wonder drug oncologists thought it might be 5 years ago. But it has a firmly established role in the treatment of common solid tumors, including metastatic breast cancer (MBC). However, the US Food and Drug Administration's recent decision to withdraw approval of the drug for MBC will ultimately impact negatively on the lives of many patients struggling with this disease.

REVIEWS

59 Denosumab in cancer patients with bone metastases

Skeletal-related events (SREs, including bone pain, spinal cord compression, fractures) are common in patients with bone metastases. Until recently, oncologists relied on intravenous bisphosphonates to prevent SREs. Now, with the FDA's recent approval of denosumab (Xgeva), a RANK ligand inhibitor, we have a new drug with a different mechanism of action and more convenient route of administration. How does it compare with zoledronic acid (Zometa)?

61 New antiresorptive agents in metastatic breast cancer: an advance or more of the same?

Adam Brufsky, MD, PhD, *University of Pittsburgh School of Medicine, Pittsburgh, PA*

65 First-line treatment of chronic myeloid leukemia: imatinib versus nilotinib and dasatinib

Nicholas J. DiBella, MD, FACP, *US Oncology and Rocky Mountain Cancer Centers, Aurora, CO*

Both nilotinib (Tasigna) and dasatinib (Sprycel) were recently approved by the FDA for first-line treatment of chronic-phase chronic myeloid leukemia, giving us three remarkably effective drugs for use in this setting. Issues to be considered in selecting among these three agents for first-line use, in addition to short-term efficacy and differences in toxicity patterns, include long-term response, survival, and toxicity; cost; sequencing in cases of resistance or intolerance; and the potential for development of BCR-ABL resistance.

73 Ixabepilone in advanced breast cancer: clinical, treatment, and cost-related studies

Adam Brufsky, MD, PhD, *Magee-Womens Hospital, Pittsburgh, PA*

Clinical data show that use of ixabepilone (Ixempra) alone and in combination with capecitabine (Xeloda) is active across the spectrum of metastatic breast cancer. Adding ixabepilone to capecitabine improves progression-free survival in patients pretreated with anthracyclines and taxanes, with toxicity that is manageable through dose reduction or delayed administration. Although ixabepilone is only marginally cost-effective in its initial late-line indications, using the drug within its FDA-approved indications will likely have minimal impact on health plan budgets. It remains to be seen whether new data in earlier lines of therapy will positively impact the cost-effectiveness of this agent.

contents 2

COMMUNITY ONCOLOGY

Correspondence

Inquiries should be addressed to *Community Oncology*, 60B Columbia Road, Morristown, NJ 07960; tel: 973-290-8200; fax: 631-424-8905.

Editorial correspondence, including submissions for publication or Letters to the Editor, should be addressed to the Editor-in-Chief, Lee S. Schwartzberg, MD, FACP, e-mail: editor@communityoncology.net.

Guidelines for authors are at www.communityoncology.net/guide.html. For further information, contact the Editorial Office, 240-221-2461, or e-mail the Managing Editor, Renee Matthews, renee.matthews@elsevier.com.

Advertising

For information on advertising rates, reprints, and supplements, contact Devin Gregorie, tel: 516-381-8613, e-mail: d.gregorie@elsevier.com.

Copyright

Copyright © 2011 by Elsevier Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission from the Publisher.

Subscriptions

Annual subscription rates (12 issues): *Domestic*: US \$363; *International*: US \$394. *Single copy*: US \$42. For further information regarding subscriptions, contact subs@elsevier.com.

Community Oncology (ISSN 1548-5315) is published monthly by Elsevier Oncology, 60B Columbia Road, Morristown, NJ 07960.

Disclaimer

Discussions, views, opinions, and recommendations as to medical procedures, products, choice of drugs, and drug dosages are the responsibility of the authors or advertisers. No responsibility is assumed by the Publisher, Editor, or Editorial Board for any injury and/or damage to persons or property as a matter of product liability, negligence, or otherwise or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. Because of rapid advances in the medical sciences, independent verification of diagnoses and drug dosages should be made. Advertiser and advertising agency recognize, accept, and assume liability for all content (including text, representations, illustrations, opinions, and facts) of advertisements printed and also assume responsibility for any claims made against the Publisher arising from or related to such advertisements.

In the event that legal action or a claim is made against the Publisher arising from or related to such advertisements, advertiser and advertising agency agree to fully defend, indemnify, and hold harmless the Publisher and to pay any judgment, expenses, and legal fees incurred by the Publisher as a result of said legal action or claim. The Publisher reserves the right to reject any advertising that he feels is not in keeping with the publication's standards.

The Publisher is not liable for delays in delivery and/or non-delivery in the event of Act of God, action by any government or quasi-governmental entity, fire, flood, insurrection, riot, explosion, embargo, strikes (whether legal or illegal), labor or material shortage, transportation interruption of any kind, work slow-down, or any condition beyond the control of the Publisher that affects production or delivery in any manner.

This journal is printed on paper meeting the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper) effective with Volume 1, Issue 1, 2004.



REVIEW

81 Management of capecitabine-related gastrointestinal toxicities in women with breast cancer

Soley Bayraktar, MD, and Stefan Glück, MD, *Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, and the University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL*

Gastrointestinal adverse events are common with capecitabine (Xeloda). Three principal strategies may be used to prevent and/or treat these side effects: dose modification and timing, symptomatic treatment, and risk reduction. Although dose and schedule modification is employed during the chronic management of capecitabine toxicities, symptomatic treatment of toxicities is critically important for managing acute events. Risk reduction strategies must be taken into consideration but, in practice, are less useful. A variety of symptomatic treatments can be helpful in patients who experience diarrhea, stomatitis, nausea, vomiting, anorexia, or dyspepsia. The risk of such toxicities can be reduced by avoiding potential drug interactions and identifying patients with genetic polymorphisms that may interfere with the metabolic pathway of capecitabine. Reducing folate consumption also may be beneficial.

ADVERSE EVENTS ALERT

89 Radiation overexposure following brain perfusion CT scans in California, Florida, and Alabama (2008–2009)

Zaina P. Qureshi, PhD, MPH, Oliver Sartor, MD, and Charles L. Bennett, MD, PHD, MPP, *South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR), South Carolina College of Pharmacy, University of South Carolina, Columbia, SC; Tulane Cancer Center and Departments of Medicine and Urology, Tulane Medical School; New Orleans, LA; and Hollings Cancer Center, Medical University of South Carolina, Charleston, SC*

Concern has been expressed that increasing use of CT scans may expose individuals to high levels of radiation exposure. These concerns were magnified in 2009, when 206 individuals at Cedars-Sinai Medical Center in Los Angeles experienced eight-fold greater irradiation than desired during brain CT perfusion scanning procedures. About 40% of these individuals reported clinical manifestations. Diligent follow-up led to the recognition that a problem in radiation overdosing may have occurred. Subsequent investigations identified similar adverse events at five other California hospitals and in at least two other states. In November 2010, FDA officials disseminated a public health communication identifying operator error as the single, most likely cause of the overexposure and outlined a range of safety initiatives designed to prevent future occurrences.

Community Oncology is indexed by EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The FDA's Avastin decision flies in the face of science-based medicine

Lee S. Schwartzberg, MD, FACP, Editor-in-Chief | The West Clinic, Memphis, TN

The implications of the US Food and Drug Administration's (FDA's) recent decision to withdraw approval of bevacizumab (Avastin) for metastatic breast cancer (MBC) are profound both practically and clinically. Given that third-party payers frequently use labeling to justify restriction of payment, the withdrawal could affect the ability of community oncologists to receive reimbursement for the drug. As long as bevacizumab is listed in the National Comprehensive Cancer Network's *NCCN Compendium* and similar works, it is likely that commercial carriers will continue to reimburse. The Centers for Medicare & Medicaid Services (CMS) depend on local and national coverage decisions. As of this writing, no CMS contractors had formally withdrawn coverage, although one announced plans to do so and then backtracked. However, given the prevailing fiscal activism regime at the CMS, coverage restrictions could still be mandated.

Roche/Genentech, the maker of Avastin, has filed a rebuttal objecting to the withdrawal, and it is likely that the final outcome will not be known for many months. Yet, the ripple effect of this decision is clearly being felt in the cancer community. The FDA used two criteria to establish its ruling: first, that progression-free survival (PFS) is not a valid endpoint in approving a breast cancer drug and, second, that the drug's risk/benefit ratio was unfavorable.

Does PFS have any clinical meaning? Our evaluation of patient reaction to therapeutics has evolved from gauging response based on an arbitrary shrinkage of tumor by measurement on a scan to taking PFS into consideration. This change occurred with the realization that stable disease in patients with advanced solid tumors was clinically beneficial. In fact, patients remaining on treatment without disease progression became the standard of practice.

Maintenance of PFS remains critical, given the use of multiple lines of therapy for breast cancer and other solid tumors. Overall survival cannot be predicted when a patient with MBC starts first-line therapy. The heterogeneity of treatment options, individual patient characteristics, and the myriad of treatment regimens preclude anything more than a rough guess.

Data from the Eastern Cooperative Oncology Group E2100 trial showed a near doubling of PFS with the addition of bevacizumab, an endpoint the FDA's European counterpart deemed as worthy of approval. To expect a first-line therapy to modify the outcome in a disease characterized by multiple treatments and years of survival is more than is ever asked for any other therapy. Such regulatory restriction hurts patient care.

Toxicity was held by the FDA to be significant enough to erase any perceived benefit to PFS. This decision was based on grade 3 criteria of adverse events, including, most prominently, hypertension. In addition, a roughly 1% incidence of bevacizumab-related bowel perforations was noted as an extreme toxicity. Many community oncologists with experience with bevacizumab strongly question the severity of its toxicity relative to the other toxic agents we use. In fact, bevacizumab is better tolerated than most therapies.

Bevacizumab in 2011 does not look like the wonder drug we thought it might be 5 years ago. But it has an established role in the treatment of common solid tumors and MBC. Withdrawing approval will impact negatively on the lives of many MBC patients.

The decision is additionally chilling, as it ushers in an era of greater conservatism for the FDA when we need bolder decision-making for cancer patients. This month, President Obama announced that the National Institutes of Health will set up an institute to promote drug development in the face of declining drug approvals in recent years. This speaks volumes about the FDA's inability to properly address the balance between the benefits of approving drugs for incurable and life-threatening diseases and the risks associated with such therapies. Community oncologists should add their voices to the debate around the decision; they should share their and their patients' experiences with bevacizumab to demonstrate how it can be used appropriately in patients with MBC—and in so doing, fight the FDA's decision.



Lee S. Schwartzberg, MD, FACP
Editor-in-Chief

© 2011 Elsevier Inc. All rights reserved.

Denosumab in cancer patients with bone metastases

First-in-class RANK ligand inhibitor reduces the risk of skeletal-related events in patients with advanced breast cancer and bone metastases and compares favorably with zoledronic acid in patients with other tumors.

Denosumab is a human monoclonal antibody that inhibits the formation, activation, and survival of bone osteoclasts by binding to receptor activator of nuclear factor κ B (RANK) ligand. Given subcutaneously (SC), denosumab (Prolia) was recently approved by the US Food and Drug Administration for the treatment of postmenopausal osteoporosis and subsequently approved at a higher dose—and more frequent dosing—under the trade name Xgeva for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors.

Recent trials have shown that denosumab is superior to the intravenous (IV) bisphosphonate zoledronic acid (Zometa) in preventing SREs in patients with advanced breast cancer and bone metastases and, further, that denosumab is noninferior to zoledronic acid in reducing the risk of SREs in patients with solid tumors or multiple myeloma and bone metastases while significantly reducing the risk of moderate-to-severe bone pain.

Denosumab in advanced breast cancer

In a multinational, phase III, double-blind, double-dummy trial, patients with advanced breast cancer and bone metastases were randomized to receive zoledronic acid, 4 mg IV (adjusted for creatinine clearance), and SC placebo (n = 1,020) or denosumab, 120 mg SC, and IV placebo (n = 1,026) every 4 weeks.¹ All patients were strongly urged to take daily calcium and vitamin D supplements.

© 2011 Elsevier Inc. All rights reserved.

What's new, what's important

Skeletal complications are common in patients with cancer. Until recently, we had only one family of medications to use. Now, with the approval of denosumab (Xgeva), a RANK (receptor activator of nuclear factor κ B) ligand inhibitor, we have a new drug with a different mechanism of action for our patients.

Denosumab is FDA approved for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors, but not for multiple myeloma. Denosumab is given as a 120-mg subcutaneous injection every 4 weeks.

Phase III studies have shown that, compared with zoledronic acid (Zometa), denosumab improved time to first on-study SREs. No difference was observed in survival outcomes. Like zoledronic acid, denosumab can cause osteonecrosis of the jaw (~2%). Hypocalcemia is another side effect to watch for with denosumab.

I think patients who are already on zoledronic acid and are doing well should continue to receive it. But those whose disease progresses on zoledronic acid or are having side effects from it could be switched to denosumab. For new patients, we now have a choice of two drugs. If clinical trials continue to show similar results, and once we are comfortable with its side-effect profile, denosumab may become the first-line therapy for prevention of SREs in the future.

—Jame Abraham, MD, Section Editor

The primary endpoint was time to first SRE, defined as pathologic fracture, radiation therapy or surgery to bone, or spinal cord compression. The median time from diagnosis of bone metastases to the start of the study was 2 months. The median time on study was 17 months, with 45% of patients being on study at the time of the primary efficacy analysis.

Efficacy

Denosumab significantly delayed the time to first SRE by 18% compared with zoledronic acid (hazard ratio [HR], 0.82; $P < 0.001$ for noninferiority and $P < 0.01$ for superiority; Figure 1). Median time to first SRE was 26.4 months in the zoledronic acid group and was not yet reached at the time of analysis in the denosumab group. Denosumab reduced the risk of first and subse-

quent SREs by 23% (rate ratio, 0.77; $P = 0.001$) and the mean skeletal morbidity rate (ratio of the number of SREs per patient divided by the patient's time at risk) by 22% (0.45 vs 0.58 SREs per patient per year; $P = 0.004$).

Treatment with denosumab was associated with greater reductions in bone turnover markers than those observed with zoledronic acid. At week 13, the median reduction in urinary *N*-telopeptide level, corrected for urine creatinine concentration, was 80% versus 68% ($P < 0.001$), and the median reduction in bone-specific alkaline phosphatase level was 44% versus 37% ($P < 0.001$). There were no differences between denosumab and zoledronic acid in over-

Summary by Matt Stenger, MS; reviewed by Adam Brufsky, MD, PhD, University of Pittsburgh School of Medicine, Pittsburgh, PA.

Commun Oncol 2011;8:59-62

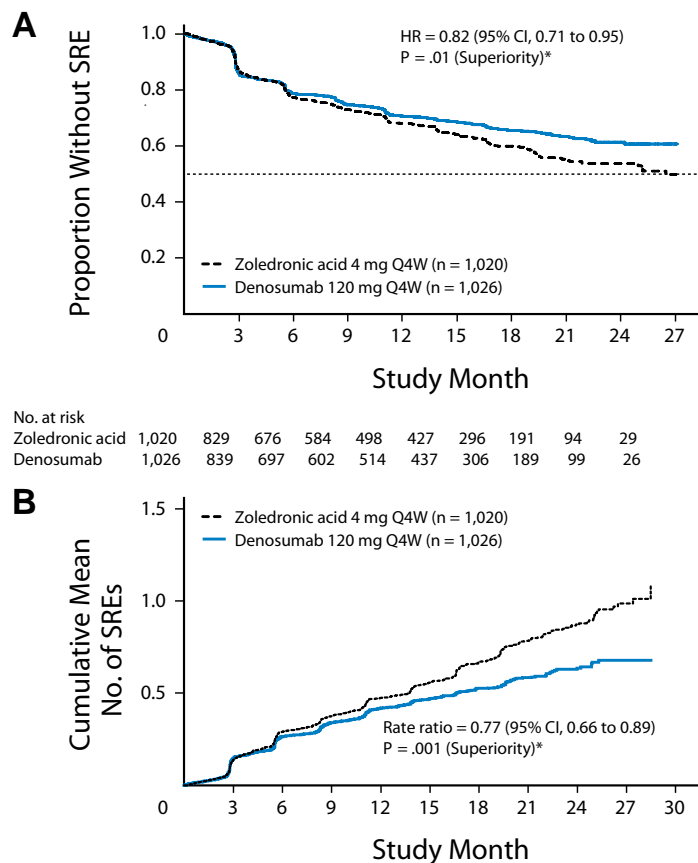


FIGURE 1 Kaplan-Meier analyses of (A) time to first skeletal-related event (SRE) and (B) time to first and subsequent SREs (represented as the cumulative mean number of SREs over time) in patients with bone metastases from advanced breast cancer receiving denosumab or zoledronic acid. Reproduced, with permission, from Stopeck et al.¹

all survival (HR, 0.95; $P =$ not significant) or disease progression (HR, 1.00; $P =$ not significant).

Adverse events

Rates of overall, severe, and serious adverse events were similar in the two treatment groups. An exploratory analysis of differences in rates of individual adverse events with a nominal P value < 0.05 (unadjusted for multiple comparisons) showed 18 events occurring more frequently in the zoledronic acid group and 2 events occurring more frequently in the denosumab group (Figure 2). Those in the denosumab group were hypocalcemia and toothache, which was not associated with osteonecrosis of the jaw (ONJ). Acute-phase reactions (ie, flu-like syndrome, including

pyrexia, chills, flushing, bone pain, arthralgias, and myalgias) within the first 3 days post injection occurred in 10.4% of denosumab patients and 27.3% of zoledronic acid patients. Adverse events potentially associated with renal toxicity occurred in 4.9% of denosumab patients versus 8.5% of zoledronic acid patients ($P = 0.001$), with severe (0.4% vs 2.2%) and serious (0.2% vs 1.5%) events being less common with denosumab. Renal adverse events in patients with a baseline renal clearance ≤ 60 mL/min occurred less frequently in the denosumab group than in the zoledronic acid group (5.9% vs 20.0%), as did a reduction in baseline creatinine clearance from ≥ 60 mL/min to < 60 mL/min (12.7% vs 16.1%).

ONJ occurred in 2.0% of the de-

nosumab group versus 1.4% of the zoledronic acid group ($P =$ not significant). ONJ was noted as early as 6 months after randomization. Cumulative incidence rates of ONJ for the denosumab versus zoledronic acid groups were 0.8% versus 0.5% at 1 year, 1.9% versus 1.2% at 2 years, and 2.0% versus 1.4% at 3 years.

Denosumab in patients with other solid tumors or multiple myeloma

A phase III, double-blind, double-dummy trial of denosumab (120 mg SC; $n = 886$) versus zoledronic acid (4 mg IV; $n = 890$) every 4 weeks in patients with bone metastases from advanced solid tumors (excluding breast and prostate cancers) or multiple myeloma* showed that denosumab was noninferior to zoledronic acid in reducing the risk for first SRE.² For assessment of changes in pain severity, patients completed the Brief Pain Inventory (BPI) at baseline, day 8, and before each monthly visit.³

Analyses included (1) the time to worsening of pain (defined as an increase of ≥ 2 points from baseline in BPI score) in all patients and in patients with no or mild pain at baseline and (2) the proportion of patients with no or mild pain at baseline who experienced moderate/severe pain during the study (worst pain score, > 4). Data were analyzed through week 45, when at least 50% of patients had discontinued study participation due to death, disease progression, or withdrawal of consent.

Denosumab was associated with a significant delay in time to pain worsening among all patients (median of 169 days vs 143 days; HR, 0.85; $P = 0.02$) and a significant delay in time to moderate/severe pain among patients (361 in the deno-

*Denosumab is not FDA approved for the prevention of SREs in patients with multiple myeloma.

sumab group, 317 in the zoledronic acid group) with no or mild pain at baseline (median 144 vs 102 days; HR, 0.81; $P = 0.04$). The proportion of patients with no or mild pain at baseline who experienced moderate/severe pain during the study was lower in the denosumab group than in the group treated with zoledronic acid at most time points.

