Reversible Pancytopenia Caused by Oral Letrozole Assumption in a Patient With Recurrent Breast Cancer

To the Editor: In hormonal treatment of postmenopausal women with hormone receptor–positive metastatic breast cancer, third generation aromatase inhibitors are well-established agents. These drugs have recently shown superior antitumor efficacy and better tolerability with respect to tamoxifen and currently represent standard hormone therapy in this clinical setting. Letrozole, a nonsteroidal triazole derivative, is one of the most potent aromatase inhibitors yet developed.

The oral administration of this drug is usually well tolerated. Common adverse events reported in phase II/III trials include headache (1.1% to 7.0%), nausea (6.0% to 10.3%), fatigue (3.0% to 5.0%), hot flushes (5.0%), peripheral edema (6.0%), rash (2.7%), somnolence (3.2%), vomiting (3.8%), and hypercholesterolemia (3.8%). Other drug-related symptoms, such as abdominal pain, asthenia, dyspepsia, and dizziness are rare (less than 2% of cases). Most of these adverse events are reported to be mild to moderate in severity. Letrozole administration has also been occasionally associated with cardiovascular and thromboembolic events, weight gain (4% to 10%), and increase of γ-glutamyl transferase levels. Significant changes in hematologic parameters have never been reported.

We describe a case of severe hematologic toxicity secondary to oral letrozole administration. In April 2001, oral letrozole therapy (one tablet, 2.5 mg daily) was prescribed to a 64-year-old female patient for locoregional breast cancer recurrence. No other drugs were concomitantly assumed, except enalapril, 10 mg daily since 1998, for mild hypertension.

Patient history is as follows: malignancy was diagnosed in February 1999 and treated with radical mastectomy (postoperative tumor-node-metastasis staging pT2, pN0 M0). Adjuvant endocrine therapy with tamoxifen, 20 mg orally, was then administered on the basis of the positive estrogen-receptor status of tumor specimens. In March 2001, routine physical examination revealed the presence of a subcutaneous lesion (1.5 cm in diameter) at the site of previous surgical approach. Local treatment consisted of surgery followed by radiation therapy (total dose received: 44 Gy). Tamoxifen administration was therefore interrupted. In August 2001, the patient presented with symptoms of severe fatigue, subjective dizziness, headache, confusion, lethargy, moderate dyspnea, anorexia, and symptomatic palpitations. General physical examination revealed mucocutaneous pallor, hypotension (90/65 mmHg), sinus tachycardia (120/min), and mild peripheral edema. Abdominal and pulmonary examination were unremarkable. Blood count showed pancytopenia, with a hemoglobin level of 6.3 g/dL, a leukocyte count of 2,000/µL (granulocyte count of 800/µL), and a platelet count of 47,000/µL. Therefore, the patient was immediately hospitalized. Routine biochemical investigations showed no renal or liver function impairment. CEA and CA 15-3 serum levels were substantially within the normal range. At the last follow-up visit, in February 2002, the patient’s hemoglobin level was 13.4 g/dL, leukocyte count was 6,000/µL (granulocyte count was 2,800/µL), and platelet count was 260,000/µL.

Aplastic anemia is thought to be a result of injury or destruction of a common pluripotential stem cell affecting all subsequent blood cell populations. Erythrocytes, granulocytes, and platelets may decrease to dangerously low levels. The pathophysiology of aplastic anemia is now believed to be immune mediated, with active destruction of blood-forming cells by lymphocytes. Drugs and chemicals are among the most frequent causes triggering the aberrant immune response. According to the International Aplastic Anemia Agranulocytosis Study, drugs associated with aplastic anemia are nonsteroidal analgesics, some antibiotics, antithyroid drugs, furosemide, phenothiazine, allopurinol, and corticosteroids. To our knowledge, this is the first case of bone marrow depression after administration of aromatase inhibitors. Absence of exposure to other drugs, lack of underlying disorders known to cause bone marrow aplasia, and prompt recovery after drug discontinuation make the causal relationship with letrozole therapy plausible. Because of the increasing use of letrozole and other aromatase inhibitors in the treatment of breast cancer patients, this observation is of interest and suggests that blood cell counts should be periodically checked in patients treated with these drugs, particularly shortly after the initiation of drug therapy.

