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Reply

to Dr. P. Reichardt and Dr. D. Miles

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Before going into a detailed discussion, three points should be mentioned: First, the argumentation of the Letter to the Editor is highly biased, trying to focus the attention on a comparison with capecitabine. Our Review [Oncology 2003;64:191–206; references relevant to our Review and the Letter to the Editor by Drs. Reichardt and Miles are cited in alphabetical order in the reference list of this Reply] was designed to evaluate the efficacy of gemcitabine and not to provide an analysis of the whole spectrum of treatments possible. While capecitabine is undoubtedly effective in breast cancer, it is certainly not the only drug gemcitabine could be compared with. Moreover, a face-to-face comparison of gemcitabine and capecitabine has never been performed. A validating comparison of both agents should, therefore, be avoided at the present time. Second, as indicated in the text, our Review is based solely on results from phase II trials. While almost everybody would agree that such data being subject to various selection biases tend to give a more optimistic picture of drug efficacy, we also need to concede that the contrast may happen and a negative result may be reported. Phase II data should, therefore, be compared with great caution. However, in view of a large and consistent body of evidence, we maintain our conclusion that gemcitabine is an effective and well-tolerated agent in the treatment of metastatic breast cancer. Third, drug development, in our view, is meant to enlarge the choice of available drugs for the patient and not to open a scenario of competing agents.

The commentary by Drs. Reichardt and Miles makes several broad statements with little data to support their claims. As reported in the Review, gemcitabine has shown activity in nine well-designed single-agent trials conducted in patients with metastatic breast cancer (table 1 in the Review). These trials have included patients with varying types of prior therapy, with responses seen in all different settings. The trials selected for our Review include adequate patient numbers as well as have passed a peer review venue. We appreciate the thoroughness in mentioning two additional studies not included in our Review and will comment further on these studies.

The US study mentioned in the report by Carmichael and Walling [1996; ref. 3 in the Letter to the Editor] included only 15 evaluable patients, none of whom achieved a remission. The European trial also described in this publication observed a response rate of 25% (95% CI 12.7–41.2%) among 40 evaluable patients. The authors of this paper conclude that 'the reasons for this difference are far from clear, although patients were more heavily pretreated in the US study and these patients received a lower dose of chemotherapy'. The mean dose of gemcitabine in the US study was 565 mg/m^2, while it was 727 mg/m^2 in the European study. By today's standards, the US dose is certainly considered inadequate.

The higher toxicity noted in the US study may be explained by a more intensive pretreatment. The European trial described by Carmichael and Walling [1996; ref. 3 in the Letter to the Editor] allowed only one previous chemotherapy. In view of the more robust data based on 40 evaluable patients, the authors concluded that 'gemcitabine was extremely well tolerated in both studies, even in heavily pretreated patients' and went on stating that 'in view of its modest toxicity profile ... and its relative lack of myelotoxicity gemcitabine would be an ideal candidate for combination chemotherapy'. Due to the low patient number and the rather incomplete data available, we confirm the decision not to include the US study into the Review. Considering the inconsistencies between the data reported by Carmichael and Walling [1996; ref. 3 in the Letter to the Editor] and those quoted by Reichardt and Miles in their commentary, the question on their database needs to be raised.

With regard to the trial performed by Smorenburg et al. [2001; ref. 21 in the Review], this study examined 23 heavily pretreated patients with metastatic breast cancer who had failed on both an anthracycline- and taxane-containing regimen and found no responders. Visceral disease was observed in 74%, and 57% of the patients had three or more organ systems involved. Despite all but 3 patients received gemcitabine as third-line (or greater) treatment for metastatic disease, 26% of these patients reached stable disease with a median duration of 4.0 months. These data should be interpreted together with two other studies performed in anthracyline- and taxane-pretreated patients showing response rates of 16–23% [Brodowicz et al., 2000; Valerio et al., 2001 – refs.

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16 and 17 in the Review]. From these trials, it is evident that gemcitabine is active in anthracycline- and taxane-pretreated breast cancer patients.

The randomized trial comparing gemcitabine and epirubicin in elderly patients presented at the European Breast Cancer Conference in April 2002 [Feher et al., 2002; ref. 11 in the Letter to the Editor]was not included into the Review, since the manuscript had been finalized long before publication of these data. Adequate room for discussion will be found at due time together with other randomized trials now available for gemcitabine-based regimens.

The commentary by Reichardt and Miles recommends that 'until gemcitabine demonstrates sufficient activity to merit regulatory approval as treatment for metastatic breast cancer...', oncologists should continue to study the available data of gemcitabine. The author apparently failed to recognize that O'Shaughnessy et al. [2003; ref. added in this Reply] presented the registration trial of gemcitabine combined with paclitaxel as compared with paclitaxel as first-line treatment in patients with metastatic breast cancer at the ASCO Meeting 2003. This trial showed statistically significant improvements in overall response rate and time to progressive disease with a manageable toxicity profile for the gemcitabine/paclitaxel combination. The results of this trial have been a key component in the global registration of gemcitabine for the treatment of metastatic breast cancer. While gemcitabine had already been registered for breast cancer treatment in several European countries, registration has now been achieved also in Germany.

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