References

1. Stopeck AT, Lipton A, Body J-J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28:5132–5139.
2. Henry D, von Moos R, Vadhan-Raj S, et al. A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Eur J Cancer* 2009;7(suppl):11. Abstract 20LBA.
3. von Moos R, Patrick D, Fallowfield L, et al. Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): results from a randomized phase III clinical trial. *J Clin Oncol* 2010;28(15S):9043.

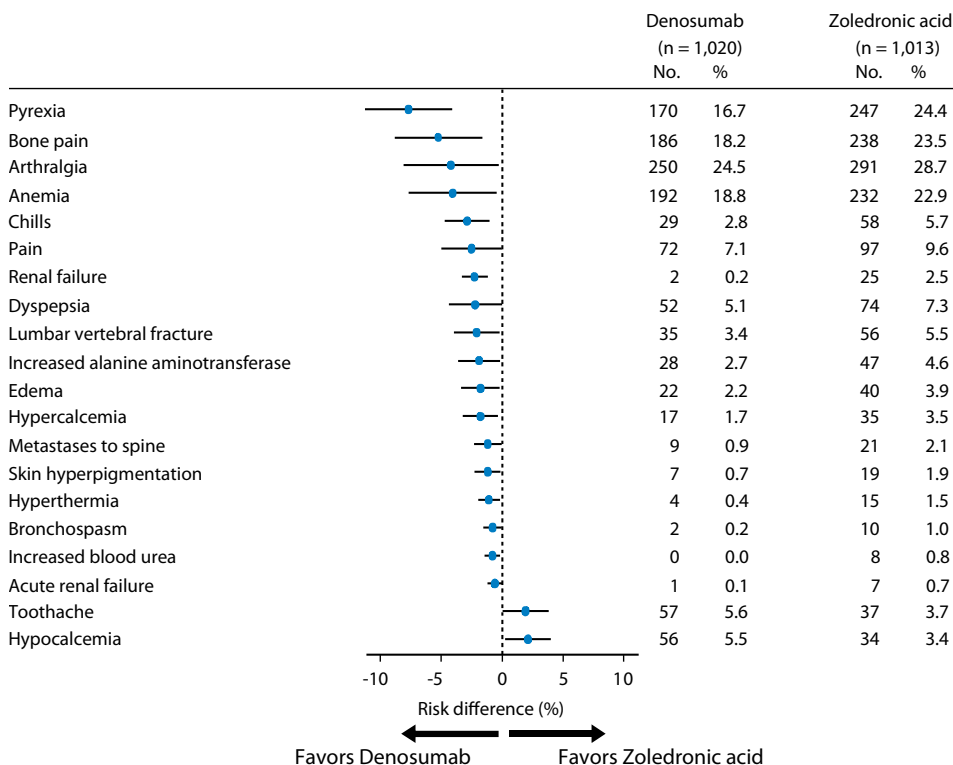


FIGURE 2 Forest plot of adverse events with between-group differences with a nominal P value of < 0.05 (unadjusted for multiple comparisons) in a trial of denosumab versus zoledronic acid in advanced breast cancer. Reproduced, with permission, from Stopeck et al.¹

From the Oncologist's Perspective

New antiresorptive agents in metastatic breast cancer: an advance or more of the same?

Adam Brufsky, MD, PhD | University of Pittsburgh School of Medicine, Pittsburgh, PA

Bone metastasis is common in metastatic breast cancer (MBC), with more than 60%–70% of women with MBC having at least one bone lesion. Women with MBC and bone metastases can survive many years with slowly progressive disease. Skeletal complications of bone metastases, such as pain, fracture, or need for surgical or radiotherapeutic intervention,

which occur with some frequency, are therefore a major cause of morbidity and mortality in this population.

Bisphosphonates

Bisphosphonate compounds, originally developed in the latter part of the 19th century as pipe-cleaning agents, inhibit osteoclast metabolism and maturation. They have been used successfully for nearly 20 years as thera-

py for hypercalcemia of malignancy and, more recently, as therapy to delay or prevent skeletal complications of malignancy. Bisphosphonates of increasing potency, as measured by their ability to inhibit the enzyme farnesyl diphosphate synthase in osteoclasts,¹ have been shown to decrease the risk of skeletal-related events (SREs) in breast and other cancers through a series of well-conducted randomized

clinical trials. Bisphosphonates are therefore part of the standard armamentarium for the treatment of MBC.

However, somewhere between 20% and 35% of women receiving bisphosphonates for MBC do not adequately demonstrate osteoclast suppression as measured by bone turnover markers, such as urinary levels of the *N*-telopeptide fragment of collagen.² Exploitation of other pathways of osteoclast suppression in MBC has a rational basis.

Denosumab

Denosumab (Xgeva), a humanized monoclonal antibody, mimics the activity of a naturally occurring protein, osteoprotegerin, and binds to the receptor activator of nuclear factor κ B (RANK) ligand present on bone marrow stromal cells; it prevents osteoclast activation by preventing interaction of osteoclast precursors with RANK ligand.³ In two phase II trials, denosumab demonstrated equivalent to superior suppression of bone turnover when compared with zoledronic acid (Zometa).^{4,5} In another phase II study, denosumab was shown to suppress bone turnover in a subset of patients refractory to zoledronic acid.⁶

It therefore comes as no surprise that denosumab is modestly superior to zoledronic acid in the prevention of skeletal complications of MBC in a well-conducted, placebo-controlled, phase III randomized trial.⁷ Denosumab also has a more convenient route of administration (subcutaneous versus intravenous) as well as minimal renal toxicity when compared with zoledronic acid.

Should we therefore switch to denosumab from bisphosphonates at this point? The cost of denosumab is approximately double that of zoledronic acid and is even higher when compared with the cost of generic pamidronate. Is the extra convenience and additional delay in SREs worth this extra cost? Pharmacoeconomic analyses are currently ongoing.

Less-frequent dosing

Additionally, it is likely that patients will be on these compounds for extended periods as the median survival of women with MBC increases. What are the long-term complications of these antiresorptive agents? Can we dose either denosumab or zoledronic acid less frequently than monthly and still maintain the same benefit? A randomized, but slowly accruing, phase III clinical trial (OPTIMIZE; ClinicalTrials.gov ID No. NCT00320710) is testing whether giving zoledronic acid every 3 months is equivalent in efficacy to monthly dosing in women with MBC. It is also worth noting that in the randomized phase II trial comparing denosumab with zoledronic acid, the every-12-week denosumab dose performed almost as well as the monthly dose in suppressing bone turnover.⁴

What is clear is that there is yet another drug to help prevent or delay a major cause of morbidity in MBC. Having choices is not a bad thing, and future work will help clarify the optimal use of denosumab and zoledronic acid (or, perhaps, both together) in the management of MBC.

References

1. Dunford JE, Thompson K, Coxon FP, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001;296:235–242.
2. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer* 2008;113:193–201.
3. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor- κ B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res* 2006;12:1221–1228.
4. Lipton A, Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 2007;25:4431–4437.
5. Lipton A, Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. *Clin Cancer Res* 2008;14:6690–6696.
6. Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol* 2009;27:1564–1571.
7. Stopeck AT, Lipton A, Body J-J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28:5132–5139.

ABOUT THE AUTHOR

Affiliation: Dr. Brufsky is Professor of Medicine and Associate Chief, Hematology-Oncology, at the University of Pittsburgh School of Medicine, Pittsburgh, PA. He can be reached at brufskyam@upmc.edu.

Conflicts of interest: Dr. Brufsky receives consulting fees from Amgen and Novartis Pharmaceuticals and serves on the medical advisory board of Thar Pharmaceuticals.

First-line treatment of chronic myeloid leukemia: imatinib versus nilotinib and dasatinib

Nicholas J. DiBella, MD, FACP

US Oncology and Rocky Mountain Cancer Centers, Aurora, CO

Recently reported phase III trials showed that the second-generation BCR-ABL tyrosine kinase inhibitors nilotinib and dasatinib produce greater rates of cytogenetic and molecular responses at 1 year compared with imatinib as first-line treatment for chronic-phase chronic myeloid leukemia. Differences in the safety profiles of the two newer agents compared with that of imatinib were modest. Both nilotinib and dasatinib were recently approved by the FDA for use in this setting, giving us three remarkably effective drugs for first-line treatment. Issues to be considered in selecting among these three agents for first-line use, in addition to short-term efficacy and differences in toxicity patterns, include long-term response, survival, and toxicity; cost; sequencing in cases of resistance or intolerance; and potential for BCR-ABL resistance.

The introduction of imatinib (Gleevec) was remarkable both because it represented an astounding breakthrough in the treatment of chronic myeloid leukemia (CML) and because it heralded the advance of kinase inhibitors and other targeted therapies into the field of cancer therapeutics. Imatinib is still a highly effective agent for the treatment of chronic-phase CML. However, two new second-generation BCR-ABL kinase inhibitors, nilotinib (Tasigna) and dasatinib (Sprycel), have recently been shown to be superior to imatinib in achieving complete cytogenetic response (CCyR) and major molecular response (MMR) at 1 year in the first-line treatment of chronic-phase CML.^{1,2} Both recently have been approved by the US Food and Drug Administration (FDA) for first-line treatment in this setting, another remarkable development that provides us with two more powerful weapons to battle this disease. This development also raises issues that will need to be considered in decisions on how best to use these highly effective agents.

New findings with imatinib

The IRIS (International Randomized Study of Interferon and STI571) trial comparing imatinib with interferon- α plus low-dose cytarabine established imatinib as standard therapy for CML.³ Imatinib treatment produced CCyR in 76% of patients at 18 months, with progression-free survival (PFS) estimated at 97%. Most long-term data on imatinib treatment come from analyses of the ima-

tinib group in IRIS, and these analyses suggest that responses with imatinib are durable. A follow-up of IRIS patients who remained on imatinib for 5 years showed a CCyR of 87% and overall survival (OS) of 89%,⁴ and the recently reported 8-year follow-up showed event-free survival (EFS) of 81%, PFS of 93%, and OS of 86% in patients remaining on imatinib for 8 years.⁵ However, outcome analyses in the IRIS population are limited by the exclusion of large numbers of patients lost to follow-up for various reasons, including adverse events and lack of efficacy/disease progression.

In another study, de Lavallade and colleagues analyzed outcomes on an intention-to-treat basis in 204 consecutive newly diagnosed patients treated with imatinib at a single center.⁶ This study showed a cumulative 5-year CCyR rate of 82.7% and an MMR rate of 50.1%, with an estimated OS of 83.2%, a PFS of 82.7%, and an EFS of 81.3%. However, at 5 years, 25% of patients had discontinued imatinib due to unsatisfactory response or toxicity, providing some evidence that the rate of discontinuation of imatinib may in actuality be surprisingly high over the long term. On the intention-to-treat analysis, the 5-year probability of cytogenetic remission while still receiving imatinib was 62.7%.

Manuscript received November 18, 2010; accepted January 24, 2011.

Matt Stenger, MS, assisted in the preparation of this article.

Correspondence to: Nicholas J. DiBella, MD, FACP, 1700 South Potomac, Aurora, CO 80012; telephone: 303-418-7608; fax: 303-750-3137; e-mail: nick.dibella@usoncology.com.

Commun Oncol 2011;8:65-72 © 2011 Elsevier Inc. All rights reserved.

Both the recent dasatinib and nilotinib trials used the standard imatinib dose of 400 mg/d as initial treatment in their control groups. Evidence from noncomparative studies indicating that better responses are achieved with imatinib 800 mg/d⁷ led to direct comparisons of the two doses. Cortes and colleagues⁸ recently reported results of the phase III Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study in which 476 previously untreated patients were randomized to receive imatinib 800 mg/d (n = 319) or 400 mg/d (n = 157). There was no difference between groups in the primary endpoint of MMR rate at 12 months (46% vs 40%; $P =$ not significant) or CCyR rate at 12 months (70% vs 66%; $P =$ not significant). However, MMR (12.2% vs 3.2%, $P = 0.001$, at 3 months; 33.5% vs 17.2%, $P = 0.0002$, at 6 months) and CCyR (56.7% vs 44.6%, $P = 0.015$, at 6 months) occurred more rapidly with the higher dose.

Grade 3/4 hematologic toxicity was more common with the 800 mg dose. The most common nonhematologic adverse events were edema, gastrointestinal (GI) events, and rash, and all were more common with the higher dose. The finding of no significant advantage for the 800 mg dose in molecular endpoints despite higher response rates earlier in the study is consistent with findings in other comparisons of the 400 mg and 800 mg doses.⁹ These findings suggest that the 400 mg starting dose has efficacy comparable to the 800 mg dose but is less toxic and is therefore preferable as the starting imatinib dose.

Another recent study of imatinib has shown that some patients maintain complete molecular remission after discontinuation of treatment, suggesting the possibility of cure of CML with kinase inhibitor therapy in at least some patients.¹⁰ In the Stop Imatinib (STIM) study, imatinib treatment was discontinued in 100 patients who had received imatinib for at least 2 years and were in complete molecular remis-

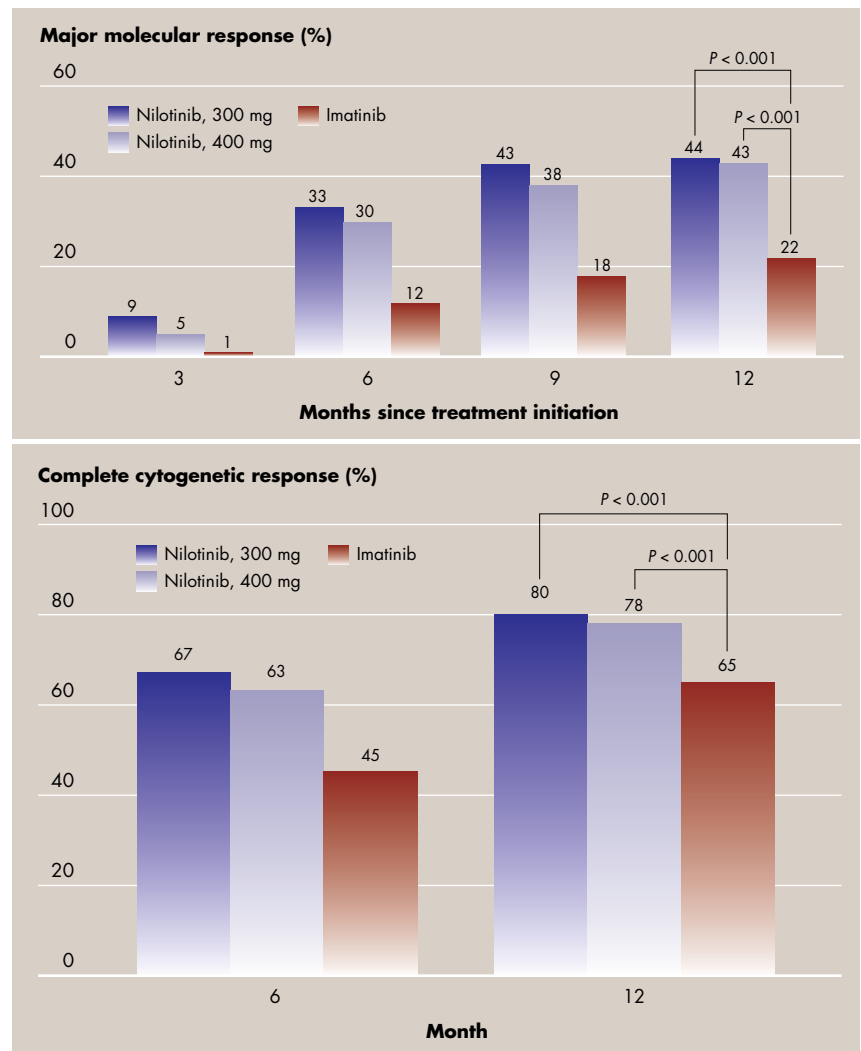


FIGURE 1 Rates of major molecular response (top) and complete cytogenetic response (bottom) in patients receiving nilotinib 300 mg or 400 mg twice daily or imatinib 400 mg once daily. Adapted, with permission, from Saglio et al.² © 2010 Massachusetts Medical Society. All rights reserved.

sion (> 5 log reduction in BCR-ABL and ABL levels and undetectable transcripts on quantitative real-time polymerase chain reaction). The recently reported interim analysis was based on 69 patients who had reached at least 12 months of follow-up. During median follow-up of 24 months in these 69 patients, relapse occurred in 42, with 40 having relapse within 6 months, 1 at 7 months, and 1 at 19 months; relapse was characterized by an increase in BCR-ABL transcripts of 1 log per month. The probability of persistent complete molecular remission at 12 months was 41%. Relapse rates did not

differ among patients with or without prior interferon- α treatment.

On univariate analysis, greater risk of relapse (lower estimated 18-month relapse-free survival) was found for female gender (30% vs 50% in men; $P = 0.03$); higher Sokal risk group (13%, 35%, and 54% for high, intermediate, and low risk, respectively; $P = 0.008$); and shorter duration of prior imatinib therapy (22% vs 47% for < 50 months vs ≥ 50 months; $P = 0.033$). On multivariate analysis, each of these factors contributed independent prognostic information, with risk of relapse being doubled for higher Sokal risk score

(hazard ratio [HR], 2.012; $P = 0.004$, for low vs intermediate vs high) and female gender (HR, 2.023; $P = 0.049$) and more than halved by greater duration of prior imatinib (HR, 0.421; $P = 0.010$ for < 50 months vs ≥ 50 months).

All patients with relapse were restarted on imatinib within 1 to 2 months of relapse and all remained sensitive to imatinib therapy, with 26 of 42 patients achieving sustained complete molecular remission (median time to remission of 3 months) and the remainder exhibiting decreases in BCR-ABL levels. No loss of hematologic response or progression to advanced-phase disease was observed in any patient.

The authors attributed the apparent lack of acquired resistance to the relatively low level of BCR-ABL at the time of relapse and the rapidity with which imatinib treatment was restarted in patients with relapse. Further study is necessary to determine precisely which patient and disease factors might allow safe discontinuation of imatinib or other kinase inhibitor therapy in patients achieving complete molecular remission.

Nilotinib vs imatinib in previously untreated patients

Nilotinib, a second-generation kinase inhibitor (an analog of imatinib) with greater selectivity and potency for BCR-ABL than imatinib,¹¹ was initially FDA approved in 2007 for treatment of patients with chronic-phase CML with resistance to or intolerance of imatinib. On the basis of the recent phase III trial reported by Saglio and colleagues,² nilotinib has been FDA approved for first-line treatment in chronic-phase CML at a dose of 300 mg twice daily.