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REFERENCES

Anastrozole Versus Tamoxifen as First-Line Therapy For Advanced Breast Cancer: Methodologic Issues

To the Editor: Studies by Bonneterre et al1 and Nabholtz et al2 published in the Journal of Clinical Oncology in November 2000, and republished as a combined analysis in November 2001,3 have not only influenced clinical practice but have also generated much debate. At least five letters have been published questioning the interpretation of the results in relation to differences in the populations treated and the manner of reporting these.4-8

We would like to bring to your attention some issues regarding the methodology of these two apparently identically designed randomized trials that have not yet been explained by the authors. First, why was the trial by Nabholtz et al2 stopped? The method of sample size calculation is described as identical to that of Bonneterre et al,1 a trial that randomized 668 patients compared with 353 by Nabholtz et al. No criteria for early stopping are described, and the authors do not state that any were met. The only explanation given is that the study was stopped when “the prespecified number of patients had been randomized to the TARGET trial, which had the same protocol and objectives.” Can completion of accrual to one trial be a criterion for stopping another when the results of both are unknown? In the context of data showing one treatment as clearly inferior or superior perhaps, but this is not the case. Although a subsequent publication4 heavily emphasizes that the trials were “designed for combined analysis,” this plan is not mentioned at all in either of the Methods sections of the initial publications. The reason why the trial of Nabholtz et al was stopped should be explained, because the circumstances imply that it was based on other than predetermined scientific criteria. This is of concern because the sponsor of both trials was also involved in a controversial decision to prematurely stop a large randomized trial in adjuvant colorectal cancer.9

Second, both studies are designed as equivalence trials to exclude with 95% confidence that tamoxifen has a 20% lower risk of progression or a 10% higher objective response (OR) rate than anastrozole. The rationale for choosing these thresholds is not stated. If tamoxifen had a 15% lower risk of progression or a 5% higher response rate, anastrozole could have been considered equivalent to tamoxifen using this design. However, under such conditions, most clinicians would consider anastrozole less effective and would not routinely use it. Equivalence trials require larger sample sizes because it is more difficult to prove two treatments are the same than to prove they are different. The lower confidence bounds chosen are generous, perhaps unrealistic, and suggest they were chosen for the convenience of smaller sample size rather than to prove reasonable clinical equivalence.

Third, two primary efficacy end points may be studied and reported, but only one can be used to determine the sample size of a study. Neither study reports which of the primary efficacy end points, time to progression (TTP) or OR rate, were used to determine the target sample size. Nabholtz et al report the method of sample size calculation, but not the actual target sample size required. The studies claim to be powered both for TTP and OR rate as primary efficacy end points, but unless the expected proportion of patients with measurable disease is considered in the sample size calculations, they run the risk of being underpowered for OR rate. All patients can progress, but only those with measurable disease can respond. This distinction is important, as vastly different sample sizes might be needed depending on the proportion of patients with measurable disease in the population studied. For example, Bonneterre et al had 87.9% of patients with measurable disease, and Nabholtz et al had 72.8%. If OR rate was the end point used to determine the sample size of 660 by Bonneterre et al, with an expectation that all had measurable disease, then both studies were relatively underpowered for comparing OR rates: Bonneterre et al by 91 patients, and Nabholtz et al by 247 patients.

Finally, by choosing two primary end points in two smaller trials (as opposed to one primary end point in one adequately powered larger trial), the probability of stopping a study prematurely due to a positive result occurring by chance alone is quadrupled.

By confirming the effectiveness of new therapies, large randomized trials are powerful tools for improving the health of cancer patients. They are also powerful tools for obtaining regulatory approval for drug marketing. Study end points, sample size estimates, the rationale for assumptions of equivalence, and stopping rules should have a sound scientific basis and be clearly articulated prior and in trial reports, to avoid the perception of decisions based on marketing expediency rather than scientific duty.

