CORRESPONDENCE

Irinotecan-Related Cholinergic Syndrome Induced by Coadministration of Oxaliplatin

Camptothecins are anticancer agents whose inhibition of topoisomerase I renders them non-cross-resistant with other common cytotoxic compounds (1–3). Promising results have been obtained with the two substances available at the moment, topotecan and irinotecan (CPT-11), in heavily pretreated patients with cancers usually resistant to second-line chemotherapy, such as small-cell lung cancer (4) or colorectal cancer (5). While both drugs share the mechanism involved in antitumor activity, CPT-11 requires metabolization to the active structure SN-38 (6) and displays a toxicity profile different from that of topotecan. Apart from its myelosuppressive properties, CPT-11 is characterized by a higher frequency of diarrhea as well as episodes of an acute cholinergic syndrome, including hypersalivation, abdominal cramps, and a drop in systemic blood pressure (7).

We report on a case in which a 53-year-old woman underwent chemotherapy in a phase II study with oxaliplatin combined with CPT-11 for colorectal cancer refractory to fluorouracil–leucovorin treatment. Therapy consisted of 85 mg/m² oxaliplatin given over a 2-hour period on days 1 and 15 followed by CPT-11 given over a 1-hour period at a dose of 80 mg/m² on days 1, 8, and 15. After uneventful administration of oxaliplatin, the patient complained of hypersalivation and abdominal pain along with a decreased blood pressure immediately after the first infusion of CPT-11. Symptoms promptly resolved after treatment with subcutaneous atropine. The patient experienced no side effects with the second dose of CPT-11 given as the only cytotoxic drug on day 8 according to the regimen. On day 15, however, symptoms promptly recurred during the infusion of the camptothecin analogue following oxaliplatin administration. After this second episode, the regimen was modified, and oxaliplatin was infused on days 1 and 14, while CPT-11 was given on days 2, 8, and 15. The second cycle of treatment with this split schedule was tolerated without any side effects. However, when we rechallenged our patient with the original schedule of both drugs given on the same day, symptoms compatible with a cholinergic syndrome were again experienced by our patient and were promptly abrogated by the administration of atropine.

We believe that the cholinergic syndrome attributable to CPT-11 was at least triggered by the coadministration of oxaliplatin in this case, since it was not seen with the application of CPT-11 alone. While the cholinergic syndrome has been described repeatedly with CPT-11, it has not been reported to be attributable to infusion of platinum compounds. Furthermore, a causative role of oxaliplatin alone in the development of these symptoms seems highly unlikely, since no side effects were seen with the application of oxaliplatin on days 1 and 14 during the second cycle, suggesting a potential interaction of both drugs in our patient. To our knowledge, this phenomenon has not been described before, and this patient was the only one out of 15 patients treated with this combination so far to develop this special form of cholinergic syndrome. Nevertheless, clinicians using similar treatment regimens should be aware of this potential drug interaction.

JULIA VALENCAK
MARKUS RADERER
GABRIELA V. KORNEK
MICHAEL H. L. HENJA
WERNER SCHEITHAUER

References


Notes

Affiliation of authors: Department of Internal Medicine I, Division of Oncology, University of Vienna, Austria.

Correspondence to: Julia Valencak, M.D., Department of Internal Medicine I, Division of Oncology, University of Vienna. Waehringer Guertel 18–20, A-1090, Vienna, Austria.

Re: Relationship Between the Size and Margin Status of Ductal Carcinoma In Situ of the Breast and Residual Disease

Silverstein (1) rightly criticizes Cheng et al. (2) for using the wrong denominator in their calculations of the proportions of patients with residual disease. As Silverstein points out, their inclusion of patients who had no additional surgery to document the absence of residual disease inappropriately dilutes their estimates. However, in addition, it also biases them. If the treating surgeons were less likely to perform additional surgery on patients with negative or close margins than on those with positive margins, the results obtained by Cheng et al. may be self-fulfilling prophecy: Residual disease was not expected; therefore, it was not looked for; therefore, it was not found. Even re-tabulation of their data by use of the correct denominator would be misleading, since the decision to perform further
surgery after the original lumpectomy may have been affected by prognostic factors not considered by the authors. If these unknown factors were distributed unequally among the different strata of margin status and tumor size, they could easily bias the results.