In the open-label, multinational Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) study, 846 patients with newly diagnosed Philadelphia chromosome (Ph)-positive chronic-phase CML were ran-

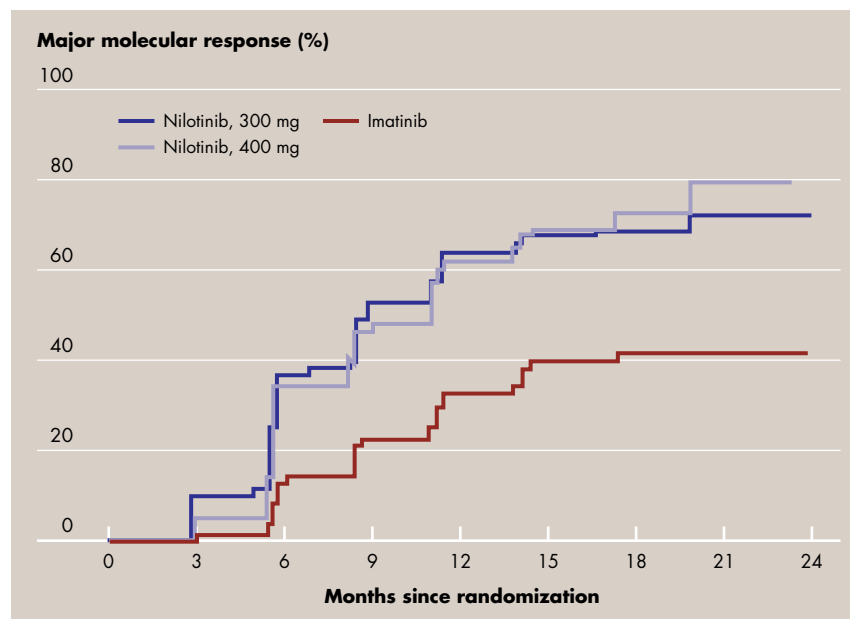


FIGURE 2 Kaplan-Meier estimates of time to first major molecular response in patients receiving nilotinib 300 or 400 mg twice daily or imatinib 400 mg once daily. Adapted, with permission, from Saglio et al.² © 2010 Massachusetts Medical Society. All rights reserved.

domized (1:1:1 ratio) to receive nilotinib 300 mg twice daily (bid; $n = 282$) or 400 mg bid ($n = 281$) or standard-dose imatinib 400 mg ($n = 283$) once daily.² The primary endpoint was MMR at 12 months. Treatment groups were well balanced for demographics and baseline characteristics. Across the three groups, patients had a median age of 46–47 years; 56%–62% were male; and Sokal risk categories were low in 37%, intermediate in 36%, and high in 28% in each group. Median time from diagnosis to randomization was approximately 1 month in all groups.

Median dose intensities were 592 mg/d (98.7% of target dose) in the nilotinib 300 mg bid group, 779 mg/d (97.4%) in the nilotinib 400 mg bid group, and 400 mg/d (100%) in the imatinib group. At the time of data cutoff (date of the 12-month visit of the final study patient), the median duration of treatment was 14 months; at this time, 84% of patients in the nilotinib 300 mg bid group, 82% in the nilotinib 400 mg bid group, and 79% in the imatinib group were receiving study drug. Imatinib dose escalation to 800 mg/d

occurred in 45 patients (16%).

At 12 months, MMR rates were 44% in the nilotinib 300 mg bid group and 43% in the 400 mg bid group versus 22% in the imatinib group ($P < 0.001$ for both nilotinib groups vs imatinib). MMR rates in patients with high Sokal risk were 41% in the nilotinib 300 mg bid group, 32% in the nilotinib 400 mg bid group, and 17% in the imatinib group. MMR was achieved more rapidly with nilotinib, with higher response rates at 3, 6, and 9 months (Figure 1) and shorter estimated median times to MMR (8.6 months for 300 mg bid and 11.0 months for 400 mg bid vs not achieved with imatinib) observed with both nilotinib doses (Figure 2); the probability of MMR at different time points was significantly higher with both nilotinib doses ($P < 0.001$ vs imatinib for both).

Rates of CCyR at 12 months (the key secondary endpoint) were significantly higher in both the nilotinib 300 mg bid and 400 mg bid groups compared with imatinib (80% and 78% vs 65%, $P < 0.001$ for both), and higher rates were observed with both nilo-

TABLE 1

Adverse events and newly occurring or worsening hematologic or biochemical abnormalities in patients receiving nilotinib or imatinib

Adverse event	Percentage of patients			
	All grades		Grade 3 or 4	
	Nilotinib 300 mg bid (n = 279)	Imatinib 400 mg (n = 280)	Nilotinib 300 mg bid (n = 279)	Imatinib 400 mg (n = 280)
Hematologic				
Neutropenia	43	68	12	20
Thrombocytopenia	48	56	10	9
Anemia	38	47	3	5
Nonhematologic ^a				
Rash	31	11	<1	1
Headache	14	8	1	0
Nausea	11	31	<1	0
Alopecia	8	4	0	0
Pruritus	15	5	<1	0
Myalgia	10	10	<1	0
Fatigue	11	8	1	<1
Vomiting	5	14	0	0
Diarrhea	8	21	1	1
Muscle spasm	7	24	0	1
Peripheral edema	5	14	0	0
Eyelid edema	1	13	0	<1
Periorbital edema	<1	12	0	0
Biochemical abnormalities				
Increased total bilirubin	53	10	4	<1
Increased alkaline phosphatase	21	33	0	<1
Decreased phosphate	32	45	5	8
Increased glucose	36	20	6	0
Increased lipase	24	11	6	3
Increased amylase	15	12	<1	1
Increased creatinine	5	13	0	<1
Increased ALT	66	20	4	2
Increased AST	40	23	1	1

ALT = alanine transaminase; AST = aspartate aminotransferase

^aEvents occurring in $\geq 10\%$ of patients in any group

Source: Saglio et al²; used with permission © 2010 Massachusetts Medical Society. All rights reserved.

tinib doses at 6 months. Among patients with a high Sokal risk, 12-month CCyR rates were 74% with nilotinib 300 mg bid, 63% with nilotinib 400 mg bid, and 49% with imatinib.

By the data cutoff date, progression to the accelerated or blast phase had occurred in 4% of imatinib patients (11 patients) and < 1% of patients in the nilotinib 300 mg bid

group (2 patients) and in the 400 mg bid group (1 patient); both the nilotinib 300 mg bid group ($P = 0.01$) and the 400 mg bid group ($P = 0.004$) had significantly increased time to disease progression. No progression to the accelerated or blast phase was observed in patients with an MMR.

The most frequently reported study-related adverse events of any

grade in patients receiving nilotinib 300 mg bid or imatinib are shown in Table 1. Grade 3/4 neutropenia was more common with imatinib. Grade 3/4 nonhematologic adverse events were rare; for adverse events of any grade, nausea, diarrhea, vomiting, muscle spasm, and edema were more common with imatinib, and rash, headache, pruritus, and alopecia were more common with nilotinib. Among grade 3/4 laboratory abnormalities, increased levels of total bilirubin, alanine transaminase (ALT), glucose, and lipase were more common with nilotinib, whereas decreased levels of phosphate were more common with imatinib. No patient had a corrected QT interval of more than 500 msec, and no decrease in mean left ventricular ejection fraction from baseline was observed at any study time point. A total of 11 patients had an ischemic heart disease event, with only one event resulting in discontinuation of treatment.

Discontinuation of treatment due to adverse events occurred in 5% of nilotinib 300 mg bid patients, 9% of nilotinib 400 mg bid patients, and 7% of imatinib patients, and dose reductions or interruptions occurred in 59%, 66%, and 52%, respectively. At the time of data cutoff, death had occurred in four imatinib patients (all of whom had discontinued treatment due to disease progression and died of CML-related causes); three nilotinib 300 mg bid patients (one from small intestine obstruction, one from suicide during the study, and one after bone marrow transplantation during follow-up); and two nilotinib 400 mg bid patients (one during follow-up after discontinuing treatment due to disease progression and one from gastric cancer after discontinuing treatment).

Dasatinib vs imatinib in previously untreated patients

Dasatinib, a second-generation kinase inhibitor with greater potency for BCR-ABL than imatinib,¹² was

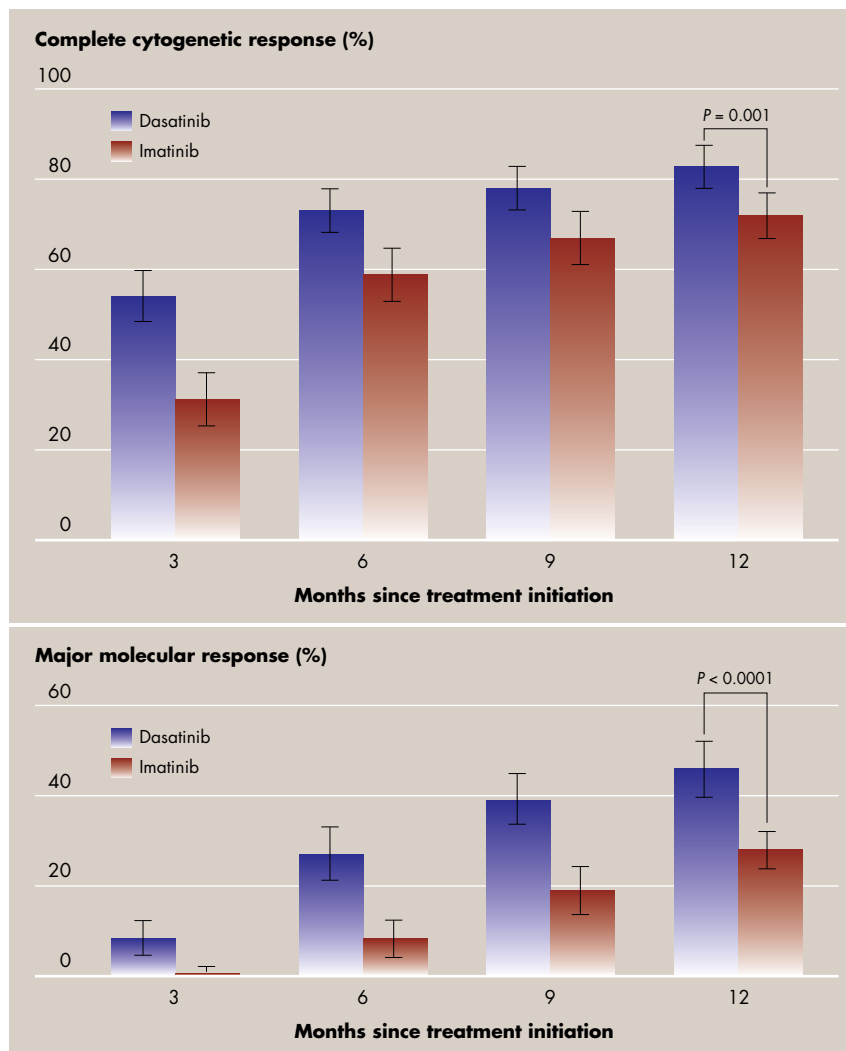


FIGURE 3 Rates of complete cytogenetic response (*top*) and major molecular response (*bottom*) in patients receiving dasatinib 100 mg once daily or imatinib 400 mg once daily. Bars show 95% confidence intervals. Adapted, with permission, from Kantarjian et al.¹ © 2010 Massachusetts Medical Society. All rights reserved.

initially FDA approved in 2006 for patients with chronic-phase CML with resistance to or intolerance of imatinib. On the basis of the recent phase III trial reported by Kantarjian and colleagues,¹ dasatinib has been FDA approved for first-line treatment of chronic-phase CML at a dose of 100 mg once daily.

In the open-label multinational Dasatinib vs Imatinib Study in Treatment-Naive CP-CML Patients (DASISION) study,¹ 519 patients with newly diagnosed, Ph-positive chronic-phase CML were randomized to receive dasatinib 100 mg

once daily (n = 259) or imatinib 400 mg once daily. The primary endpoint was confirmed CCyR at 12 months (confirmed at two consecutive assessments at least 28 days apart). Treatment groups were well balanced for demographics and baseline characteristics. For the dasatinib and imatinib groups, median ages were 46 and 49 years, and 56% and 63% of patients were male, respectively; Hasford risk (which assigns a smaller proportion of patients to high risk compared with Sokal risk) was low in 33% of patients in both groups, intermediate in 47% of dasatinib and 48% of

imatinib patients, and high in 19% in both groups. Median time from diagnosis to randomization was 1 month in both groups.

Median doses were 99 mg/d (99% of target dose) for dasatinib and 400 mg/d (100%) for imatinib. The median duration of treatment at the time of reporting was 14.0 months in the dasatinib group and 14.3 months in the imatinib group; 84% of dasatinib patients and 81% of imatinib patients continued to receive study drug for the duration of treatment reflected in this report.

After 12 months, confirmed CCyR occurred in 77% of dasatinib patients versus 66% of imatinib patients ($P = 0.007$), with the rate of complete response on at least one assessment also being significantly greater with dasatinib (83% vs 72%; $P = 0.0001$). The MMR rate at 12 months (key secondary endpoint) was 46% with dasatinib versus 28% with imatinib ($P < 0.0001$), and the rate of MMR at any time point was also significantly greater with dasatinib (52% vs 34%; $P < 0.0001$). Responses were achieved more rapidly with dasatinib than with imatinib (Figure 3). Times to confirmed CCyR and any CCyR were both significantly shorter with dasatinib (HR 1.5, $P < 0.0001$ for both), as was the time to MMR (HR, 2.0; $P < 0.0001$). For the dasatinib versus imatinib group, 12-month CCyR rates were 78% versus 64% in patients at high Hasford risk, 78% versus 72% for intermediate risk, and 94% versus 76% for low risk.

MMR rates according to Hasford risk were 31% versus 16% for high risk, 45% versus 28% for intermediate risk, and 56% versus 36% for low risk, respectively. Progression to the accelerated or blastic phase occurred in 1.9% of dasatinib patients and 3.5% of imatinib patients; no disease progression was observed in patients with an MMR. At 12 months, estimated PFS rates were 96% with dasatinib and 97% with imatinib, and OS rates were

TABLE 2

Treatment-related adverse events occurring in $\geq 10\%$ of patients receiving dasatinib or imatinib

Adverse event	Percentage of patients			
	All grades		Grade 3 or 4	
	Dasatinib 100 mg (n = 258)	Imatinib 400 mg (n = 258)	Dasatinib 100 mg (n = 258)	Imatinib 400 mg (n = 258)
Hematologic				
Neutropenia	65	58	21	20
Thrombocytopenia	70	62	19	10
Anemia	90	84	10	7
Nonhematologic				
Fluid retention	19	42	1	1
Superficial edema	9	36	0	<1
Pleural effusion	10	0	0	0
Other	5	8	1	<1
Diarrhea	17	17	<1	1
Nausea	8	20	0	0
Vomiting	5	10	0	0
Myalgia	6	12	0	0
Muscle inflammation	4	17	0	<1
Musculoskeletal pain	11	14	0	<1
Rash	11	17	0	1
Headache	12	10	0	0
Fatigue	8	10	<1	0

Source: Kantarjian et al¹; used with permission © 2010 Massachusetts Medical Society. All rights reserved.

97% and 99%, respectively.

Drug-related adverse events occurring in at least 10% of treated patients are shown in Table 2. Grade 3/4 neutropenia occurred with similar frequency in both groups, and thrombocytopenia and anemia were more common with dasatinib. Grade 3/4 nonhematologic adverse events were rare. Among nonhematologic adverse events of any grade, most were more common in imatinib patients, including nausea, vomiting, myalgia, muscle inflammation, rash, and fluid retention. Pleural effusion of grade 1 or 2 occurred in 10% of dasatinib patients and in no imatinib patients; three dasatinib patients discontinued treatment due to grade 2 pleural effusion.

GI or other types of bleeding occurred in 5% of patients in both treatment groups (grade 3/4 in one dasatinib patient and two imatinib

patients). Grade 3/4 hypophosphatemia occurred in 4% of dasatinib patients and 19% of imatinib patients. Corrected QT intervals of 450–500 msec were observed in 2% of dasatinib patients and 4% of imatinib patients, and one patient in each group had an interval greater than 500 msec.

Rates of treatment discontinuation due to drug toxicity were 5% in the dasatinib group and 4% in the imatinib group. One death in each group, both due to myocardial infarction, was attributed to study treatment.

Considerations in selecting first-line treatment

The phase III trials of nilotinib and dasatinib in the first-line treatment of chronic-phase CML have shown that these two agents produce higher cytogenetic and molecular response rates at 1 year than imatinib, with

modest differences in toxicity. Dasatinib 100 mg once daily and nilotinib 300 mg bid produced 12-month CCyR rates that were more than 10% greater and 12-month MMR rates that were around 20% greater than those seen with imatinib 400 mg/d. Both treatments were associated with reduced rates of progression to accelerated or blast phases. Available data indicate that increasing the starting imatinib dose from 400 mg/d to 800 mg/d does not improve cytogenetic or molecular response while increasing toxicity, indicating that nilotinib and dasatinib were compared with the optimal starting dose of imatinib in these trials.

Selecting among these three agents for first-line treatment of CML will present a challenge for many treating physicians. For some physicians, the differences in short-term efficacy in achieving CCyR and MMR will be very compelling in favoring nilotinib or dasatinib over imatinib as initial treatment on the reasoning that it is best to lead with the strongest weapons, giving patients the greatest chance of a sustained remission from the start of treatment. For now, though, it is unclear whether either nilotinib or dasatinib has an advantage over the other agent in terms of efficacy, and a direct comparative trial of the two in CML is unlikely to be performed.

Other physicians may find compelling reasons to continue to use imatinib as first-line treatment, reserving nilotinib or dasatinib for cases of imatinib failure or intolerance. The downside of this approach is the emotional stress for the patient as well as the physician of dealing with a poor response to imatinib. Also, there is always the small risk that a patient's disease may progress rapidly from chronic to accelerated phase or blast crisis and not respond to the alternative kinase inhibitor.

One concern with immediately adopting one of the new agents into first-line treatment is the absence of

long-term data in this setting. There is evidence indicating that both MMR and CCyR at 12 months with imatinib therapy are predictive of low risk of long-term disease progression,^{4-6,13,14} suggesting that responses with nilotinib and dasatinib will be durable. However, data on long-term discontinuation of treatment, remission, survival rates, and toxicity currently are lacking for both of these agents.

In the absence of such data, some practitioners may opt to continue to use imatinib up front and reserve dasatinib or nilotinib for patients who fail to respond to or cannot tolerate imatinib treatment. Both dasatinib^{15,16} and nilotinib^{17,18} are effective in this setting. However, not all patients respond to a second kinase inhibitor, with one analysis indicating that better EFS with a second agent is predicted by prior cytogenetic response to imatinib and better performance status.¹⁹

Cost will also be a consideration that may favor continued use of imatinib as first-line therapy. Imatinib is less expensive than either of the new agents and will probably be markedly less expensive when generic forms become available several years from now. Many patients have an excellent response to imatinib, and a strategy of starting therapy with a less expensive drug and switching if response is suboptimal seems like a reasonable approach, particularly in today's economic environment.

Will resistance be a problem?

Another unanswered question regarding dasatinib and nilotinib is to what degree BCR-ABL resistance to these kinase inhibitors will become a problem in first-line treatment. The likelihood of resistance to the newer agents would seem smaller, since both are more potent inhibitors of BCR-ABL than imatinib, exhibit activity against most imatinib-resistant mutations, and are associated with fewer BCR-ABL mutations that confer

reduced sensitivity. The BCR-ABL T315I mutation confers resistance to all three kinase inhibitors. Reduced sensitivity to dasatinib, which exhibits a different conformational binding to BCR-ABL than nilotinib and imatinib, also appears to be associated with Q252H, F317L, V299L, and E255K/V mutations,^{20,21} whereas Y253H, E255K/V, and F359C/V mutations confer reduced sensitivity to nilotinib.^{20,22} Apart from the issues of whether significant resistance to dasatinib or nilotinib will be observed and what the options for subsequent treatment might be, the differences between the two agents in resistance profiles may play a role in selecting therapy.

Difference in safety profiles

Although all three drugs have remarkably good safety profiles, differences in potential toxicities may also play a role in selecting initial and subsequent therapies. All three kinase inhibitors have myelosuppressive effects requiring periodic monitoring of blood counts. All are associated with a risk of cardiac toxicity, although there may be an enhanced risk with nilotinib. Nilotinib has a black-box warning for QT prolongation and sudden death; sudden death has been observed in imatinib-resistant or imatinib-intolerant patients, with a potential association with ventricular repolarization abnormalities.²³ It is recommended that electrocardiograms be obtained at baseline, at 7 days, and periodically thereafter and following any dose adjustment. Hypokalemia and hypomagnesemia must be corrected prior to starting treatment and checked periodically. Other drugs known to prolong the QT interval and strong CYP3A4 inhibitors must be avoided with nilotinib; if a patient must receive a strong CYP3A4 inhibitor, a nilotinib dose reduction should be considered and the QT interval should be monitored.