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REFERENCES

In Reply: Thank you for giving us the opportunity to respond to the queries of Winquist et al relating to the methodologies used in the anastrozole versus tamoxifen trials and the combined analysis. We agree with the authors that the results of these studies, in which anastrozole was shown to have superior efficacy and safety compared with tamoxifen in patients with hormone receptor–positive metastatic disease, have indeed influenced clinical practice.

In regards to the statistical calculations, the sample size of both trials was originally set at 660 patients per trial, based on the time to progression (TTP) end point. This also provided sufficient power to analyze objective response rate, including taking into account the proportion of patients with measurable disease recruited into the trial. As pointed out in the publication and noted by Winquist et al, both trials were prospectively planned for combined analysis. With a final recruitment of 1,021 patients across both trials (n = 668, Europe/rest of the world; n = 353, North America), this represents the largest clinical program of any aromatase inhibitor in the first-line treatment of advanced breast cancer in postmenopausal women.

The North American trial (0030) halted accrual with less than 660 patients because of difficulty in recruitment resulting from the strict entry criteria. This difficulty in enrolling patients in North America is not unique to the anastrozole versus tamoxifen trials. In the recently published trial of letrozole versus tamoxifen, of the 907 patients randomized, only 100 (11%) were recruited from North America; the majority of patients were recruited from Europe (n = 580, 64%) and the rest of the world (n = 227, 25%).

The decision to stop trial 0030 was made after consultation between the trial sponsors, the principal investigators of the trial, and the Food and Drug Administration. Subsequently, it was decided that trial 0030 could be stopped, with data still blinded, when the Europerest of the world trial reached the target recruitment of 660 patients. Given the superior result of TTP in trial 0030, which showed a much larger treatment difference than previously expected (median TTP was 11.1 months for anastrozole and 5.6 months for tamoxifen), a retrospective power calculation indicated that the power was sufficient based on the current recruitment.

The authors are correct in their comment that both trials were designed as noninferiority trials. This was clearly identified in both articles. However, trials designed to prove noninferiority can, in some cases, be used to demonstrate superiority based on the nature of the equivalence trial and the larger sample size included in such trials.

In summary, we believe the decision to halt accrual to trial 0030 was acceptable. Both trials 0027 and 0030 showed noninferiority to tamoxifen, with trial 0030 showing superiority for TTP and clinical benefit. The combined analysis showed that in receptor-positive patients, anastrozole was superior to tamoxifen in terms of TTP. Combined with the favorable tolerability profile, we feel that these data support anastrozole as a therapeutic option in first-line treatment of postmenopausal women with hormone-responsive advanced breast cancer.

Finally, we fully agree with the authors on the importance of large randomized trials. Further support for our data comes from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which enrolled more than 9,300 patients with early breast cancer who were candidates for adjuvant endocrine therapy. Recently released results from a planned analysis indicate that anastrozole prolonged disease-free survival (P = .013) compared with tamoxifen; in addition, there was a significant reduction (P = .007) in the incidence of contralateral breast cancer. Although further follow-up is required, these data suggest that the benefit observed with anastrozole for the treatment of advanced disease may also be seen in early breast cancer.

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REFERENCES


6. Committee for Proprietary Medicinal Products (Pan European Guideline), London, United Kingdom, Scientific Committee of the European Agency for Evaluation of Medicinal Products, July 2000
Eniluracil’s Need for a Targeted Approach: A Lesson in Drug Development