Of additional concern is that Cheng et al. have confused residual disease with local failure. These two problems are quite different, although the authors equate them. It is certainly not clear that all in situ carcinomas will progress to clinically evident disease, and we do not know what proportion will develop into invasive disease. There were 30 patients in the study who were found to have residual disease but only 10 who had local failure (half of them with invasive disease). Four of these 10 had positive margins, three had close margins, and three had negative margins. We are not told how the patients in each of these subsets were treated, other than the fact that none of them had a mastectomy. However, this sample size is too small to provide meaningful data, and the results could be biased by the retrospective nature of the study.

What makes the treatment of ductal carcinoma in situ controversial is that the results with mastectomy are so good; yet, given the success of conservative surgery for infiltrating carcinoma, many are concerned that mastectomy represents overtreatment. Cheng et al. do not resolve this conflict. Their intimation that untreated residual disease will always result in local failure may not hold. Margin status may be important in predicting residual disease, as Silverstein suggests, but what does it tell us about local relapse? We need data to answer this question.

Carl D. Atkins

References


Note

Correspondence to: Carl D. Atkins, M.D., 242 Merrick Rd., Rockville Centre, NY 11570.

Responses

We do not view Dr. Silverstein’s editorial comment as criticism of our data. Dr. Atkins’ misinterpretation of some of our data, as reflected in his statement, “There were 30 patients in this study who were found to have residual disease,” probably contributed to his confusion.

Residual disease was actually observed in the re-excision/mastectomy specimens of 66 patients. Although residual disease is defined as “persistence of DCIS [ductal carcinoma in situ] in the re-excision and/or mastectomy specimens,” recurrence of disease at the site of a previous lumpectomy is considered in our study to be an indication of local failure in patients without subsequent re-excision or mastectomy. We assume that residual disease is a marker of the potential for local failure. Hence, the prospective value of residual disease is equivalent to the retrospective value of disease recurrence in determining local failure. As reports of studies of the true “focality” of DCIS emerge, it is evident that many DCIS lesions, especially the high nuclear grade “comedo” types, are multifocal rather than multifocal, but rather extensive.

We therefore believe that disease recurrence and local failure are mostly related to, and can be attributed to, disease left behind following surgical excision. Hence, the recurrence of DCIS in lumpectomy-only patients, in our opinion, indicates residual disease left behind following lumpectomy rather than new disease. In the 84 patients who did not have subsequent re-excision or mastectomy, local recurrence is considered evidence of residual disease.

Silverstein is correct in commenting that the true incidence of residual disease would be 45% if the 84 patients who did not have subsequent excision or mastectomy were excluded. However, excluding these 84 patients would deprive us of valuable information regarding the natural history of conservatively treated DCIS. Furthermore, although a mastectomy implies removal of all breast tissue on that side, examples of recurrence of DCIS at mastectomy sites provide evidence that some breast tissue may be left behind in some patients following mastectomy. We believe that our data provide valuable insight into the success or failure of conservative surgery in treating DCIS. In 142 conservatively treated DCIS patients, only 10 (7%) had disease recurrence. Admittedly, the mean follow-up period of 49 months is probably too short to draw accurate conclusions about the overall recurrence rate of conservatively treated DCIS. Most importantly, these data provide evidence of the role of margin status in recurrences in these conservatively treated patients (seven patients had either positive or close margins). It is true that, at our stage of knowledge, we do not know if all or what proportion of in situ carcinoma will progress to invasive disease. Our study is probably a step in the right direction.

Liang Cheng

Nadia K. Al-Kaisi

Nahida H. Gordon

Alison Y. Liu

Fadi Gebrail

Robert R. Shenk

Notes

Affiliations of authors: L. Cheng, N. K. Al-Kaisi, F. Gebrail (Institute of Pathology), N. H. Gordon, A. Y. Liu (Department of Epidemiology and Biostatistics), R. R. Shenk (Department of Surgery), Case Western Reserve University and University Hospitals of Cleveland, OH.

Correspondence to: Nadia K. Al-Kaisi, M.D., Department of Pathology, University Hospitals of Cleveland, 11100 Euclid Ave., Cleveland, OH 44106–5000.

I thank Dr. Atkins for his response to my editorial (1) on the value of margins as one tries to completely excise ductal carcinoma in situ (DCIS). Dr. Atkins correctly comments that we do not know what proportion of DCIS lesions (if untreated or left behind) will ultimately progress to invasive breast cancer.