Food increases blood nilotinib lev-

els, and thus food needs to be avoided 2 hours before and 1 hour after a dose. Nilotinib dose reduction is recommended for patients with hepatic impairment, with close monitoring of the QT interval. Other warnings for nilotinib include those for electrolyte abnormalities, including hypokalemia, serum lipase elevations (with caution recommended in patients with a history of pancreatitis), and liver function abnormalities (requiring periodic monitoring).

No routine ECG monitoring is recommended with dasatinib or imatinib, although monitoring of patients with cardiac disease or signs and symptoms of cardiac dysfunction is recommended. Dasatinib has a warning for QT prolongation, requiring caution in patients who have or may develop prolonged QT, and it is recommended that patients have hypokalemia or hypomagnesemia corrected before starting treatment.²⁴ Dasatinib also has warnings for fluid retention and bleeding-related events.

Imatinib carries warnings for congestive heart failure and left ventricular dysfunction, particularly in patients with risk factors, and for cardiogenic shock/left ventricular dysfunction in patients with conditions associated with eosinophilia.²⁵ Other warnings for imatinib include those for edema and fluid retention, hepatotoxicity (requiring periodic monitoring), bleeding, and GI perforation.

In the phase III trial in newly diagnosed CML patients,¹ dasatinib was associated with a greater frequency of grade 3/4 thrombocytopenia and anemia than imatinib, a higher frequency of grade 1/2 pleural effusion, and a similar bleeding rate, but lower frequencies of most other nonhematologic adverse events. Nilotinib was associated with a lower rate of grade 3/4 neutropenia; higher rates of grade 3/4 abnormalities in bilirubin, ALT, glucose, and lipase levels; and higher rates of mostly grade 1/2 rash, headache, pruritus, and alopecia compared

with imatinib,² whereas imatinib was associated with higher rates of mostly grade 1/2 nausea, diarrhea, vomiting, muscle spasm, and edema.

Convenience

Convenience could also play a role in treatment decisions. Imatinib and dasatinib are given once daily, and nilotinib is given twice daily. As noted, food has a significant effect in increasing nilotinib blood levels, posing increased risk of toxicity, and thus needs to be avoided 2 hours prior to and 1 hour after each dose.

Closing remarks

It is amazing to witness the recent advances in the management of what was once a uniformly fatal disease. Another second-generation tyrosine kinase inhibitor, bosutinib,²⁰ has also recently shown promise for use in first-line treatment of chronic-phase CML, and other inhibitors are in development.

The treating physician, however, must remain vigilant to the fact that a few patients who fail to respond to tyrosine kinase inhibitor therapy will need to be evaluated for possible transplantation. It is critical that we identify those patients who have resistant disease early in their clinical course so that the search for a suitable donor can be initiated.

Another caveat is that physicians need to be aware of appropriate management of patients with cardiac disease who are candidates for or are receiving kinase inhibitor therapy. As noted above, all three agents have the potential to exacerbate preexisting heart failure.

References

1. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2010;362:2260–2270.
2. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010;362:2251–2259.
3. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low

dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994–1004.

4. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355:2408–2417.

5. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs. STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib [abstract]. *Blood* 2009;114:1126.

6. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol* 2008;26:3358–3363.

7. Cortes J, Kantarjian H, Goldberg S, et al. High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: high rates of rapid cytogenetic and molecular responses. *J Clin Oncol* 2009;27:4754–4759.

8. Cortes JE, Baccarani M, Guilhot F, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. *J Clin Oncol* 2010;28:424–430.

9. Hehlmann R, Jung-Munkwitz S, Lauseker M, et al. Randomized comparison of imatinib 800 mg vs imatinib 400 mg +/- IFN in newly diagnosed BCR/ABL positive chronic phase CML: analysis of molecular remission at 12 months [abstract]. *Blood* 2009;114:339.

10. Mahon F-X, Réa D, Guilhot F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol* 2010;11:1029–1035.

11. Weisberg E, Manley PW, Breitenstein W. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. *Cancer Cell* 2005;7:129–141.

12. Lombardo LJ, Lee FY, Chen P, et al. Discovery of *N*-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem* 2004;47:6658–6661.

13. Roy L, Guilhot J, Krahnke T, et al. Survival advantage from imatinib compared with the combination interferon-alpha plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials. *Blood* 2006;108:1478–1484.

14. Quintás-Cardama A, Kantarjian H, Jones D, et al. Delayed achievement of cytogenetic and molecular response is associated with

increased risk of progression among patients with chronic myeloid leukemia in early chronic phase receiving high-dose or standard-dose imatinib therapy. *Blood* 2009;113:6315–6321.

15. Cervantes F, Baccarani M, Lipton J, et al. Dasatinib long-term efficacy in patients with chronic myeloid leukemia in chronic phase (CML-CP) with resistance or intolerance to imatinib: a two-year update of the START-C study [abstract]. *Haematologica* 2008;93:372.

16. Kantarjian H, Pasquinin R, Levy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). *Cancer* 2009;115:4136–4147.

17. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance or intolerance. *Blood* 2007;110:3540–3546.

18. Kantarjian H, Giles F, Bhalla K, et al. Update on imatinib-resistant chronic myeloid leukemia patients in chronic phase (CML-CP) on nilotinib therapy at 24 months: clinical response, safety, and long-term outcomes [abstract]. *Blood* 2009;114:1129.

19. Jabbour E, Jones D, Kantarjian HM, et al. Long-term outcome of patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors after imatinib failure is predicted by the in vitro sensitivity of BCR-ABL kinase domain mutations. *Blood* 2009;114:2037–2043.

20. Jabbour E, Kantarjian H, Cortes J. Chronic myeloid leukemia and second-generation tyrosine kinase inhibitors: when, how, and which one? *Semin Hematol* 2010;47:344–353.

21. Müller MC, Cortes JE, Kim D-W, et al. Dasatinib treatment of chronic phase chronic myeloid leukemia: analysis of responses according to pre-existing BCR-ABL mutations. *Blood* 2009;114:6914–6915.

22. Jabbour E, Kantarjian H, O'Brien S, et al. Predictive factors for response and outcome in patients (pts) treated with second-generation tyrosine kinase inhibitors (2-TKI) for chronic myeloid leukemia in chronic phase (CML-CP) post imatinib failure [abstract]. *Blood* 2009;114:210.

23. Tasigna [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2010.

24. Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Co.; 2010.

25. Gleevec [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2003.

ABOUT THE AUTHOR

Affiliation: Dr. DiBella is Co-Chair of the Hematology Research Committee of US Oncology and past President of Rocky Mountain Cancer Centers, Aurora, CO.

Conflicts of interest: The author has no conflicts of interest to disclose.

Ixabepilone in advanced breast cancer: clinical, treatment, and cost-related studies

Adam Brufsky, MD, PhD

Women's Cancer Center, Magee-Womens Hospital, Pittsburgh, PA

This review provides a rationale for integrating the epothilone ixabepilone into clinical practice, taking into account cost considerations. Clinical data show that both single-agent ixabepilone and combination therapy with capecitabine are active across the spectrum of metastatic breast cancer (MBC). Adding ixabepilone to capecitabine improves progression-free survival in patients pretreated with anthracyclines and taxanes, with toxicity that is manageable through dose reduction or delay. Cost-effectiveness and budget impact analyses indicate that although ixabepilone is only marginally cost-effective in its initial late-line indications, providing ixabepilone in its approved indications may have minimal impact on health plan budgets. Ixabepilone is an important but costly agent for patients with MBC whose disease progresses after other therapies. When the drug is used in-label, the impact to health plans should be reasonable. It remains to be seen whether new data in earlier lines of therapy will positively impact the cost-effectiveness of this agent.

Breast cancer (BC) is the most commonly diagnosed malignancy and the second leading cause of cancer death among women in the United States. It was diagnosed in an estimated 192,370 women in 2009, representing 26% of all cancer diagnoses in this population, and was responsible for an estimated 40,170 deaths or 15% of all cancer deaths in women.¹ The overall economic burden of BC in the United States was estimated to be \$15–\$20 billion in 2001.²

Patients with metastatic BC (MBC) are often treated with cytotoxic agents such as anthracyclines, eg, doxorubicin, epirubicin; taxanes, eg, paclitaxel, docetaxel (Taxotere); or newer agents, eg, capecitabine (Xeloda), gemcitabine (Gemzar), either alone or in combination, to reduce symptoms, improve quality of life, and extend survival.³ Unfortunately, most patients will ultimately develop resistance to anthracyclines or taxanes over time, heralded by disease progression while still receiving treatment or by recurrence shortly after stopping treatment.⁴ Many women will have already received one or both of these agents during adjuvant therapy, and as a result, some will already be resistant to these drugs once advanced disease develops. Moreover, response rates to these agents progressively decline with each subsequent line of therapy.

A critical goal in cancer research is the development of drugs that can circumvent or overcome

tumor survival mechanisms that render once-effective drugs useless in individual patients. The epothilones are a relatively new class of anticancer drugs that may offer significant clinical benefits over established core drugs for BC, particularly in terms of tumor resistance.^{5–7}

The first available member of the epothilone class, ixabepilone (Ixempra), is listed as an active option for MBC in the current National Comprehensive Cancer Network (NCCN) guidelines.³ Since the US Food and Drug Administration (FDA) approval of ixabepilone as monotherapy and with capecitabine in 2007, newer data have emerged regarding its effect on progression-free and overall survival (PFS and OS, respectively), efficacy in combination with targeted agents, cost-effectiveness, effect on quality of life, and selection of patients most likely to benefit from treatment.

Epothilones as anticancer agents

Like the taxanes, epothilones stabilize microtubule structures to block cellular entrance into mitosis to undergo cell division, ultimately leading to cell death or apoptosis.⁸ Although both taxanes and

Manuscript received July 29, 2010; accepted November 30, 2010.

Correspondence to: Adam Brufsky, MD, PhD, UPMC Magee-Womens Cancer Program, 300 Halket Street, Suite 4628, Pittsburgh, PA 15213; telephone: 412-641-4530; fax: 412-641-1085; e-mail: brufskyam@upmc.edu.

Commun Oncol 2011;8:73–80 © 2011 Elsevier Inc. All rights reserved.

epothilones stabilize microtubules by interacting with β -tubulin, the major component of microtubules, epothilones appear to bind to β -tubulin in a distinct manner, which may help to explain their anticancer profile.⁹

A key feature of the epothilones is their low susceptibility to tumor resistance and survival mechanisms.⁵ Ixabepilone has been shown to maintain efficacy in tumors that overexpress β -tubulin isoforms to which taxanes cannot bind, notably β III-tubulin.¹⁰ Tumors may upregulate expression of this tubulin isoform in response to taxane treatment, which decreases the ability of these agents to promote cell death. Tumors with high levels of β III-tubulin exhibit a response to ixabepilone^{11,12} but respond poorly to taxanes and vinca alkaloids.^{13,14}

In some cases, tumor cells may become resistant to a variety of chemically unrelated classes of cytotoxic chemotherapeutic agents through upregulation of P-glycoprotein, a transport protein that spans the cell membrane and actively pumps cytotoxic drugs out of the cell interior.^{15,16} Tumor cells may respond to anticancer drugs with enhanced cell-surface expression of P-glycoprotein and other drug efflux pump proteins. Upregulation of drug efflux pumps may blunt the effects of taxanes, anthracyclines, vinca alkaloids, and multiple other classes of agents used in BC, so tumor cells exposed to one class may exhibit resistance to a drug in a different class despite not having been previously exposed to the drug. Epothilones have much lower susceptibility to drug efflux mediated by P-glycoprotein or other drug efflux pumps, giving these agents sustained activity in tumors where other more susceptible agents have failed.^{10,17,18}

Ixabepilone: the first epothilone approved for advanced BC

In the United States, ixabepilone is currently indicated for the treatment of MBC or locally advanced BC (LABC)

in combination with capecitabine after failure of an anthracycline and a taxane and as monotherapy in triple-refractory BC after failure of an anthracycline, a taxane, and capecitabine.¹⁹ The objective of this article is to provide a rationale for integrating this drug into clinical practice and to discuss the feasibility thereof from a payer perspective. Current clinical data will be utilized to describe the clinical benefits of ixabepilone and identify which BC patients are most likely to benefit. In addition, cost considerations of ixabepilone are discussed and compared with those for other agents used in advanced BC.

Materials and methods

PubMed and the Proceedings of the American Society of Clinical Oncology (ASCO) were searched for phase II or III clinical data on ixabepilone in BC published between January 2001 and February 2010. "Ixabepilone" or "BMS-247550" and "breast" were used as search terms, yielding 114 publications and 27 ASCO abstracts. Phase II and phase III clinical studies of ixabepilone in BC were selected for inclusion in this review via a manual search. In addition, any correlative studies that were deemed relevant to a managed-care audience were retained for inclusion. To ensure inclusion of only the most current data in this review, ASCO abstracts were excluded if they corresponded to a subsequent full-length published article. Phase I studies, preclinical data, editorials, and reviews were excluded. In total, 12 articles and nine abstracts were retained, including clinical trial reports; studies of cost-effectiveness, quality of life, or biomarkers; and analyses of efficacy in subgroups.

During the writing of this review article, ad hoc searches (eg, a PubMed search for studies or reviews related to cost-effectiveness of other agents in the setting of advanced BC; a search of www.clinicaltrials.gov for ongoing clinical studies of ixabepilone) were

conducted and their results incorporated where relevant.

Results

Across the spectrum of BC, six phase II clinical trials have evaluated single-agent ixabepilone. Patients ranged from those receiving neoadjuvant treatment to those whose disease had progressed in the metastatic setting after multiple lines of chemotherapy.²⁰⁻²⁶ In MBC, ixabepilone has also been evaluated in combination with other agents in three phase II trials and two phase III trials.^{25,27-30} Table 1^{14,20-29} delineates the relevant studies identified from the search.

Single-agent ixabepilone after failure of an anthracycline, a taxane, and capecitabine

In one phase II study, single-agent ixabepilone therapy demonstrated efficacy in 126 patients with MBC resistant to anthracyclines, a taxane, and capecitabine.²³ These patients received ixabepilone 40 mg/m² administered via IV infusion over 3 hours on day 1 of a 21-day cycle (now the FDA-approved dose and schedule). Ixabepilone provided a clinical benefit in 70 of 126 patients (62%), according to treatment responses as assessed by an independent radiology facility. The median time to response was 6.1 weeks, and the median duration of response was 5.7 months. The median PFS was 3.1 months, and the median OS was 8.6 months. It is worth noting the poor prognosis of most of the patients in this study: 88% had received two or more lines of chemotherapy prior to enrollment and 48% had received three or more. Further, 93% were human epidermal growth factor receptor 2 (HER2)-negative, and 77% had visceral disease.

Single-agent ixabepilone in anthracycline- and/or taxane-pretreated/resistant patients

Four other phase II studies evaluated ixabepilone monotherapy in pa-

TABLE 1

Phase II and phase III clinical trials of ixabepilone

Study	Phase (n)	Dosage ^a	Monotherapy or combination therapy	Setting, line of therapy	Prior chemotherapy	Response duration, mo	PFS (OS), ^b mo	Adverse events ≥ 10%
Baselga et al, 2009 ¹⁴	II (161)	40 mg/m ² q3w	Monotherapy	Neoadjuvant ^c	None	–	–	Neutropenia, leukopenia
Roché et al, 2007 ²¹	II (65)	40 mg/m ² q3w	Monotherapy	MBC, 1 st	Anthracyclines (100%) ± taxanes (17%) ^d	8.2	4.8 ^e (22.0)	Neutropenia, sensory neuropathy, leukopenia
Moulder et al, 2010 ²⁵	II (59)	15 mg/m ² qw	With weekly trastuzumab (4 mg/kg LD then 2 mg/kg) and carboplatin (AUC 2)	MBC, 1 st	Anthracyclines (59%) ± taxanes (31%) ^d	7.8	8.2 ^e (34.7)	Neutropenia, thrombocytopenia, fatigue
Rugo et al, 2009 ²⁶	II	40 mg/m ² q3w (ixa 40) vs 16 mg/m ² qw (ixa 16) vs paclitaxel 90 mg/m ² (pac)	With bevacizumab (10 mg/kg q2w or 15 mg/kg q3w)	MBC, 1 st	–	24-week PFS: • 75% for ixa 16 • 86% for ixa 40 • 94% for pac		Neutropenia; peripheral neuropathy
Denduluri et al, 2007 ²⁰	II (23)	6 mg/m ² × 5 days q3w	Monotherapy	MBC, 1 st to 3 rd	Anthracyclines ± capecitabine (82%)	5.6	5.5 ^e	Neutropenia, fatigue
Low et al, 2005 ²²	II (37)	6 mg/m ² × 5 days q3w	Monotherapy	MBC, 1 st to ≥ 4 th	Taxanes (100%) ^g	3.9	2.6 ^e	Neutropenia, febrile neutropenia, fatigue, diarrhea
Bunnell et al, 2008 ²⁹	II (72)	40 mg/m ² q3w	With capecitabine 2,000 mg/m ² × 14 days	MBC, 1 st to ≥ 3 rd	Anthracyclines, taxanes (100%)	6.9	3.8	Neutropenia, leukopenia, fatigue, hand-foot syndrome, myalgia, GI symptoms, peripheral neuropathy
Thomas et al, 2007 ²⁷ ; Hortobagyi et al, 2008 ²⁸	III (752)	40 mg/m ² q3w vs capecitabine 2,500 mg/m ² × 14 days (C)	With capecitabine 2,000 mg/m ² × 14 days	MBC, 1 st to 4 th	Anthracyclines, taxanes (100%)	6.4 vs 5.6 for C	5.8 vs 4.2 for C ^h (12.9 vs 11.1 for C)	Neutropenia, leukopenia, sensory neuropathy, hand-foot syndrome
Hortobagyi et al, 2008 ²⁸	III (1,221)	40 mg/m ² q3w vs capecitabine 2,500 mg/m ² × 14 days (C)	With capecitabine 2,000 mg/m ² × 14 days	MBC, 1 st to 4 th	Anthracyclines, taxanes (100%)	–	6.2 vs 4.4 for C (16.4 vs 15.6 for C)	Neutropenia, leukopenia, sensory neuropathy, hand-foot syndrome
Perez et al, 2007 ²³	II (126)	40 mg/m ² q3w	Monotherapy	MBC, 2 nd to 4 th	Anthracyclines, capecitabine, taxanes (100%)	5.7	3.1 (8.6)	Neutropenia, leukopenia, sensory neuropathy, fatigue
Thomas et al, 2007 ²⁴	II (49)	40 mg/m ² q3w	Monotherapy	MBC, 2 nd to ≥ 4 th	Taxanes (100%); trastuzumab (8%)	10.4	2.2 ^e (7.9)	GI symptoms, fatigue, neuropathy, pain

PFS = progression-free survival; OS = overall survival; q3w = every 3 weeks; MBC = metastatic breast cancer; qw = weekly; LD = loading dose; AUC = area under the curve; q2w = every 2 weeks; GI = gastrointestinal

^a All doses are intravenous except for capecitabine (oral).

^b Investigator-assessed, unless stated otherwise

^c Eighteen percent of patients receiving neoadjuvant ixabepilone had a pathologic complete response (pCR); 29% of estrogen receptor-negative patients had a pCR.

^d As adjuvant therapy in all cases

^e Measured as time to disease progression

^f Interim results

^g All patients (n = 37) had received at least two cycles of a taxane-containing regimen as neoadjuvant, adjuvant, or metastatic therapy.