To the Editor: In the February 15, 2002, issue of the Journal of Clinical Oncology, Rivera et al1 reported a response rate of only 10% with a median survival of 40.4 weeks in patients with anthracycline- and taxane-resistant metastatic breast cancer. In the accompanying editorial, Robert Diasio2 comments that “it may be premature to dismiss a drug like eniluracil . . . which may have pharmacologic attributes that would prove useful in the future,” but he goes on to conclude that it is unlikely that eniluracil, uracil/tegafur, or S1 fluoropyrimidines will be used in the United States. In my opinion, such an outcome for fluoropyrimidines that possess dihydropyrimidine dehydrogenase (DPD) inhibition would be an unfortunate mistake for drug development and for a select group of patients who might benefit. Trials comparing eniluracil and fluorouracil (5-FU) with 5-FU and leucovorin in colorectal cancer patients showed no advantage for the DPD inhibitor, but the trial design suffered from taking a lowest-common-denominator approach to cancer. Consider, instead, that molecular analyses performed by Salonga et al3 reveal a striking heterogeneity with regard to susceptibility and resistance to 5-FU. Among a group of 33 patients, 12 had a favorable enzyme profile (ie, regarding thymidylate synthase [TS] and DPD expression levels), defined by a response rate of 92% and a median survival of 18 months. In the resistant group, in which no responses occurred and median survival was only approximately 6 months, patients did not respond either because of TS overexpression (30%) or because of DPD overexpression (18%) or both (12%). By extension, these observations could mean that only the group of 18% DPD overexpressors would derive benefit from an eniluracil/5-FU combination compared with 5-FU alone, either because 5-FU is already efficacious for some patients (29%) or because resistance driven by TS overexpression (57%) is not overcome by a pure DPD inhibitor.

Should a drug that can only help a minority of patients be evaluated in a trial that includes a majority for whom there will be no advantage to receiving the drug? Eniluracil was conceived as a molecularly targeted therapy but was taken into clinical trials without investigators bothering to evaluate patients’ potential molecular susceptibility. Plausibly, a drug like trastuzumab might have met with the same demise if it had been given to all breast cancer patients rather than only to HER2 overexpression group. On the other hand, there may be an unrealized hope for patients with a DPD overexpression phenotype, a far more compelling group for study with eniluracil rather than patients selected on the basis of resistance to anthracycline and taxanes alone.

Should we test the tissue specimens in Rivera et al’s trial1 with quantitative assays for TS and DPD levels? Until recently, such a question may have been impractical, but polymerase chain reaction–based technology is commercially available for paraffin-embedded tissues. A correlation between enzyme profile and susceptibility could outline a new strategy for DPD inhibitor development and extend the concept of molecularly targeted therapy to the design of chemotherapeutic regimens in general. Conceivably, DPD inhibition is a highly effective treatment strategy for 10% to 20% of patients with breast and colon cancers. It would be a loss for such a promising hypothesis not to have its legitimate day in clinical trials court for this select group.

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Cost-Effectiveness of Chemotherapy in Non–Small-Cell Lung Cancer

To the Editor: In the March 1, 2002, issue of the Journal of Clinical Oncology, Leigh et al1 determined the cost-effectiveness of chemotherapy in non–small-cell lung cancer (NSCLC). In Turkey, chemotherapy expenses are generally paid by state insurance organizations, but the costs remain a major issue, especially in light of our current economic crisis. This letter expresses our point of view with respect to second-line treatment of NSCLC.

The World Health Organization recently declared that, by the year 2005, 60% of cancer cases will be in global regions that have only 5% of the world economic resources to fight the disease.2 These areas include developing nations. In 2001, our economy experienced the sharpest recession in the history of the Turkish Republic, and annual per capita income fell from US $3,095 to US $2,160. The country’s gross national product also decreased in 2001, from US $201 billion to US $147 billion.3 Poor economic conditions and lack of financial resources are forcing the developing world to carefully analyze the cost-effectiveness of cancer treatments. In Turkey and throughout the world, lung cancer represents the largest proportion of cancer cases in both sexes.4 In NSCLC, a disease the world has labeled “the big killer,” second- and third-line chemotherapies are the most expensive steps of maintenance treatment.5 Leigh et al1 used docetaxel as a second-line chemotherapy drug in their trial on NSCLC patients and reported that the cost per year of life gained was US $37,749. The incremental survival benefit in the docetaxel arm over the trial arm that received optimum supportive care was only 2 months.6 Should we not be administering the most cost-effective treatment to these patients? At such high cost, just 2 months of life gain may not be of significant value. We agree that, ideally, medical treatment should not be governed by a country’s economic situation or an individual’s personal wealth. However, budgets for cancer treatment are extremely limited in developing countries, and efficacious second- or even third-line therapy for malignancy further increases the cost burden. Finally, in our opinion, it is more economical and effective for developing nations to focus on preventive measures, such as educating the public about the...
consequences of smoking, than to administer second- and third-line treatment for lung cancer.