Page et al. (2) reported long-term follow-up on 28 patients with low-grade, non-comedo lesions considered benign on original evaluation. None of the patients received any treatment other than biopsy. These patients were accrued during the 1950s and 1960s, at a time when margins were not routinely marked. Some of the lesions may have been excised completely, and others were likely transected. There is really no way to tell. After an average follow-up

Journal of the National Cancer Institute, Vol. 90, No. 2, January 21, 1998
of almost 30 years, 42% of the patients developed invasive breast cancer, and 22% died of breast cancer (Kaplan-Meier analysis). When I first looked at these figures, I thought they were quite high. An epidemiologist told me that, considering the long follow-up period, they were relatively low. Regardless of which position one takes, the study by Page et al. clearly shows that not all patients with untreated DCIS go on to develop invasive breast cancer. If these patients had had high-grade lesions, one would expect the percentage of invasive breast cancer to be greater than those reported in this study, which consisted of only patients with low-grade DCIS (3,4), but it would certainly not reach 100%.

Dr. Atkin’s comments that the results with mastectomy are “so good” when compared with breast conservation. This is true when local recurrence is used as the endpoint of treatment failure. With mastectomy, one expects an extremely low local failure rate of approximately 1% (5). With breast conservation, depending on tumor size, margins, grade, etc., and on whether or not radiation therapy is used, local failure rates range from 10% to 40% (3,4,6,7). But if one uses the endpoint that really matters, breast cancer-specific mortality, no statistically significant difference by treatment has been reported by any group anywhere in the world. In the Van Nuys series, which consists of more than 700 patients, we have observed only five breast cancer deaths following a total of 73 local recurrences—an extremely low breast cancer-specific mortality. The mortality rate from breast cancer is so low in carefully followed DCIS patients that it will take an enormous prospective, randomized study to document any statistically significant differences based on treatment. Using our current data, I would estimate that the mortality rate after 10–15 years of follow-up would be approximately 1% for patients treated with mastectomy and approximately 4%–5% for patients treated with breast conservation (7).

Predicting local failure after breast conservation is difficult, but there are features that can be helpful. The size of the lesion and the adequacy of excision go hand in hand. The larger the lesion, the more difficult it is to adequately excise. The biology of the lesion is important: The more aggressive it is (higher grade), the more likely it is to recur and the more quickly it will probably recur. The genetics of the surrounding tissue may be important. Morphologically normal appearing tissue may already harbor the genetic changes necessary to develop DCIS or invasive disease at a later time. And, finally, treatment such as radiation therapy (and perhaps tamoxifen) is clearly important.

MELVIN J. SILVERSTEIN

References


Note

Correspondence to: Melvin J. Silverstein, M.D., The Van Nuys Breast Center, 14624 Sherman Way #600, Van Nuys, CA 91405. E-mail: melsilver9@aol.com

Ms. Napoli makes a serious error when she refers to “off-label” drug prescription as the use of drugs “in instances when efficacy is unproved” (1). The U.S. Food and Drug Administration (FDA) is not in the business of cataloging all of the “proven” uses of drugs. Its responsibility is to determine that a drug is safe and effective for at least one indication before it can be marketed by a pharmaceutical company. Labeled uses are merely those that the FDA allows the manufacturer to state as indications based on the information provided by the manufacturer. The FDA’s authority is limited to monitoring the marketing practices of pharmaceutical companies. It has always, appropriately, left decisions about the proper uses of approved drugs to clinicians.

Unfortunately, many third-party payers share Napoli’s view. They do not understand that, if a drug is proven to be useful for a new indication, its labeling will not change to reflect that, unless the manufacturer decides to go to the substantial expense of presenting evidence to the FDA to request it. Furthermore, there are many instances in which a drug can be reasonably expected to be useful even in the absence of “proof.” An example of this situation involves the treatment of rare cancers. Extrapolmonary small-cell carcinomas share biologic and clinical features with their pulmonary counterparts and are therefore widely recognized to be appropriately treated with similar drug regimens (2). Likewise, bile duct carcinomas are histogenetically similar to pancreatic cancer and might be expected to respond to treatments that are effective for the latter tumor. Yet both of these scenarios are so rare that they will never be subjected to evaluation by randomized, controlled trials. Furthermore, they would be unlikely to head any pharmaceutical company’s list of priorities for obtaining approval for FDA labeling.

When I prescribe a drug for a nonlabeled indication, it is always because of scientific evidence supporting its use. I have no qualms about using my judge-