^h Independent radiology facility assessed

ⁱ A total of 113 patients were assessable.

tients with MBC or LABC. Overall response rates (ORR) ranged from 57% in taxane-naïve patients to 12% in heavily pretreated anthracycline/

taxane-resistant patients. Two of these studies used the standard ixabepilone administration schedule (40 mg/m² via a 3-hour infusion on day

1 every 3 weeks),^{21,24} whereas the remaining two studies used a lower dose administered more frequently (6 mg/m²/day via 1-hour IV infusion on

days 1–5 every 3 weeks).^{20,22}

The largest of these phase II studies, which utilized the standard administration schedule, was conducted in 65 anthracycline-pretreated patients, 77% of whom had baseline visceral disease (liver or lung) and 43% of whom had at least three target lesions. Even in women with such significant baseline disease, the trial reported an ORR of 41.5% and a median duration of response of 8.2 months.²¹ Six of the 27 patients who responded to ixabepilone retained clinical benefit for 12 months or longer. The median PFS was 4.8 months, and the median OS was 22 months.²¹ A second study used the same dose and schedule in taxane-resistant patients ($n = 49$), producing an ORR in six patients (12%), with a median response duration of 10.4 months.²⁴ An additional 20 patients (41%) achieved stable disease. Median PFS was 2.2 months, and median OS was 7.9 months.²⁴

In the two other phase II trials in MBC, ixabepilone was administered more frequently at a lower dose (6 mg/m²/day on days 1–5 of a 30-day cycle).^{20,22} In taxane-naïve patients with MBC ($n = 23$), this regimen produced a partial response in 13 patients; the ORR was 57%, lasting a median of 5.6 months.²⁰ Median PFS was 5.5 months.²⁰ In the other study of taxane-pretreated women,²² one patient had a complete response (CR) and seven others had a partial response to ixabepilone therapy, for an ORR of 22%. An additional 13 patients (35%) achieved stable disease that lasted for at least 6 weeks. Median PFS was 2.6 months.²²

Ixabepilone plus capecitabine after failure of an anthracycline and a taxane

The benefits of adding ixabepilone to capecitabine were demonstrated in a randomized phase III study of 752 patients with MBC that was resistant to anthracyclines and taxanes.²⁷ Patients received 21-day cycles of every-3-week ixabepilone (40 mg/m²)

in combination with oral capecitabine (2,000 mg/m²) administered in two divided doses on days 1–14 or single-agent capecitabine (2,500 mg/m²) administered on the same schedule. In general, patients in both arms had a heavy disease burden: 90% of patients had metastases at two or more sites, and 84% had visceral disease involving the liver and/or lungs. Patients were also heavily pretreated before entering the study, with 44% having received at least two lines of chemotherapy for MBC. A quarter of patients had triple-negative disease (ie, tumors negative for estrogen receptor [ER], progesterone receptor, and HER2) and 15% had tumors that overexpressed HER2. Both of these phenotypes are also associated with compromised outcomes.²⁷

A blinded independent radiology review panel found that ixabepilone plus capecitabine significantly prolonged PFS, the primary endpoint of the study, over capecitabine alone (5.8 vs 4.2 months; hazard ratio [HR] = 0.69; 95% confidence interval [CI] = 0.58–0.83; $P < 0.001$).³¹ Combination therapy reduced the risk of disease progression by 31% relative to capecitabine alone,³² and predefined subset analyses confirmed that this clinical benefit was consistently maintained across subgroups with a particularly poor prognosis: those with visceral metastases; more than two metastatic sites; age ≥ 65 years; or triple-negative tumors (Figure 1).²⁷

ORR was a secondary endpoint, and combination therapy produced a higher ORR than did capecitabine alone (35% vs 14%; $P < 0.001$).²⁷ Although the median OS did not differ between treatment groups, adjustment for selected prognostic factors (performance status, number of organ sites, visceral disease, and ER status) in a predefined Cox regression statistical analysis found that combination therapy produced a nonsignificant 13% reduction in the risk of death ($P = 0.080$).²⁸ This phase III study was

the first to demonstrate that adding a second agent to capecitabine in MBC that had progressed after anthracyclines and taxanes can improve PFS and ORR.

A subsequent confirmatory phase III randomized study of ixabepilone plus capecitabine in patients who were pretreated with or resistant to anthracyclines or taxanes supported the results of the pivotal phase III trial.²⁸ Prospective subset analyses using pooled data from these two trials showed a statistically significant improvement in PFS when ixabepilone was added to capecitabine for first-line treatment (5.6 vs 2.8 months; HR = 0.58 [95% CI = 0.45–0.76]) and also in patients with triple-negative disease (4.2 vs 1.7 months; HR = 0.63 [95% CI = 0.52–0.77]).^{33,34} Like the pivotal study, the confirmatory study showed no significant difference in median OS between combination therapy with ixabepilone and capecitabine and single-agent capecitabine. However, adjusting for the same prognostic factors utilized in Cox analysis from the pivotal phase III trial, combination therapy significantly reduced the risk of death by 15% ($P = 0.023$).²⁸

Ixabepilone in earlier lines of therapy

Ixabepilone (40 mg/m² every 3 weeks) has also been evaluated in the neoadjuvant setting, where it demonstrated a pathologic complete response (pCR) of 18% in the breast in 161 chemotherapy-naïve women.¹⁴ Among those with ER-negative disease, the pCR jumped to 29%. In fact, ER expression was inversely related to pCR to ixabepilone therapy. All grade 3/4 adverse events (AEs) occurred at rates at or below 3%, except for neutropenia (10%) and leukopenia (7%).¹⁴

Several regimens of ixabepilone plus targeted agents have undergone phase II evaluation in first-line treatment of MBC.²⁵ In one study in HER2-positive women, ixabepilone was administered at a dose of 15 mg/m² and car-

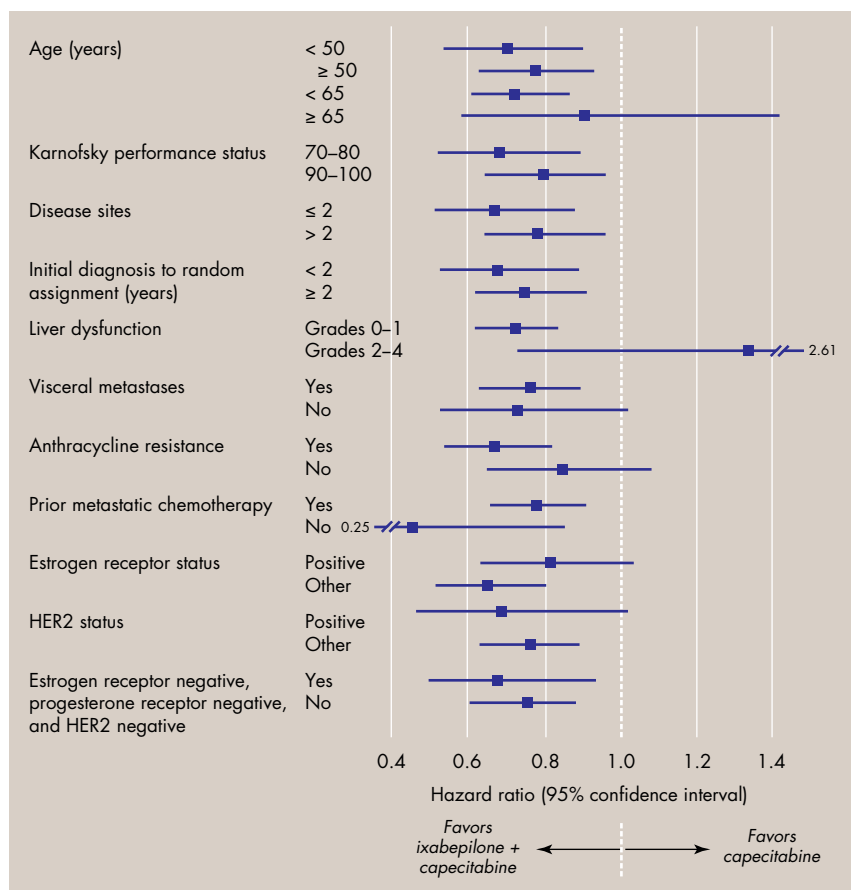


FIGURE 1 Improvement in progression-free survival with ixabepilone plus capecitabine versus capecitabine alone in patients with advanced breast cancer resistant to an anthracycline and a taxane. Shown are hazard ratios (crossbars) with 95% confidence intervals (length of bar) for progression-free survival in various predefined subgroups. Hazard ratios that are less than 1.0 (ie, those that fall to the left of the dashed line) favor combination therapy with ixabepilone and capecitabine over single-agent capecitabine. HER2 = human epidermal growth factor receptor 2. Adapted from Thomas et al.²⁷

toplatin at an area under the curve (AUC) of 2, each on days 1, 8, and 15 of a 4-week cycle for a maximum of six cycles, whereas trastuzumab (Herceptin) was administered at a loading dose of 4 mg/kg, then weekly at 2 mg/kg during chemotherapy, and finally at 6 mg/kg until disease progression. Objective responses were seen in 26 of 59 evaluable patients (44%), including four CRs. An additional nine patients (15%) achieved stable disease for > 6 months. Median time to disease progression was 8.2 months (95% CI = 6.3–9.9) and median OS was 34.7 months (95% CI = 25.7 to [not reached]). Grade 3/4 neutropenia was the most common severe toxicity, oc-

curing in 49% of patients. Among nonhematologic AEs, grade 3 fatigue occurred in 12% of patients and grade 3 neuropathy, in 7%.²⁵

An ongoing trial is comparing ixabepilone plus trastuzumab versus docetaxel plus trastuzumab in first-line treatment of metastatic or locally advanced HER2-positive BC.³⁵ In HER2-negative patients, two doses and schedules of ixabepilone plus bevacizumab (Avastin; arm A: ixabepilone 16 mg/m² weekly for 3 of 4 weeks, with bevacizumab 10 mg/kg every 2 weeks; arm B: ixabepilone 40 mg/m² with bevacizumab 15 mg/kg, both every 3 weeks) were compared with standard weekly paclitaxel (90

mg/m²) plus bevacizumab (10 mg/kg every 2 weeks; arm C).²⁶ A 24-week follow-up revealed comparable ORRs (50% [34.9–65.1], 71% [55.7–83.6], and 56% [37.7–73.6] in arms A, B, and C, respectively) and PFS rates (75% [62.4–87.9], 86% [75.7–96.4], and 94% [85.4–100] in arms A, B, and C, respectively). AEs were also comparable, with the exception of neutropenia, which occurred more often in arm B (55%) than in arm A (11%) or C (22%). Rates of neuropathy were around 20%, and rates of febrile neutropenia were 2% or less, for all arms.

Ixabepilone tolerability

AEs with ixabepilone are significant, as to be expected from cytotoxic chemotherapy. However, clinical study has confirmed that these AEs are predictable, reversible, and manageable through dose reduction or delay, whether the drug is administered in combination with capecitabine or as single-agent therapy.

In the clinical studies with single-agent ixabepilone, the most common nonhematologic AEs were peripheral neuropathy, fatigue/weakness, muscle/joint pain, alopecia, and nausea.¹⁹ It is also important to note that AEs associated with ixabepilone typically occur less frequently in patients who are not heavily pretreated with other BC therapies.^{20–24,27}

In the phase III study of combination ixabepilone plus capecitabine therapy, the most common nonhematologic toxicities were peripheral neuropathy, hand-foot syndrome (pain, swelling, numbness, tingling, or redness of the hands or feet), fatigue/weakness, nausea, and diarrhea.^{19,27} Ixabepilone-capecitabine combination therapy did result in greater toxicity than was observed with single-agent ixabepilone or single-agent capecitabine,^{23,27} but the toxicities observed with ixabepilone did not overlap with those associated with capecitabine.²⁷

The peripheral neuropathy described with ixabepilone is common-

ly sensory rather than motor, resolving within a median time of 5 weeks (monotherapy) or 6.0 to 6.2 weeks (in combination with capecitabine) following dose reduction or discontinuation of ixabepilone.³² In the pivotal phase III study, 80% of patients who received ixabepilone had improvement or stabilization in their peripheral neuropathy following dose reduction,¹⁹ indicating that many patients with peripheral neuropathy are able to continue therapy after dose reduction. In the event of grade 2 neuropathy lasting ≥ 7 days or any grade 3 neuropathy, the dose of ixabepilone used in the next cycle should be lowered by 20% (to 32 mg/m²) and, if it recurs, by an additional 20% (to 25 mg/m²). Peripheral neuropathy should be allowed to resolve to at least grade 1 before initiation of the following cycle.¹⁹ Ixabepilone should be discontinued in any patient with grade 3 neuropathy that is disabling or lasts ≥ 7 days.¹⁹ In those with grade 3/4 neuropathy, 76% had documented improvement to baseline or grade 1 by 12 weeks after stopping treatment.¹⁹ Notably, reducing the dose of ixabepilone is also a recommended management strategy for other grade 3 nonhematologic AEs, as is discontinuation for any grade 4 nonhematologic toxicities.¹⁹

The most significant hematologic toxicity with ixabepilone was the dose-dependent, grade 3/4 neutropenia that occurred in 54% and 68% of patients who received single-agent ixabepilone or ixabepilone plus capecitabine, respectively.^{23,27} The incidence of febrile neutropenia was low (3% and 4%, respectively). Hematologic toxicity was also found to be responsive to 20% dose reduction in the next cycle.¹⁹ Blood cell support, in the form of growth factors, may be used at the discretion of the oncologist.

In clinical trials, the rates of febrile neutropenia and infection-related deaths were increased in patients treated with ixabepilone who had preexisting liver impairment. There-

fore, treatment should be given with extreme caution or avoided in patients with extensive baseline liver dysfunction and/or a history of liver insufficiency. Specifically, combination ixabepilone plus capecitabine therapy is contraindicated in patients with abnormally high liver enzymes at baseline (AST or ALT $> 2.5 \times$ ULN or bilirubin level $> 1 \times$ ULN), whereas the starting dose of single-agent ixabepilone should be reduced in some patients with mild baseline liver impairment (AST or ALT $\leq 10 \times$ ULN and bilirubin level $\leq 1.5 \times$ ULN) and in all patients with moderate baseline impairment (AST and ALT $\leq 10 \times$ ULN and bilirubin level $> 1.5 \times$ ULN to $\leq 3 \times$ ULN). Patients with severe baseline liver impairment (AST or ALT $> 10 \times$ ULN or bilirubin level > 3) should not receive ixabepilone.¹⁹

Selecting patients most likely to benefit from ixabepilone

Appropriate selection of patients most likely to benefit from ixabepilone, with or without capecitabine, will help to ensure the most rational and cost-effective integration of this therapy into current clinical practice. Based on the clinical trials described here, patients with MBC or LABC who have disease progression after receiving an anthracycline and a taxane, whether administered in the adjuvant or metastatic setting, are candidates for ixabepilone plus capecitabine. Patients whose disease has progressed after previous capecitabine may be candidates for single-agent ixabepilone (Table 2).¹⁹

Patient selection should be guided by safety considerations, including whether there is preexisting liver impairment or peripheral neuropathy. Liver function tests should be evaluated prior to treatment initiation to ensure that liver function is adequate and to reduce the risk of severe AEs such as febrile neutropenia. Patients with diabetes may be at increased risk of severe neuropathy¹⁹; therefore, caution should be exer-

cised when using ixabepilone in diabetic patients. The presence of grade 1 neuropathy or previous treatment with neurotoxic chemotherapy does not appear to predict development or worsening of neuropathy. However, patients with preexisting moderate to severe neuropathy (grade 2 or worse) were excluded from clinical trials with ixabepilone, and therefore caution is needed if such patients are treated.

Cost of ixabepilone

The wholesale average cost (WAC) of ixabepilone was \$921.96 for the 15-mg kit and \$2,765.89 for the 45-mg kit as of February 2010 (pricing has not changed since launch in October 2007). For most women, the body surface area is 1.6–1.7 m², and consequently 64–68 mg of drug would be required. The WAC for doses up to 75 mg (one 45-mg kit plus two 15-mg kits) would be \$4,609.81. Based on an average of four cycles of monotherapy or five cycles of combination treatment, the total cost of ixabepilone therapy would range from \$20,000 to \$25,000 for an average patient.³⁶

A cost-effectiveness analysis of medical resource and health utility data collected prospectively during the pivotal phase III study of ixabepilone plus capecitabine indicated that quality-adjusted survival associated with this regimen is modest in relation to the additional costs of therapy that are incurred.³⁷ Despite its expense, a 2009 budget impact analysis suggested that the effect of adding ixabepilone to a million-member health plan would be minimal, assuming that the only patients who received ixabepilone would be those eligible for in-label treatment.³⁸

Discussion

Ixabepilone is the first member of the epothilone class to be approved for use in BC patients, and substantial clinical data support the use of ixabepilone in late-line MBC therapy as a

TABLE 2

Suitability of patients with advanced breast cancer for ixabepilone therapy

Patient type	Ixabepilone plus capecitabine	Single-agent ixabepilone
Patient with disease progression after previous treatment with an anthracycline and a taxane	Yes (preferred)	Yes
Patient with disease progression after previous treatment with an anthracycline, a taxane, and capecitabine	No	Yes
Patient with preexisting liver impairment ^a	Contraindicated	Dose reduction
Patient with neutrophil count < 1,500 cells/mm ³ or platelet count < 100,000 cells/mm ³	Contraindicated until blood counts increase	Contraindicated until blood counts increase
Patient with diabetes or preexisting peripheral neuropathy ^b	Allowed; caution recommended	Allowed; caution recommended
Patient with a history of cardiac disease	Allowed; caution recommended	Allowed; caution recommended
Patient receiving concomitant strong CYP3A4 inhibitors ^c	Concomitant drug should be withdrawn, if feasible; otherwise, dose reduction	

^aLiver transaminase level > 2.5 × upper limit of normal (ULN) or bilirubin level > 1 × ULN

^bPatients with grade 2 or worse neuropathy were excluded from clinical trials.

^cExamples include azole antifungal agents (eg, ketoconazole, itraconazole, voriconazole), some antibiotics (eg, clarithromycin, telithromycin), anti-HIV agents (eg, atazanavir, saquinavir, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine), and grapefruit juice

Source: Ixempra package insert¹⁹

single agent or with capecitabine. The value of ixabepilone derives from its low susceptibility to resistance mechanisms that affect core chemotherapeutic drugs used in BC, including anthracyclines and taxanes. Ixabepilone can be used in patients who are already refractory to these agents, thereby providing these patients, who have few options, with an effective treatment. In its approved indications, ixabepilone has demonstrated clinical benefit in all subgroups tested; in subgroups of patients with characteristics of a poor prognosis, the efficacy of ixabepilone is at least maintained and in some cases augmented (eg, triple-negative BC). This trend holds true when ixabepilone is added to capecitabine or when it is used as monotherapy, although monotherapy data are more limited.

This clinical benefit in late-line MBC comes at the expense of cost-effectiveness, with a drug price and an incremental cost-effectiveness ratio (as combination therapy, compared with capecitabine alone) that are higher than those for agents that have been indicated for the treatment of MBC for a longer time. Ixabepilone's modest cost-effectiveness is tempered by the understanding that substantial gains in health benefit are more diffi-

cult to achieve with late-line therapies for advanced metastatic disease than with earlier lines of therapy. The patients studied in the registration trials for ixabepilone monotherapy and with capecitabine were heavily pretreated, had a substantial tumor burden, and had few remaining treatment options.

It is worth considering the prevailing pattern in the life cycles of oncology products: costly therapies are initially approved as palliative care to extend life expectancy, sometimes by no more than several months. The difficulties inherent in developing novel agents that significantly extend survival in patients with considerable tumor burden who have already been heavily pretreated with current standard-of-care therapies represent an enormous challenge and clearly impact cost-effectiveness analyses. Further research may aid in the identification of certain patient subgroups that might derive greater benefit from this therapy. For example, pooled analysis of patients enrolled in the phase III ixabepilone clinical trials indicated that in symptomatic patients with a Karnofsky performance status of 70–80, addition of ixabepilone to capecitabine significantly increased OS by approximately 3 months com-

pared with capecitabine alone (12.3 vs 9.5 months; $P = 0.0015$).³⁹

Furthermore, it is likely that future study will further characterize the utilization of ixabepilone in combination with targeted therapies or other cytotoxic agents earlier during the course of treatment (eg, in the neoadjuvant, adjuvant, and first-line MBC settings) and in place of taxanes in new regimens. Reassessment of the cost-effectiveness of ixabepilone at each line of therapy will be useful as data from these studies mature, as greater cost-effectiveness and clinical benefit may be realized from the use of this agent in earlier-stage settings.