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REFERENCES

2. Costa A: Will our planet be able to cope with the cancer burden in the next decade? Semin Oncol 28:140-142, 2001

In Reply: We agree with Drs Saglam et al and would certainly prefer to prevent or cure lung cancer rather than palliate our patients who have this disease. There is no argument that the eradication of tobacco use would bring us closer to decreasing the incidence of lung cancer and other tobacco-related diseases around the world.

When given as second-line palliative chemotherapy to fit patients with advanced non–small-cell lung cancer, docetaxel at the recommended dose of 75 mg/m² every 3 weeks yields a modest median survival improvement of 2.9 months over best supportive care (7.5 v 4.6 months, \( P = .01 \)). One-year survival in chemotherapy-treated patients in the TAX 317 randomized trial was 37% with the recommended dose of docetaxel, compared with 11% for those patients randomized to best supportive care alone. Palliative treatment with docetaxel was also associated with greater clinical benefit and with less need for pain medications and palliative radiotherapy. This improvement in palliative care for lung cancer yields modest benefits, similar to those achieved with first-line palliative chemotherapy in lung cancer. The intervention is suitable for a select, small population of fit, interested patients with advanced lung cancer who have received prior chemotherapy.

Our analysis estimates that the cost per year of life gained from this treatment is $31,776 (1999 Canadian dollars), at the recommended dose of 75 mg/m² every 3 weeks. This is in the range of cost-effectiveness for other health care expenditures, palliative or otherwise. Best supportive care is less expensive in the second-line setting, but it is inferior with respect to survival and clinical benefit. Improvements in palliative treatment should not lead to complacency in our efforts to prevent and/or cure lung cancer. Smoking-related illness results in billions of dollars of health care expenditure and lost productivity. Smoking cessation campaigns, although expected to yield cessation in only 1% to 2% of the smoking population, are important and must not be neglected as a component of primary prevention of cancer and other diseases. Smoking cessation strategies are also cost effective. In one study, physician counseling cost as little as $705 to $988 per year of life saved in men and $1,204 to $2,058 in women (1984 US dollars). Another study estimated the incremental cost-effectiveness of adding nicotine gum to counseling at $4,113 to $6,465 per year of life saved for men and $6,880 to $9,473 for women (1984 US dollars). Thus we agree that global eradication of tobacco use and smoking-related illnesses has the potential to yield substantial health benefits to many, as opposed to docetaxel’s modest palliative benefit to a few.

The rational allocation of health care resources to maximize society’s health benefits is a complex undertaking. Use of cost-effectiveness ratios alone to determine what interventions will be funded in a health system can lead to unsatisfactory results, as seen in the state of Oregon in the late 1980s. Interventions need to be evaluated against their alternatives, and their health effects need to be valued not just from the patient’s perspective but also from the community’s perspective. For example, a “life-year” gained in an older individual through palliative chemotherapy may not be as valuable to society as a life-year gained from a renal transplant in a younger individual, who is more likely to return to the workforce. Concepts of equity, community compassion, and the societal impact of adopting an intervention must also be considered. In the grading system put forth by Laupacis et al for the adoption and appropriate utilization of new technologies, palliative docetaxel would be graded as having moderate evidence for adoption, as it is more effective than supportive care alone but likely costs between US $20,000 to US $100,000 per quality of life-years gained. This may be compelling enough to adopt second-line docetaxel therapy in some countries, but not in others.

The decision to adopt this therapy or not, after reviewing the proven palliative benefit over supportive care, will rest on each country’s assessment of available funding, the patient and community perspectives, and competing programs.