References

1. Horner MJ, Ries LAG, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975–2006, National Cancer Institute. http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009. Accessed December 27, 2010.
2. Radice D, Redaelli A. Breast cancer management: quality-of-life and cost considerations. *Pharmacoeconomics* 2003;21:383–396.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Breast cancer. V2.2008. <http://www.nccn.org>. Accessed August 20, 2008.
4. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Adv Exp Med Biol* 2007;608:1–22.

5. Goodin S, Kane MP, Rubin EH. Epothilones: mechanism of action and biologic activity. *J Clin Oncol* 2004;22:2015–2025.
6. Goodin S. Novel cytotoxic agents: epothilones. *Am J Health-Syst Pharm* 2008;65(suppl 3):S10–S15.
7. Vahdat L. Ixabepilone: a novel antineoplastic agent with low susceptibility to multiple tumor resistance mechanisms. *Oncologist* 2008;13:214–221.
8. Bollag DM, McQueney PA, Zhu J, et al. Epothilones, a new class of microtubule-stabilizing agents with a Taxol-like mechanism of action. *Cancer Res* 1995;55:2325–2333.
9. Bode CJ, Gupta ML Jr, Reiff EA, Suprenant KA, Georg GI, Himes RH. Epothilone and paclitaxel: unexpected differences in promoting the assembly and stabilization of yeast microtubules. *Biochemistry* 2002;41:3870–3874.
10. Lee FY, Smykla R, Johnston K, et al. Preclinical efficacy spectrum and pharmacokinetics of ixabepilone. *Cancer Chemother Pharmacol* 2009;63:201–212.
11. Sève P, Isaac S, Trédan O, et al. Expression of class III β -tubulin is predictive of patient outcome in patients with non-small cell lung cancer receiving vinorelbine-based therapy. *Clin Cancer Res* 2005;11:5481–5486.
12. Horak CE, Lee FY, Xu L, et al. High β III-tubulin expression in triple-negative (TN) breast cancer (BC) subtype and correlation to ixabepilone response: a retrospective analysis. *J Clin Oncol* 2009;27(15S): 3587.
13. Hasegawa S, Miyoshi Y, Egawa C, et al. Prediction of response to docetaxel by quantitative analysis of class I and III β -tubulin isotype mRNA expression in human breast cancers. *Clin Cancer Res* 2003;9:2992–2997.
14. Baselga J, Zambetti M, Llombart-Cusac A, et al. Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer. *J Clin Oncol* 2009;27:526–534.
15. Fojo T, Menefee M. Mechanisms of multidrug resistance: the potential role of microtubule-stabilizing agents. *Ann Oncol* 2007;18(suppl 5):v3–v8.
16. Kuo MT. Roles of multidrug resistance genes in breast cancer chemoresistance. *Adv Exp Med Biol* 2007;608:23–30.
17. Lee FYF, Borzilleri R, Fairchild CR, et al. BMS-247550: a novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. *Clin Cancer Res* 2001;7:1429–1437.
18. Kowalski RJ, Giannakakou P, Hamel E. Activities of the microtubule-stabilizing agents epothilones A and B with purified tubulin and in cells resistant to paclitaxel (Taxol). *J Biol Chem* 1997;272:2534–2541.
19. Ixempra Kit (ixabepilone) for Injection [package insert]. Princeton, NJ: Bristol-Myers Squibb; January 2010. http://packageinserts.bms.com/pi/pi_ixempra.pdf. Accessed December 27, 2010.
20. Denduluri N, Low JA, Lee JJ, et al. Phase II trial of ixabepilone, an epothilone B analog, in patients with metastatic breast cancer previously untreated with taxanes. *J Clin Oncol* 2007;25:3421–3427.
21. Roché H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol* 2007;25:3415–3420.
22. Low JA, Wedam SB, Lee JJ, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. *J Clin Oncol* 2005;23:2726–2734.
23. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2007;25:3407–3414.
24. Thomas ES, Taberner J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol* 2007;25:3399–3406.
25. Moulder SL, Wang M, Gradishar W, et al. A phase II trial of trastuzumab, weekly ixabepilone and carboplatin in patients with HER2-positive metastatic breast cancer: an Eastern Cooperative Oncology Group trial. *Breast Cancer Res Treat* 2010;119:663–671.
26. Rugo HS, Campone M, Amadori D, et al. Randomized phase II study of weekly versus every-3-week ixabepilone plus bevacizumab (IXA/BEV) versus paclitaxel plus bevacizumab (PAC/BEV) as first-line therapy for metastatic breast cancer (MBC). *J Clin Oncol* 2009;27(15S):1029.
27. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007;25:5210–5217.
28. Hortobagyi GN, Perez E, Vrdoljak E, et al. Analysis of overall survival (OS) among patients (pts) with metastatic breast cancer (MBC) receiving either ixabepilone (I) plus capecitabine (C) or C alone: results from two randomized phase III trials. Proceedings of the 2008 San Antonio Breast Cancer Symposium 2008:178. Abstract 186.
29. Bunnell C, Vahdat L, Schwartzberg L, et al. Phase I/II study of ixabepilone plus capecitabine in anthracycline-pretreated/resistant and taxane-resistant metastatic breast cancer. *Clin Breast Cancer* 2008;8:234–241.
30. Vahdat L, Fein LE, Karwal MW, et al. Ixabepilone plus capecitabine vs capecitabine in patients with metastatic breast cancer receiving ixabepilone in the first line setting: a pooled analysis from two phase III studies. *Cancer Res* 2009;69(suppl 2):394s. Abstract 6117.
31. Dranitsaris G, Cottrell W, Spirovski B, Hopkins S. Economic analysis of albumin-bound paclitaxel for the treatment of metastatic breast cancer. *J Oncol Pharm Pract* 2009;15:67–78.
32. Perez E, Pivot X, Vrdoljak E, et al. A prospective characterization of the resolution of ixabepilone induced peripheral neuropathy: data from a large registration program in patients with metastatic breast cancer. *Cancer Res* 2009;69(suppl 2):401s. Abstract 6140.
33. Rugo HS, Roché H, Thomas E, et al. Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. *Cancer Res* 2009;69(suppl 2):225s. Abstract 3057.
34. Thomas E. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2008;26:2223.
35. Steinbrook R. Saying no isn't NICE—the travails of Britain's National Institute for Health and Clinical Excellence. *N Engl J Med* 2008;359:1977–1981.
36. Ixabepilone (Ixempra) for breast cancer. *Med Lett Drugs Ther* 2008;50:7–8.
37. Reed SD, Li Y, Anstrom KJ, Schulman KA. Cost effectiveness of ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2009;27:2185–2191.
38. Ho J, Zhang L, Todorova L, et al. Budget impact analysis of ixabepilone used according to FDA-approved labeling in treatment-resistant metastatic breast cancer. *J Manag Care Pharm* 2009;15:467–475.
39. Conte P, Roche H, Perez E, et al. Ixabepilone plus capecitabine improves overall survival in symptomatic patients with metastatic breast cancer previously treated with anthracycline and taxane in 2 large phase III studies. *Cancer Res* 2009;69(suppl 2):393s. Abstract 6114.

ABOUT THE AUTHOR

Affiliation: Dr. Brufsky is Medical Director of the Women's Cancer Center at Magee-Womens Hospital, Pittsburgh, PA.

Conflicts of interest: Dr. Brufsky is a member of the speakers' bureau of Bristol-Myers Squibb and receives compensation for these services. He also acknowledges funding from Bristol-Myers Squibb for writing and editing services provided by Rebecca Goldstein, PhD, at StemScientific. Neither Bristol-Myers Squibb nor StemScientific influenced the content of this article, nor did Dr. Brufsky receive financial compensation for authoring it.

Management of capecitabine-related gastrointestinal toxicities in women with breast cancer

Soley Bayraktar, MD,¹ and Stefan Glück, MD²

¹Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, and

²University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Gastrointestinal (GI) adverse events (AEs) are common with capecitabine, although the mechanism is unknown. We present two case studies involving patients with capecitabine GI AEs managed with dose modification. Three principal strategies can be employed to prevent and/or treat GI AEs associated with capecitabine: dose modification and timing, symptomatic treatment, and risk reduction. While dose and schedule modification is employed during the chronic management of capecitabine toxicities, symptomatic treatment of toxicities is critically important for managing acute events. Finally, risk reduction strategies must be taken into consideration but, in practice, are less useful. Dosing regimens utilizing a dose lower than the conventional capecitabine dose have generally shown similar efficacy but reduced toxicity. A variety of symptomatic treatments used with other anticancer drugs can be helpful in patients treated with capecitabine who experience diarrhea, stomatitis, nausea, vomiting, anorexia, or dyspepsia. The risk of GI AEs can be reduced before initiating capecitabine by avoiding potential drug interactions and identifying patients with genetic polymorphisms that may interfere with the metabolic pathway of capecitabine. In addition, reducing folate consumption may be beneficial.

Capecitabine (Xeloda) is an oral pro-drug that is converted through a series of enzymatic steps to 5'-deoxy-5-fluorouridine (5'-DFUR) and finally to the cytotoxic agent 5-fluorouracil (5-FU).¹ Approved for use in metastatic breast cancer patients as monotherapy or in combination,¹ capecitabine is associated with a lower incidence of serious gastrointestinal (GI) adverse events (AEs) compared with 5-FU-based chemotherapy regimens.^{1,2} In stage IV breast cancer clinical trials, the most common grade 3 GI AEs associated with the administration of single-agent capecitabine 1,250 mg/m² twice daily for 2 weeks of an every-3-week cycle were diarrhea (12%), stomatitis (7%), nausea (4%), vomiting (4%), abdominal pain (4%), anorexia (3%), constipation (1%), and dyspepsia (3%).¹ Grade 4 diarrhea was reported in 3% of patients. Diarrhea (with or without abdominal pain) is the most common and dangerous GI AE associated with capecitabine.² Patients age 80 years or older are more likely to experience GI AEs.¹

It is believed that intestinal conversion of capecitabine to 5'-deoxy-5-fluorocytidine (5'-DFCR) is responsible for GI AEs, but the exact mechanism is not yet known.² The incidence of GI AEs appears to be higher in US versus non-US patients,³ although ethnic differences in pharmacokinetics are unlikely

to be the cause.⁴ Serum folate may play a role, as a higher incidence of GI AEs has been observed with higher baseline folate levels.⁵ This may be due to the greater consumption of folate-enriched foods in the United States than in other countries.

Management of GI toxicities

Three strategies can be employed to prevent and/or treat GI AEs associated with capecitabine: dose or schedule modification, symptomatic treatment, and risk reduction (Table 1).

Dose or schedule modification

Early clinical observation suggested that reducing the dose of capecitabine had no adverse impact on efficacy but reduced GI toxicity. The confirmation of this observation in four phase II clinical trials⁶ and one phase III clinical trial⁷ has led to clinical trials investigating dosing strategies other than the conventional 1,250 mg/m² twice daily for

Manuscript received October 19, 2010; accepted January 4, 2011.

Correspondence to: Soley Bayraktar, MD, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030; telephone: 832-350-6654; fax: 713-563-0910; e-mail: sbayraktar@mdanderson.org.

Commun Oncol 2011;8:81-87 © 2011 Elsevier Inc. All rights reserved.

TABLE 1**Strategies to prevent or treat gastrointestinal adverse events associated with capecitabine****Dose or schedule modification**

- 1,000–2,000 mg/m² daily on days 1–14 every 21 days
- Continuous administration
- 28-day cycle
- 5-days-on/2-days-off cycle
- 7-days-on/7-days-off cycle

Symptomatic treatment

- Patient education
- *Diarrhea*: loperamide, hydration, electrolytes, probiotics
- *Stomatitis*: soft toothbrush, flossing, hydration, mouthwash, topical anesthetics; avoidance of spicy/acidic foods, chlorhexidine, sucralfate, and acyclovir
- *Nausea/vomiting*: if needed, metoclopramide or prochlorperazine (with or without lorazepam or an H₂-antagonist or a proton pump inhibitor) or low-dose corticosteroid; oral 5-hydroxytryptamine type 3 antagonist (if persistent)
- *Anorexia*: small, frequent, tasty, spicy meals
- *Dyspepsia*: antacids other than aluminum hydroxide/magnesium hydroxide combinations or an H₂-antagonist other than cimetidine

Risk reduction

- *Drug interactions*: warfarin, phenytoin, leucovorin, interferon-alpha
- *Folate*: reduce consumption of folic acid and foods fortified with folate (flour, rice, pasta, cornmeal, grains)
- *Gene polymorphisms*: dihydropyrimidine dehydrogenase deficiency; possibly thymidylate synthase, methylenetetrahydrofolate reductase

2 weeks followed by a 1-week rest period given as 3-week cycles.

Several of these subsequent clinical trials utilized a 14-days-on/7-days-off cycle with a reduced capecitabine dose. As monotherapy, doses of 2,000 mg/m²/d have demonstrated efficacy comparable to 2,130–2,560 mg/m²/d, with a reduced incidence of diarrhea (6% vs 12%–13%, respectively).^{5,8–11} Another clinical trial, comparing 1,000 mg/m² twice daily with 1,250 mg/m² twice daily, confirmed that the lower dose was active and had a good toxicity profile.¹² Reduced-dose capecitabine in combination with other agents has demonstrated similar results. Capecitabine 825–1,250 mg/m² twice daily in combination with a taxane resulted in response rates, progression-free survival, and tolerability comparable to the combination of a taxane plus epirubicin.^{13–15}

Various other dosing regimens have been investigated, including

a 28-day cycle,^{16–18} a 5-days-on/2-days-off cycle,^{19–22} and a 7-days-on/7-days-off cycle.²³ The general finding of these trials was that toxicity, including GI, is decreased. For example, compared with standard-dose capecitabine, capecitabine 800 mg/m² twice daily continuous dose led to a decreased incidence of diarrhea (43% vs 0%) and stomatitis (29% vs 14%) in patients with metastatic breast cancer previously treated with anthracyclines and/or taxanes.²⁴

These clinical trials suggest that capecitabine-related toxicity, including GI AEs, can be reduced with dose modification while providing efficacy comparable to the standard capecitabine regimen. Until these findings can be confirmed in larger clinical trials, grade 1 GI AEs require no dose adjustment. For grade 2 GI AEs, dose modification is not required on the first occurrence, but is required for subsequent occurrences.

Grade 3/4 GI AEs require dose reduction at the first occurrence.

Symptomatic treatment

The symptomatic treatment of GI AEs associated with capecitabine is similar to that of other anticancer agents, with some treatments intended as primary prevention and others as palliation. All patients given capecitabine should be encouraged to drink large quantities of liquids.² Patient education regarding the types of GI AEs that could occur, and cautions to take should they occur, is important so that the patient can take appropriate actions at the earliest possible stage. Recently, a randomized, controlled trial demonstrated that patients who received a symptom-focused home care program experienced significant improvement in their diarrhea, constipation, nausea, and mucositis, particularly during the first 2 cycles of capecitabine. Also, unplanned service utilization, particularly the number of inpatient days (57 vs 167 days; *P* = 0.02), was lower in the home care group.²⁷

Constipation, although rare, can be managed by increasing liquid, vegetable, and fruit intake.² The treatment of diarrhea requires careful assessment of the duration, severity, and constellation of signs and symptoms.²⁸ Grade 1 or 2 uncomplicated diarrhea, ie, diarrhea with no complicating symptoms such as cramping, nausea/vomiting, fever, or dehydration, may be managed conservatively. This includes stopping all lactose-containing products, alcohol, and high-osmolar supplements; drinking 8–10 large glasses of clear liquids daily; and eating small meals frequently. Loperamide should be initiated at a dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool.²⁸ Symptoms should be reassessed in 12–24 hours and treatment modified as appropriate. If diarrhea is unresolved, loperamide can be increased to 2 mg every 2 hours and oral anti-

biotics begun. Second-line treatment with octreotide or tincture of opium can be initiated if diarrhea persists. Patients with complicated diarrhea, ie, grade 1/2 diarrhea with complicating symptoms or grade 3/4 diarrhea, should be admitted to the hospital for treatment with octreotide, IV fluids, and antibiotics.²⁸

Loperamide may reduce diarrhea not only through its anticholinergic properties but also by reducing the local concentrations of 5'-DFCR.²⁹ For patients who do not respond to or are intolerant of loperamide, an alternative to octreotide is the use of probiotics. Abd El-Atti et al reported the case of a stage IV breast cancer patient who experienced capecitabine-induced grade 3 diarrhea, characterized by seven to nine stools per day, that was associated with incontinence and abdominal cramping and led to neutropenic fever requiring hospitalization.³⁰ The patient was treated successfully with a multispecies combination of probiotics containing eight strains of live freeze-dried lactic acid bacteria.

Stomatitis occurs in up to 25% of patients treated with capecitabine but is usually mild.¹ The general care of patients with stomatitis includes the use of a soft toothbrush, flossing, and adequate hydration.^{31,32} A mouthwash with salt or baking soda (1 tsp per 250 mL of water) can be used to treat symptoms of grade 1 stomatitis. Avoidance of spicy foods and acidic fruits may be beneficial.² Topical anesthetics are recommended to treat stomatitis,^{31,32} whereas chlorhexidine,^{31,32} sucralfate,³³ and acyclovir are not recommended.³²

Capecitabine has a low emetogenic potential among oral chemotherapy drugs. Consequently, antiemetic treatment is recommended only when nausea and/or vomiting has occurred.³⁴ Acute nausea and vomiting can be treated with metoclopramide or prochlorperazine alone or in combination with lorazepam or a histamine 2 (H₂)-antagonist or pro-

Case study #1

A 65-year-old Latina female was diagnosed in 1999 with stage I inflammatory ductal carcinoma of the breast (stage T1b, N0, M0), subtype estrogen-receptor positive (ER+)/progesterone-receptor positive (PgR+), human epidermal growth factor receptor 2 negative (HER2-). She was treated with lumpectomy followed by radiation therapy and then tamoxifen, to which she had a good response. A solitary liver metastasis was identified in November 2004, for which she underwent a metastasectomy.

She had no evidence of disease on anastrozole (Arimidex) therapy until March 2007, when she developed multiple liver lesions. Liver biopsy confirmed metastatic disease consistent with a primary tumor in the breast. Fulvestrant (Faslodex) was initiated. However, this therapy was discontinued in August 2007 because of progressively increasing liver lesions.

Two months later, she was entered into a clinical trial using a combination regimen including nanoparticle albumin-bound paclitaxel (Abraxane), bevacizumab (Avastin), and gemcitabine (Gemzar). Again, because of progression of the liver metastatic lesions within 3 months, chemotherapy was changed to capecitabine (Xeloda), 1,250 mg/m² twice daily for 2 weeks on and 1 week off, combined with docetaxel (Taxotere) given every 21 days. Her disease was stable on docetaxel and capecitabine; however, she experienced grade 3 fatigue related to docetaxel. Therefore, docetaxel was discontinued after 3 cycles, and capecitabine was continued at the full dose.