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REFERENCES

7. Laupacis A, Feeny D, Detsky AS, et al: How attractive does a new technology have to be to warrant adoption and utilization?
Estrogen Receptor-Beta Expression in Hereditary Breast Cancer

To the Editor: The recent article by Lakhani et al3 provides solid data in favor of a distinctive morphologic and immunohistochemical profile of breast cancers from patients carrying mutations in BRCA1 gene and confirms previous results2 indicating a significant role of estrogen receptor (ER), in association with histologic grade and patient age, in predicting BRCA1 status. Based on risk estimates, the Lakhani et al4 exemplify that a 30- to 34-year-old woman presenting with ER-negative, histologic grade 3 breast cancer would have a 27% probability of harboring a BRCA1 mutation compared with the 5% probability observed for a woman with ER-positive tumor. This level of risk of carrying a BRCA1 mutation would justify the need of expensive genetic testing to be extended to family members and specific preventive interventions.

Standard recommendations for breast and ovarian cancer surveillance include annual mammography, two to four times annually clinical breast examination, biannual transvaginal ultrasound, serum CA-125 screening, and monthly breast self-examination. In addition, the more harsh procedures of prophylactic bilateral mastectomy and oophorectomy are effective risk reducers, but acceptance by women is obviously low. A recent study by Scheuer et al3 points to the poor effectiveness of prophylactic bilateral mastectomy and oophorectomy. Interestingly, tamoxifen seems to exert a greater benefit compared with the 5% probability of harboring a BRCA1 mutation observed for a woman with ER-negative tumor. This level of risk of carrying a BRCA1 mutation would justify the need of expensive genetic testing to be extended to family members and specific preventive interventions.

In an attempt to understand tamoxifen protective effect in BRCA1 mutation carriers and to further characterize hereditary breast tumors, we investigated whether hereditary breast cancers differ in the expression of the novel ER-ß subtype, involved in the modulation of the cellular response to estrogens and antiestrogens. The role of ER-ß in favoring the antagonistic effect of antiestrogens is supported by the association between protein expression and favorable outcome after tamoxifen treatment, recently demonstrated in an adjuvant setting6 and the dominant regulatory role of ER-ß in estrogen signaling,7,8 which would potentiate the antagonistic effects of tamoxifen. In addition, we observed a two- to four-fold upregulation of ER-ß mRNA compared with controls after 24- to 48-hour treatment with 10^{-8}M and 10^{-7}M tamoxifen in the hormone-dependent T47D cell line (data not shown).

We immunohistochemically evaluated ER-ß expression (using a polyclonal antibody developed by M. Younes9) in formalin-fixed, paraffin-embedded primary breast cancer specimens from 44 familial cases, including 28 mutation carriers (16 BRCA1 and 12 BRCA2) and 16 subjects negative to mutation testing (BRCA-X), and compared it with that of 90 nonfamilial breast cancer patients matched for age and year of initial diagnosis. ER-ß positivity (greater than 10% immunoreactive cells) was observed in 84% (37 of 44) of hereditary breast cancers compared with 69% (62 of 90) of nonfamilial tumors. In particular, positive staining for ER-ß was detectable in almost all (94%, or 15 of 16) BRCA1 tumors (BRCA1 v nonfamilial cancers, \( P = .06 \) by two-tailed Fisher’s exact test), in 75% (nine of 12) of BRCA2 tumors, and 81% (13 of 16) of BRCA-X cancers.

ER-ß has been described to act as a dominant negative regulator of ER-α-mediated transcription, thus attenuating massive estrogen stimulation.1 This regulatory role might be of utmost importance in the subset of BRCA1 mutation carriers because ER-ß could replace wild-type BRCA1 protein in controlling proliferative response after estrogen exposure.9 Our observation of a prevalent expression of ER-ß protein in BRCA1-associated tumors (which needs to be further validated) would explain the antiestrogen protective effect and its independence of oophorectomy. In fact, ER-ß would favor tamoxifen action by direct binding, even in the absence of ER-α, and by restoring the ability of cells (impaired for modulation of strong estrogenic exposure because BRCA1 mutated) to cope with stimulation by estrogens produced by peripheral aromatization even after oophorectomy. We thus suggest that ER-ß high expression could be an additional immunohistochemical characteristic of the BRCA1-mutated phenotype.