A year later, she developed grade 2 hand-foot syndrome (HFS), grade 1 diarrhea, and grade 1 rash. The adverse events from capecitabine resolved within 4 weeks after the treatment schedule was modified to a cycle of 1 week on and 1 week off every 2 weeks, keeping the same dose.

ton pump inhibitor.³⁴ Alternatively, a low-dose corticosteroid such as dexamethasone 4–8 mg can be used.³⁵ If nausea and/or vomiting remain problematic, an oral 5-hydroxytryptamine type 3-antagonist can be used.³⁴ Although uncommon, anorexia is best managed by eating frequent, small, tasty meals, even spicy foods.²

Dyspepsia can be managed by the use of antacids or H₂-antagonists other than cimetidine.² Antacids should be given 2 hours before or after capecitabine administration² because of enhanced capecitabine absorption.¹ The administration of an aluminum hydroxide/magnesium hydroxide-containing antacid immediately after capecitabine has been reported to increase the absorption of capecitabine.¹

Risk reduction

Recognizing situations in which the risk of capecitabine-related GI AEs may be increased is important as a preventive strategy. These situations

include drug interactions, folate consumption, and gene polymorphisms. Of note, consideration should be given to possible AEs when capecitabine is given concurrent with radiotherapy.

Drug interactions. There appears to be no clinically relevant interaction between capecitabine and other anticancer drugs, including paclitaxel,³⁶ docetaxel (Taxotere),³⁷ irinotecan,³⁸ and the combination of epirubicin and cisplatin.³⁹ Furthermore, in vitro studies with human liver microsomes have shown that capecitabine and its metabolites have no inhibitory effect on numerous cytochrome P (CYP) 450 isoenzymes, including 1A2, 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1.¹ However, 5-FU has been shown to inhibit CYP 2C9 activity up to five-fold in a dose-dependent manner⁴⁰ and may be involved in reported interactions between capecitabine and other drugs.

Warfarin, one of the most commonly used oral anticoagulants, is metabolized by liver CYP 2C9 iso-

Case study #2

In October 2006, an asymptomatic 59-year-old woman was diagnosed with stage IV ductal carcinoma of the left breast (ER+/PgR-, HER2-) metastatic to bone only. She was started on zoledronic acid (Zometa) 4 mg IV every 4 weeks and letrozole (Femara) 2.5 mg/d orally. Within 4 months of the initiation of therapy, she achieved decreased size of the left breast mass to < 1 cm. Bone metastatic lesions remained stable, and she was asymptomatic.

Based on the excellent tumor response to antihormonal therapy and recent finding of improved survival in patients with low-burden metastatic breast cancer after mastectomy,^{25,26} she underwent bilateral mastectomy (right, modified radical mastectomy; left, simple prophylactic) followed by immediate reconstruction in April 2007. She was then treated with zoledronic acid and letrozole, and her disease remained stable until March 2009, when progressive disease was demonstrated by new focal liver lesions (the largest of which was 2.5 cm) and progressively worsening bone metastatic lesions. Liver biopsy demonstrated conversion of her tumor to ER+/PgR-/HER2+ subtype.

The patient was started on capecitabine (Xeloda), 1,250 mg/m² orally twice daily for 14 days every 3 weeks, in combination with trastuzumab (Herceptin), 8 mg/kg × 1, then 6 mg/kg every 3 weeks. Zoledronic acid 4 mg IV was continued but given less frequently (every 6 weeks). Staging computed tomography (CT) scans done 3 months later demonstrated decreased size of the liver lesions. Moreover, her circulating tumor cells decreased to 5/7.5 mL in whole blood. She tolerated chemotherapy very well.

Six months later, she experienced grade 1 hand-foot syndrome (HFS) and diarrhea, and grade 3 skin rash, which was worse typically during the second week of capecitabine therapy. The treatment schedule was changed to 1,250 mg/m² orally twice daily 1 week on, 1 week off. The diarrhea and HFS completely resolved within 4 weeks, and the skin lesions improved to grade 1 within the next 6 weeks. On this modified treatment schedule, the patient continued to demonstrate response to capecitabine therapy, as evidenced by decreased size of the liver lesions to < 1 cm and complete disappearance of the circulating tumor cells. She remains asymptomatic, and her disease has been stable.

enzymes. Retrospective analysis has shown GI bleeding with a prolonged prothrombin time and increased international normalized ratio levels in patients simultaneously receiving capecitabine and warfarin.⁴¹ The mechanism for this interaction is believed to be related to the downregulation of CYP 2C9 by capecitabine or its metabolites or to a pharmacodynamic interaction with warfarin.⁴² Coagulation parameters are recommended to be measured frequently in these patients, with the warfarin dose adjusted as needed.¹

The inhibition of liver CYP 2C9 isoenzymes is also thought to play a role in an interaction between phenytoin and capecitabine. There have been three case reports of phenytoin toxicity within a few weeks of

starting capecitabine, characterized by cerebellar symptoms of unsteady gait, falls, and weakness.^{43,44} Therefore, patients receiving concomitant capecitabine and phenytoin should be monitored for increased plasma levels of phenytoin as well as for any associated clinical symptom.

Early clinical studies revealed that concurrent administration of capecitabine with leucovorin⁴⁵ and interferon-alpha⁴⁶ reduces the maximum tolerated dose of capecitabine. Moreover, a randomized study suggested a severe sequence-specific toxicity when capecitabine is given after 5-FU/leucovorin.⁴⁷ Eleven of 14 patients (79%) treated with capecitabine as their second treatment experienced ≥ grade 3 toxicity, compared with 5 of 18 patients (28%) receiving

capecitabine as the first treatment, and no patients receiving 5-FU/leucovorin as the first treatment (0 of 16) or second treatment (0 of 12). The mechanism has not been determined, but interaction with intracellularly retained folate after 5-FU/leucovorin therapy is a possibility. Consequently, the combined use of capecitabine and leucovorin or interferon-alpha should be avoided or used with caution.

Folate consumption. Limiting the intake of folate might be of value in reducing the incidence of capecitabine toxicity. As noted earlier, an association between dietary folate consumption and fluoropyrimidine toxicity is emerging. In fact, grade 3/4 GI AEs followed by death have been reported after the initiation of capecitabine therapy in a patient treated with 15 mg/d of folic acid.⁴⁸ Therefore, consideration should be given to discontinuing folate supplements in patients experiencing capecitabine toxicity.

One adjuvant study of 5-FU and leucovorin in 89 patients with advanced colorectal cancer showed that the odds ratio for grade 3/4 toxicity for each 10 nmol/L increment in the serum folate level was 2.20 ($P = 0.016$).⁴⁹ Similar results were observed in a phase II trial of 55 patients with advanced or metastatic colorectal cancer treated with capecitabine 2,000 mg twice daily on days 1-14 every 3 weeks.⁵ Patients with higher baseline serum folate levels (≥ 17.96 nmol/L) had a significantly increased incidence of toxicity ($P = 0.04$). Compared with grade 0/1 toxicity, there was a higher incidence of grade 2/3 diarrhea ($P = 0.001$) and grade 2/3 nausea and vomiting ($P = 0.032$). From a practical viewpoint, limiting folate consumption may be difficult in the United States, where many foods, including flour, rice, pasta, cornmeal, and other grain products, are fortified with folate.

Gene polymorphisms. It is well known that dihydropyrimidine dehydrogenase (DPD) deficiency leads

to severe toxicities with 5-FU or capecitabine exposure.^{50,51} In addition, drugs such as the antiviral agents sorivudine and brivudine⁵² and the H₂-antagonist cimetidine^{53,54} are thought to inhibit DPD and may increase the risk of capecitabine toxicity.

Catabolism and deactivation of fluoropyrimidine drugs depend on a single and exclusive enzymatic step driven by DPD. In humans, 80%–90% of the administered dose of 5-FU is degraded by DPD.⁵⁵ DPD is prone to marked circadian rhythms, drug–drug interactions, and genetic polymorphisms, one of which is DPD deficiency with a prevalence of 3%–5% in the general population.⁵⁶ There appears to be a strong allele–dose-dependent association between toxicity and two genetic variants of DPD.⁵⁷ Consequently, capecitabine is not recommended in patients with DPD deficiency. Potential screening with phenotypic approaches such as the oral uracil breath tests, which are 96% specific and 100% sensitive for the assessment of DPD activity,⁵⁸ or the uracil/dihydrouracil ratio appears to have better predictive performance than genotypic testing strategies because DPD polymorphisms do not correlate with expression in many cases. Consequently, phenotypic approaches may facilitate the detection of DPD deficiency and help identify cancer patients at risk for severe toxic side effects before the administration of 5-FU or capecitabine.

In addition to DPD, defects in other enzymes may affect patient tolerability of capecitabine. These include thymidylate synthase (TS) and methylenetetrahydrofolate reductase (MTHFR). A prospective pilot study in 105 consecutive patients with advanced breast cancer treated with capecitabine monotherapy showed a trend ($P = 0.064$) in higher grade 3/4 global toxicity in patients homozygous for a specific TS allele compared with those heterozygous for or not carrying the allele.⁵⁹ A subsequent in-

vestigation in patients with advanced colorectal cancer suggested that genetic variation in MTHFR (but not TS) may predict toxicity.⁶⁰ The role of these other enzymes involved in fluoropyrimidine metabolism for prediction of adverse events remains unclear, however.

Conclusion

Capecitabine, an oral prodrug of 5-FU, frequently causes GI AEs, particularly diarrhea, nausea, vomiting, and stomatitis. As shown by the two cases presented, dose modification can significantly lower the incidence and severity of GI AEs. Another approach to managing GI AEs is symptomatic management using treatments commonly employed with other cancer chemotherapy agents. A third approach is to reduce the risk by avoiding potential drug interactions, reducing folate consumption, and identifying patients with genetic polymorphisms, such as DPD, that may interfere with the metabolic pathway of capecitabine.

References

- Xeloda [package insert]. South San Francisco, CA: Genentech, Inc.; 2009.
- Saif MW, Katirtzoglou NA, Syrigos KN: Capecitabine: an overview of the side effects and their management. *Anticancer Drugs* 2008;19:447–464.
- Haller DG, Cassidy J, Clarke SJ, Cunningham D, Van Cutsem E, Hoff PM, et al: Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 2008;26:2118–2123.
- Reigner B, Watanabe T, Schüller J, Lufcraft H, Sasaki Y, Bridgewater J, et al: Pharmacokinetics of capecitabine (Xeloda) in Japanese and Caucasian patients with breast cancer. *Cancer Chemother Pharmacol* 2003;52:193–201.
- Sharma R, Rivory L, Beale P, Ong S, Horvath L, Clarke SJ: A phase II study of fixed-dose capecitabine and assessment of predictors of toxicity in patients with advanced/metastatic colorectal cancer. *Br J Cancer* 2006;94:964–968.
- O'Shaughnessy J, Blum J: A retrospective evaluation of the impact of dose reduction in patients treated with Xeloda (capecitabine). *Proc Am Soc Clin Oncol* 2000;19:A400.
- Leonard R, O'Shaughnessy J, Vukelja S, Gorbounova V, Chan-Navarro CA, Marinchi D, et al: Detailed analysis of a randomized phase III trial: can the tolerability of capecitabine plus docetaxel be improved without compromising its survival advantage? *Ann Oncol* 2006;17:1379–1385.
- Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, et al: Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol* 2005;23:2155–2161.
- El Helw L, Coleman RE: Reduced dose capecitabine is an effective and well-tolerated treatment in patients with metastatic breast cancer. *Breast* 2005;14:368–374.
- Yap YS, Kendall A, Walsh G, Banerji U, Johnston SR, Smith IE, et al: Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer—how low can you go? *Breast* 2007;16:420–424.
- Sezgin C, Kurt E, Evrensel T, Ozdemir N, Manavoglu O, Goker E: Efficacy of lower dose capecitabine in patients with metastatic breast cancer and factors influencing therapeutic response and outcome. *South Med J* 2007;100:27–32.
- Rossi D, Alessandrini P, Catalano V, Giordani P, Fedeli SL, Fedeli A, et al: Safety profile and activity of lower capecitabine dose in patients with metastatic breast cancer. *Clin Breast Cancer* 2007;7:857–860.
- Mavroudis D, Papakotoulas P, Ardavanis A, Kakolyris S, Kouroussis Ch, Malamos N, et al: Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer. *Ann Oncol* 2010;21:48–54.
- Luporsi E, Bachelot T, Bajard A, Provencal J, Coefic D, Platini C, et al: Comparative efficacy of first-line docetaxel + capecitabine (XT) versus docetaxel + epirubicin (ET): pooled analysis of two randomised trials. *J Clin Oncol* 2008;26(suppl 20):A1049.
- Lück H-J, du Bois A, Schrader I, Huober J, Heilmann V, Fasching PA, et al: Final results of the AGO breast cancer study group MAMMA-3 trial: first-line capecitabine + paclitaxel vs epirubicin + paclitaxel for high-risk metastatic breast cancer. *Breast Cancer Res Treat* 2007;106(suppl 1):S67, A1076.
- Watanabe T, Katsumata N, Sasaki Y, Saeki T, Aogi K, Toi M, et al: A multicenter phase II trial of Xeloda (capecitabine) in patients with docetaxel-refractory advanced/metastatic breast cancer. *Proc Am Soc Clin Oncol* 2001;20:A1991.
- Kusama M, Nomizu T, Aogi K, Yoshimoto M, Horikoshi N, Tabei T, et al: Phase II study of 4-weekly capecitabine monotherapy in advanced/metastatic breast cancer. *Breast Cancer* 2010;17:233–244.
- Saeki T, Kimura T, Toi M, Taguchi T: A pilot phase II study of capecitabine in advanced or recurrent breast cancer. *Breast Cancer* 2006;13:49–57.
- Brell JM, Krishnamurthi SS, Javle M, Saltzman J, Wollner I, Pelley R, et al: A multi-

- center phase II study of oxaliplatin, irinotecan, and capecitabine in advanced gastric/gastroesophageal junction carcinoma. *Cancer Chemother Pharmacol* 2009;63:851-857.
20. Krishnamurthi SS, Brell JM, Hoppe CL, Egorin MJ, Weaver KC, Lee X, et al: Phase I clinical and pharmacokinetic study of oxaliplatin, irinotecan and capecitabine. *Cancer Chemother Pharmacol* 2009;63:441-450.
21. Ugidos L, Delgado S, Conill C, Ginés A, Gallego R, Ayuso JR, et al: Phase I trial of neoadjuvant chemoradiotherapy (CRT) with capecitabine and weekly irinotecan followed by laparoscopic total mesorectal excision (LTME) in rectal cancer patients. *Invest New Drugs* 2009;27:262-268.
22. Pentheroudakis G, Pappas P, Goufopoulos V, Fountzilas G, Nikolaidou M, Boumba VA, et al: Weekday on-weekend oral capecitabine: a phase I study of a continuous schedule better simulating protracted fluoropyrimidine therapy. *Cancer Chemother Pharmacol* 2007;60:733-739.
23. Traina TA, Theodoulou M, Feigin K, Patil S, Tan KL, Edwards C, et al: Phase I study of a novel capecitabine schedule based on the Norton-Simon mathematical model in patients with metastatic breast cancer. *J Clin Oncol* 2008;26:1797-1802.
24. Martin M, Casado A, Garcia-Saenz JA, Calvo L, Constenia M, Diaz-Rubio E: Phase II randomized study of capecitabine (C) administered as continuous versus standard (cyclic) treatment in patients (pts) with metastatic breast cancer (MBC). *Ann Oncol* 2006;17(suppl 9):158P.
25. Rapiti E, Verkooijen HM, Vlastos G: Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006;24:2743-2749.
26. Khan SA, Stewart AK, Morrow M: Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery* 2002;132:620-627.
27. Molassiotis A, Brearley S, Saunders M, Craven O, Wardley A, Farrell C, et al: Effectiveness of a home care nursing program in the symptom management of patients with colorectal and breast cancer receiving oral chemotherapy: a randomized, controlled trial. *J Clin Oncol* 2009;27:6191-6198.
28. Benson AB III, Ajani JA, Catalano RB, et al: Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004;22:2918-2926.
29. Quinney SK, Sanghani SP, Davis WI, Hurley TD, Sun Z, Murry DJ, et al: Hydrolysis of capecitabine to 5'-deoxy-5-fluorocytidine by human carboxylesterases and inhibition by loperamide. *J Pharmacol Exp Ther* 2005;313:1011-1016.
30. Abd El-Atti S, Wasicek K, Mark S, Hegazi R: Use of probiotics in the management of chemotherapy-induced diarrhea: a case study. *J Parenter Enteral Nutr* 2009;33:569-570.
31. Peterson DE, Bensadoun RJ, Roila F: Management of oral and gastrointestinal mucositis: ESMO clinical recommendations. *Ann Oncol* 2008;19(suppl 2):ii122-ii125.
32. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, et al: Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology: Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007;109:820-831.
33. Nottage M, McLachlan SA, Brittain MA, Oza A, Hedley D, Feld R, et al: Sucralose mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Support Care Cancer* 2003;11:41-47.
34. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Antiemesis. http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed July 8, 2010.
35. Multinational Association of Supportive Care in Cancer. Perugia International Cancer Conference VII: Antiemetic guidelines. http://data.memberclicks.com/site/mascc/MASCC_Guidelines_English_2010.pdf. Accessed July 8, 2010.
36. Villalona-Calero MA, Weiss GR, Burris HA, Kraynak M, Rodrigues G, Drengler RL, et al: Phase I and pharmacokinetic study of the oral fluoropyrimidine capecitabine in combination with paclitaxel in patients with advanced solid malignancies. *J Clin Oncol* 1999;17:1915-1925.
37. O'Shaughnessy J: Capecitabine and docetaxel in advanced breast cancer: analyses of a phase III comparative trial. *Oncology (Williston Park)* 2002;16(10 suppl 12):17-22.
38. Delord JP, Pierga JY, Dieras V, Bertheault-Cvrtkovic F, Turpin FL, Lokiec F, et al: Dose escalation and pharmacokinetic study of capecitabine (Xeloda) and irinotecan (CPT-11) in gastrointestinal tumors: preliminary results. *Proc Am Soc Clin Oncol* 2002;21:A397.
39. Evans TR, Pentheroudakis G, Paul J, McInnes A, Blackie R, Raby N, et al: A phase I and pharmacokinetic study of capecitabine in combination with epirubicin and cisplatin in patients with inoperable oesophago-gastric adenocarcinoma. *Ann Oncol* 2002;13:1469-1478.
40. Gunes A, Coskun U, Boruban C, Gunel N, Babaoglu MO, Sencan O, et al: Inhibitory effect of 5-fluorouracil on cytochrome P450 2C9 activity in cancer patients. *Basic Clin Pharmacol Toxicol* 2006;98:197-200.
41. Shah HR, Ledbetter L, Diasio R, Saif MW: A retrospective study of coagulation abnormalities in patients receiving concomitant capecitabine and warfarin. *Clin Colorectal Cancer* 2006;5:354-358.
42. Saif MW: An adverse interaction between warfarin and fluoropyrimidines revisited. *Clin Colorectal Cancer* 2005;5:175-180.
43. Brickell K, Porter D, Thompson P: Phenitoin toxicity due to fluoropyrimidines (5FU/capecitabine): three case reports. *Br J Cancer* 2003;89:615-616.
44. Schaller G, Ebert A, Kuhle A, Bange-mann N: Drug interaction of capecitabine and phenitoin in the therapy of cerebral and visceral metastatic breast cancer. *Ann Oncol* 2000;11(suppl 4):139.
45. Cassidy J, Dirix L, Bissett D, Reigner B, Griffin T, Allman D, et al: A phase I study of capecitabine in combination with oral leucovorin in patients with intractable solid tumors. *Clin Cancer Res* 1998;4:2755-2761.
46. Chang DZ, Olencki T, Budd GT, Peereboom D, Ganapathi R, Osterwalder B, et al: Phase I trial of capecitabine in combination with interferon alpha in patients with metastatic renal cancer: toxicity and pharmacokinetics. *Cancer Chemother Pharmacol* 2001;48:493-498.
47. Hennig IM, Naik JD, Brown S, Szubert A, Anthony DA, Jackson DP, et al: Severe sequence-specific toxicity when capecitabine is given after fluorouracil and leucovorin. *J Clin Oncol* 2008;26:3411-3417.
48. Clippe C, Freyer G, Milano G, Trillet-Lenoir V: Lethal toxicity of capecitabine due to abusive folic acid prescription? *Clin Oncol (R Coll Radiol)* 2003;15:299-300.
49. Ho C, Ng K, O'Reilly S, Gill S: Outcomes in elderly patients with advanced colorectal cancer treated with capecitabine: a population-based analysis. *Clin Colorectal Cancer* 2005;5:279-282.
50. Saif MW, Diasio R: Is capecitabine safe in patients with gastrointestinal cancer and dihydropyrimidine dehydrogenase deficiency? *Clin Colorectal Cancer* 2006;5:359-362.
51. Hooiveld EA, van Kuilenburg AB, Haanen JB, Westermann AM: Severe toxicity after treatment with capecitabine and fluorouracil due to partial dihydropyrimidine dehydrogenase deficiency [in Dutch]. *Ned Tijdschr Geneesk* 2004;148:626-628.
52. Kanamitsu SI, Ito K, Okuda H, Ogura K, Watabe T, Muro K, et al: Prediction of in vivo drug-drug interactions based on mechanism-based inhibition from in vitro data: inhibition of 5-fluorouracil metabolism by (E)-5-(2-bromovinyl)uracil. *Drug Metab Dispos* 2000;28:467-474.
53. Harvey VJ, Slevin ML, Dilloway MR, Clark PI, Johnston A, Lant AF: The influence of cimetidine on the pharmacokinetics of 5-fluorouracil. *Br J Clin Pharmacol* 1984;18:421-430.
54. Dilloway MR, Lant AF: Effect of H2-receptor antagonists on the pharmacokinetics of 5-fluorouracil in the rat and monkey. *Bio-pharm Drug Dispos* 1991;12:17-28.
55. Longley DB, Harkin DP, Johnston PG: 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer* 2003;3:330-338.
56. Lu Z, Zhang R, Carpenter JT, Diasio RB: Decreased dihydropyrimidine dehydrogenase activity in a population of patients with breast cancer: implication for 5-fluoro-

uracil-based chemotherapy. *Clin Cancer Res* 1998;4:325-329.