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REFERENCES

8. Hall JM, McDonnell DP: The estrogen receptor β-isofrom (ERβ) of the human estrogen receptor modulates ERα transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinol 140:5566-5578, 1999

In Reply: The letter to the editor by Daidone et al is intriguing and provides a possible biologic rationale for the use of hormonal therapy for breast cancer prevention in BRCA1 mutation carriers. In a recent report in the Journal of Clinical Oncology, we showed that a combination of intensive screening and “risk-reducing” surgeries led to the detection of early-stage breast and ovarian cancers in a series of 251 individuals with BRCA1 and BRCA2 mutations. Although these results were encouraging, they did not address the issue of chemoprevention in these patients.

Other published studies examining this issue have yielded conflicting results. A case-control series by Narod et al showed tamoxifen lowered contralateral breast cancer risk in both BRCA1 and BRCA2 mutations carriers. However, King et al did not demonstrate a benefit for tamoxifen chemoprevention in BRCA1 carriers participating in the National Surgical Adjuvant Breast and Bowel Project P-1 trial. A prospective series by our group and a retrospective series by Rebbeck et al both recently reported a significant reduction in subsequent breast and BRCA-related gynecologic cancers after risk-reducing oophorectomy in BRCA1 and BRCA2 mutation carriers.

However, neither of these series was powered to examine possible differences in risk-reducing between BRCA1 and BRCA2 mutation carriers. Studies such as those reported by Lakhani et al and Daidone et al will help to clarify the biologic mechanisms by which hormonal manipulation may alter breast cancer risk. These insights will provide the foundation for clinical trials of chemoprevention in women at highest hereditary risk for breast cancer.

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REFERENCES

Oxaliplatin: Bimonthly, Biweekly, or Semimonthly? No, Fortnightly!

To the Editor: Dr Pestalozzi raises an important point in the first June issue of the Journal of Clinical Oncology. The terms bimonthly and biweekly, rightly or wrongly and regardless of what is said in Webster’s dictionary, are interpreted in different ways by different English speakers and are, therefore, in practice, ambiguous. This is not just semantic curiosity, as it could potentially lead to four-fold overdosing. Even 2-weekly can cause confusion: I recently received page proofs of an article in which I had used this term in the abstract, only to find that the copy editor had corrected it (sic) to twice-weekly! But I’m afraid that Dr Pestalozzi’s proposal, that we should all use the term biweekly, although strictly correct, will simply perpetuate the confusion.

The solution, to native English speakers east of the Dana-Farber, seems pretty obvious. We have a perfectly good and unambiguous word in the English language, fortnight. It means 2 weeks. Fortnightly means occurring every 14 days, cannot be confused, and is understood by everyone over the age of 5.

At least, that’s what I thought. But I’m distressed to learn that this useful little word got left on the quay when the Mayflower’s gangplank was drawn up and, like some stranded marsupial, never made it into the gene pool of American English. Maybe this is why your holidays (sorry, vacations) are so short — it’s for the want of a neat way to tell them you’ll be away for...a fortnight. We’ve willingly embraced any number of useful words heading east over the Atlantic, and our language is richer as a result. So now here’s one in return, simple and long overdue but useful nonetheless. Enjoy!

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REFERENCE
ERRATUM

The April 1, 2002, article entitled by Hinton et al, entitled “Phase II Study of Paclitaxel Plus Gemcitabine in Refractory Germ Cell Tumors (E9897): A Trial of the Eastern Cooperative Oncology Group (J Clin Oncol 20:1859-1863, 2002), contained an error. Table 2, Nonhematologic Toxicities, was inadvertently omitted from the article. It is printed here, and the online version of the article has been corrected in departure from print.

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<td>50</td>
</tr>
<tr>
<td><strong>Other (except grade 2 alopecia)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>Full dose</td>
<td>Full dose</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>3-4</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Nausea and vomiting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>Full dose</td>
<td>Full dose</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>