57. Gross E, Busse B, Riemenschneider M, Neubauer S, Seck K, Klein HG, et al: Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. *PLoS ONE* 2008;3:e4003.

58. Mattison LK, Ezzeldin H, Carpenter M, Modak A, Johnson MR, Diasio RB: Rapid identification of dihydropyrimidine dehydrogenase deficiency by using a novel 2-13C-uracil breath test. *Clin Cancer Res*

2004;10:2652-2658.

59. Largillier R, Etienne-Grimaldi MC, Formento JL, Ciccolini J, Nebbia JF, Ginot A, et al: Pharmacogenetics of capecitabine in advanced breast cancer patients. *Clin Cancer Res* 2006;12:5496-5502.

60. Sharma R, Hoskins JM, Rivory LP, Zucknick M, London R, Liddle C, et al: Thymidylate synthase and methylenetetrahydrofolate reductase gene polymorphisms and toxicity to capecitabine in advanced colorectal cancer patients. *Clin Cancer Res* 2008;14:817-825.

ABOUT THE AUTHORS

Affiliations: Dr. Bayraktar is a Clinical Fellow in Hematology/Oncology in the Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX. Dr. Glück is Professor of Medicine, Associate Division Chief of Clinical Affairs in the Division of Hematology/Oncology, and Clinical Director of the Braman Family Breast Cancer Institute at the University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL.

Conflicts of interest: The authors have no financial interests to disclose.

Radiation overexposure following brain perfusion CT scans in California, Florida, and Alabama (2008–2009)

Zaina P. Qureshi, PhD, MPH,¹ Oliver Sartor, MD,² and Charles L. Bennett, MD, PhD, MPP^{1,3}

¹South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR), South Carolina College of Pharmacy, University of South Carolina, Columbia, SC;

²Tulane Cancer Center and Departments of Medicine and Urology, Tulane Medical School; New Orleans, LA; and

³Hollings Cancer Center, Medical University of South Carolina, Charleston, SC

The number of computerized tomography (CT) scans performed each year in the United States has been growing steadily over the past 15 years,¹ reaching an estimated 68.7 million scans in 2007.^{2,3} Because of the urgency of ruling out a hemorrhagic bleed as the cause of an acute cerebrovascular accident, 64-slice CT scanners have been incorporated into the diagnostic pathway for acute stroke evaluation at tertiary stroke centers. Between 2008 and 2009, a total of 206 individuals at Cedars-Sinai Medical Center in Los Angeles experienced up to eight-fold radiation overexposure following 64-slice CT scanning.⁴ About 40% of these individuals reported clinical manifestations, including scalp hair loss, decreased mental concentration, confusion, and skin allergies.⁵ These signs and symptoms generally resolved over 2–4 weeks. However, two people reported their clinical symptoms to their internist, who, in turn, reported these findings to radiation safety personnel at the hospital. A radiation

Manuscript received December 2, 2010; accepted January 28, 2011.

Correspondence to: Charles L. Bennett, MD, PhD, MPP, CoEE Endowed Chair in Medication Safety and Efficacy, South Carolina College of Pharmacy/USC Campus, 715 Sumter Street, Columbia, SC 29208; telephone: 803-777-2289; fax: 803-777-2820; e-mail: bennettc@sccp.sc.edu.

© 2011 Elsevier Inc. All rights reserved.

Fast Facts

Concern has been expressed that increasing use of CT scans may expose individuals to high levels of radiation exposure. These concerns were magnified in 2009, when 206 individuals at Cedars-Sinai Medical Center in Los Angeles experienced eight-fold greater irradiation than desired during brain CT perfusion scanning procedures. About 40% of these individuals reported clinical manifestations, primarily short-term loss of scalp hair but also loss of concentration and mental confusion. Diligent follow-up by a hospital radiation safety officer of the symptoms reported by two patients led to the recognition that a problem in radiation overdosing may have occurred. Follow-up studies conducted independently by hospital safety personnel, the manufacturer of the scanner, and California Department of Public Health radiation safety personnel identified a confluence of factors that may have led to the adverse event—including a modification in the computer software on the scanner, miscommunication between radiology technicians and training/safety personnel employed by the manufacturer of the equipment, and nonstandard readouts of radiation dosages on the CT scanner.

Regulatory evaluations by California Department of Public Health officials identified similar adverse events at five other California hospitals. In at least two other states, hospital officials voluntarily conducted similar safety evaluations. Additional persons with radiation overexposure following brain CT perfusion scans were identified at one hospital in Alabama and one hospital in Florida. According to the California Department of Public Health, over an 18-month period, 206 people in Los Angeles undergoing CT perfusion scans suffered radiation overexposure. In all, more than 385 individuals at eight hospitals reportedly received excessive radiation dosages during brain CT perfusion scans. In 2010, several former FDA officials reported that they had previously expressed concern over the potential for radiation overexposure associated with brain CT perfusion scans.

In November 2010, FDA officials disseminated a public health communication identifying operator error as the single, most likely cause of the overexposure and outlined a range of safety initiatives designed to prevent future occurrences.

Commun Oncol 2011;8:89–91

safety officer at Cedars-Sinai subsequently reported her concerns to safety personnel employed by the Los Angeles County Department of Health, who, in turn, reported these findings to the California Department of Public Health and to the Office of Radiologic Devices and Health of the US Food and Drug Administration (FDA).

Analyses by safety employees of the hospital to identify the root causes of the overdosages highlighted a lack of familiarity of radiation personnel with modifications of the computer software on the CT scanner, presentation of radiation dosimetry levels in non-standard units on the scanner's LED displays, reliance of technicians on the software package for calibration of dosages, and difficulty comparing planned with delivered dosing levels.^{5,6}

A retrospective review conducted by regulatory officials employed by the California Department of Public Health singled out five other California hospitals that had exposed individuals to excessive radiation doses during 64-slice brain CT scans.⁷ Voluntarily conducted safety studies identified similar adverse events at a tertiary stroke center in Alabama and one in Florida (Table 1). As of October 26, 2010, about 385 individuals nationwide reportedly experienced radiation overexposure during brain perfusion CT scanning.⁸

This paper describes a rare overexposure to radiation in patients undergoing brain CT perfusion scanning at a handful of institutions. Although cancer patients rarely undergo this particular form of imaging, community oncologists should be aware of the potential for overexposure. Discussion with radiology colleagues as to their safety protocols will assure patients that they are receiving appropriate doses of diagnostic radiation when undergoing CT procedures.

— Lee S. Schwartzberg, MD, FACP
Editor-in-Chief

Where reported

To date, information on these cases has been reported in newspapers published in California, New York, Alabama, and Florida and in Public Safety Notifications disseminated by the FDA, the individual hospitals involved, and the manufacturers of the CT scanners, but not in the general medical literature.^{5,6,9-11} Upon reading details of this large-scale adverse event in *The New York Times*, radiation officials at an Alabama hospital and a hospital in Florida identified additional individuals who received higher-than-expected radiation dosing during a 64-slice CT scans. In June 2009, nine former officials of the FDA's Office of Radiologic Devices

and Health reported that they had expressed concerns over the potential safety of CT scans for colon cancer.¹²

Whose fault was it?

Although retrospective studies have been conducted by hospital officials, safety personnel employed by the manufacturers of the CT scanners, regulatory officials at the California State Department of Public Health, and regulatory personnel at the FDA, no clear consensus on the root cause of the safety problem has emerged.¹³ Generally proposed theories range from operator and system errors to machine malfunction, poor communication between hospital personnel and safety trainers employed by the manufacturers, and a lack of standard operating procedures. A wide range of remedies, such as investigation of each case, additional training for operators, and revised protocols for using the scanner, have been instituted at each of the affected hospitals.

Recommendations

According to the Emergency Care Research Institute (ECRI), a nonprofit organization that employs scientific research for establishing best practices for improving patient care and a collaborating center of the World Health Organization, radiation therapy overdose was the number-one health technology hazard in its list of the top-10 hazards heading into 2011.¹⁴ In their initial communication in 2009, FDA officials encouraged CT facilities to review their protocols and to make sure that the values displayed on the control panel corresponded to the doses normally associated with the protocol.⁴ Based on continued investigation, the FDA recommended in November 2010 that facilities take the following actions,⁸ some of which are critical safety practices for all CT procedures:

- Assess whether any patients at individual hospitals have received ex-

TABLE 1

Cases of CT scan overexposure in hospitals nationwide^{5,7,8,10,15,16}

Hospital	Beds	Cases ^a
Cedars-Sinai Medical Center, Los Angeles, CA	868	206-269
Providence Saint Joseph Medical Center, Burbank, CA	431	34-37
South Lake Hospital, Clermont, FL	104	40-77
Huntsville Hospital, Huntsville, AL	794	60-65
Bakersfield Memorial Hospital, Bakersfield, CA	340	16
UCSF Medical Center, San Francisco, CA	600	NA
Alta Bates Summit Medical Center, Berkeley, CA	555	NA
Marin General Hospital, Greenbrae, CA	235	NA
California Pacific Medical Center, San Francisco, CA	1,300	NA
Total	5,227	356-464

NA = not available

^a Multiple sources provided different numbers.

cess radiation during CT perfusion scans.

■ Review radiation dosing protocols for all CT perfusion scans to ensure that the correct dose is planned for each study. Any change to the default protocol should be cleared through the facility's quality assurance program and approved for image quality and dose by a radiologist and a physicist.

■ If more than one study is performed on a patient during one CT perfusion imaging session, the dose of radiation should be adjusted so that it is appropriate for each study.

■ Implement quality control procedures to ensure that dosing protocols are followed every time—and that the planned amount of radiation is administered.

■ Check the display panel before performing each scan to make sure the amount of radiation to be delivered is appropriate for the individual patient.

■ Be certain and document that radiologic technologists are trained on the specific scanner and for the specific imaging protocol they are using. They should understand the meaning of the dose index reported on the CT control screen, as well as the expected ranges for each imaging protocol and body scan region.

■ CT operators should be specifically trained on dose-saving features, such as automatic exposure control (AEC), before using them. If the user activates AEC without carefully reviewing and adjusting the associated parameters, the prepopulated (“default”) values may not be appropriate for that scan, which could lead to an overexposure with more radiation dose than intended or an underexposure with poor image quality. Proto-

cols using AEC should be reviewed by a radiologist and a physicist.

In addition, clinicians should be vigilant for toxicity among persons undergoing CT scans and report any clinical concerns to the FDA's MedWatch program (www.fda.gov/medwatch).

References

1. IMV 2006 CT market summary report. IMVinfo.com Web site. http://www.imvinfo.com/user/documents/content_documents/nws_rad/MS_CT_DSandTOC.pdf. Accessed January 7, 2011.

2. Amis ES Jr, Butler PF, Applegate KE, et al. American College of Radiology white paper on radiation dose in medicine. *J Am Coll Radiol* 2007;4:272–284.

3. Caoili EM, Cohan RH, Ellis JH, Dillman J, Schipper MJ, Francis IR. Medical decision making regarding computed tomographic radiation dose and associated risk: the patient's perspective. *Arch Intern Med* 2009;169:1069–1071.

4. Safety investigation of CT brain perfusion scans: initial notification. FDA Web site. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm193293.htm>. Accessed October 1, 2010.

5. Zarembo A. Cedars-Sinai investigated for significant radiation overdoses of 206 patients. *Los Angeles Times* 2009.

6. Bogdanich W. After stroke scans, patients face serious health risks. *The New York Times*; July 31, 2010. <http://www.nytimes.com/2010/08/01/health/01radiation.html?scp=1&sq=After%20stroke%20scans,%20patients%20face%20serious%20health%20risks&st=cse>. Accessed October 1, 2010.

7. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;169:2078–2086.

8. Safety investigation of CT brain perfusion scans: update 12/8/2009. FDA Web site. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm185898.htm>. Accessed October 1, 2010.

9. Suit filed against Cedars-Sinai, GE for brain perfusion radiation overexposure. *HealthImaging.com* Web site. http://www.healthimaging.com/index.php?option=com_articles&view=article&id=19187:suit-filed-against-cedars-sinai-ge-for-brain-perfusion-radiation-overexposure. Accessed October 1, 2010.

10. New details emerge in CT scan radiation overdose scandal. *NewsInferno.com* Web site. <http://www.newsinferno.com/archive/new-details-emerge-in-ct-scan-radiation-overdose-scandal/>. Accessed October 1, 2010.

11. Clark C. Cedars-Sinai caused immediate jeopardy in CT scanner case, say state officials. *HealthLeaders Media* Web site. <http://www.healthleadersmedia.com/page-1/QUA-242685/CedarsSinai-Caused-Immediate-Jeopardy-in-CT-Scanner-Case-Say-State-Officials>. Accessed October 1, 2010.

12. Scientist: FDA suppressed CT scan safety concerns. *Fox News* Web site. <http://www.foxnews.com/health/2010/03/30/scientist-fda-suppressed-ct-scan-safety-concerns/>. Accessed October 1, 2010.

13. Mertens M. Radiation overdoses at Cedars-Sinai prompt investigation. *National Public Radio* Web site. http://www.npr.org/blogs/health/2009/10/cedars_sinai_ge_found_to_be_be_1.html?ps=rs. Accessed December 1, 2010.

14. Emergency Care Research Institute. Top 10 health technology hazards for 2011. *Health Devices*. 2010;39:387–397. https://www.ecri.org/Forms/Documents/Top_10_Health_Tech_Hazards_2011.pdf. Accessed December 14, 2010.

15. Hyman H. Protect yourself from excessive radiation during CT scans. *Lawyers Well-being* Web site. <http://lawyerswellbeing.com/blog/?p=356>. Accessed October 1, 2010.

16. Bogdanich W. Radiation offers new cures, and ways to do harm. *The New York Times*; January 23, 2010. <http://www.nytimes.com/2010/01/24/health/24radiation.html?pagewanted=4&r=1>. Accessed October 1, 2010.

ABOUT THE AUTHORS

Affiliations: Dr. Qureshi is a postdoctoral fellow at South Carolina College of Pharmacy, University of South Carolina, Columbia, SC; Dr. Sartor is Medical Director of the Tulane Cancer Center and Laborde Professor of Cancer Research in the Departments of Medicine and Urology at Tulane Medical School, New Orleans, LA; and Dr. Bennett is the Endowed Chair for the South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR), South Carolina College of Pharmacy, and Hollings Cancer Center, Medical University of South Carolina, Charleston, SC.

Conflicts of interest: Dr. Qureshi has no potential conflicts of interest to disclose; Dr. Sartor is a consultant to and clinical investigator for sanofi-aventis; and Dr. Bennett is supported by funding from the South Carolina Center of Economic Excellence for Medication Safety and Efficacy initiative.

One transition at a time, please

Susan London and Mary Ellen Schneider

Slow down and give us more time. That seems to be the push-back message from physician practices to the federal government regarding its latest incentive requirement. Many practices were focusing on the January 3 launch of the federal initiative offering bonus payments to those who successfully implement electronic health records (EHRs), until the Centers for Medicare & Medicaid Services (CMS) announced a decision requiring physicians to use e-prescribing during the first 6 months of 2011 or face penalties in 2012 and 2013.

In response to the announcement, state and specialty medical societies have appealed to Health and Human Services Secretary Kathleen Sebelius to urge the CMS to reverse its “last-minute” decision. The signatories, which include the American Society of Clinical Oncology, American Society for Radiation Oncology, and the Society of Gynecologic Oncologists, have asked for an extension to allow physicians more time to comply with the requirement. They argue that physicians need the extra time to educate themselves about the system and fully address the financial and staff-training implications for their practices.

It is “unfair and unreasonable to penalize physicians who are working in good faith to adopt a certified EHR product for participation in the Medicare EHR incentive program,” wrote the signatories. They suggested that CMS “at the very least” extend the reporting period to allow physicians to report the e-prescribing code at least 10 times in the

next 10 months (January 1, 2011, to October 31, 2011) instead of 6 (from January 1 to June 30).

The Medicare Electronic Prescribing (eRx) Incentive Program, which began in 2009 and runs through 2013, provides bonus payments for e-prescribing when certain eligibility criteria are met, with bonus percentages being reduced over the span of the program. But under



HHS Secretary Kathleen Sebelius

the current regulation, the CMS also will start financially penalizing providers who did not begin e-prescribing in January.

The penalty for failing to e-prescribe will be 1%, 1.5%, and 2% of all Medicare Part B charges in 2012, 2013, and 2014, respectively.

The 2010 reporting criteria require that healthcare providers report e-prescribing for at least 25 eligible patient encounters (which can include multiple encounters for a single patient) and that Medicare account for at least 10% of the pro-

vider's payer mix.

A noteworthy caveat is that providers will not be able to earn both the e-prescribing bonus and another bonus for implementing the EHRs that the CMS is offering, because e-prescribing is among the 15 core measures of EHR implementation.

The EHR incentive programs offer payments to physicians for using health information technology (HIT) to improve patient care. The federal government recently issued regulations detailing how physicians and hospitals can meet standards for so-called “meaningful use” of the technology (*Community Oncology* 2010;7:480). Physicians who meet the criteria are eligible to receive up to \$44,000 over 5 years under the Medicare program or \$63,750 in 6 years under the Medicaid program. Eligible hospitals could receive millions of dollars, according to the CMS.

However, there are concerns, as noted in the letter to Ms. Sebelius, that the unexpected e-prescribing requirement would result in physicians using standalone e-prescribing programs to avoid the penalties but that most of those programs would not survive the transition to a complete EHR implementation. “The HHS and CMS should minimize the financial and administrative hardships created by the various, overlapping Medicare incentive and penalty programs by establishing additional exemption categories,” the signatories asserted, a reference to the CMS’ dismissal of all exemption categories from outside parties, except its own. At press time, there was no response to the letter.