Cancer Chemother Pharmacol (1986) 17: 296–297

Cancer Chemotherapy and Pharmacology

Letter to the editors

Sir,

In the report of the south African study of Daniel A. Vorobiof et al., *Cancer Chemother Pharmacol* (1985) 15: 253–257, it was postulated that the cardiotoxicity of mitoxantrone (Mito) and epirubicin (Epi) were the same. This is not in accordance with the literature, and what is worse, it is not in line with the results of the study. In fact, the results show that epirubicin may have only half the toxicity of mitoxantrone.

The patients in the two groups are not scientifically comparable and the trial is not randomized. Nor are the groups equivalent clinically; for example, patient no. 9 in the Epi group already had a lowered LVEF of only 45% of normal at the start of therapy. This patient must be omitted, especially as the LVEF is not a linear function for which every percentage point is worth as much as any other: a reduction from 100% to 90% is not of the same importance as a reduction from 50% to 40%, even though the difference in both cases is 10%. A reduction from 20% to 10%, for example, means that the patient will die.

Hopefully by mere chance, a mistake has meant that four of the six Mito patients in whom the effect of LVEF reduction was shown had had varions doses of doxorubicin before the study. This makes the results very difficult to interpret. If, in spite of this, we proceed to calculate on indicated doses we find the following:

Assumption

Equipotential doses of mitoxantrone and doxorubicin are at a ratio of 1:5. With farmorubicin the same figure will apply for antitumor activity.

This assumption justifies conversion of all figures related to doxorubicin, by multiplying the Mito dose by 5.

Result

The total doses of Mito or Epi, converted to the equipotential quantity of doxorubicin for the nine or six patients respectively, who experienced a reduction of more than 10% in LVEF are given below:

Epirubicin

Median dose: 750 mg/m^2; range 224–1200 mg/m^2.

Mitoxantrone

Median dose: 208 mg/m^2; range 130–490 mg/m^2. If we take into consideration that four of the six Mito patients had already been treated with doxorubicin at doses ranging from 85 to 242 mg/m^2, and if we add these doses to the equipotential doxorubicin dose for the estimated mitoxantrone dose, then we find the following result:

Median dose: 412 mg/m^2; range 157–490 mg/m^2.

Conclusion

The Epi group has tested a median dose equivalent to 750 mg/m^2, compared with one equivalent to 412 mg/m^2 tested by the Mito group. The difference is significant. This means that in effect the authors gave the Epi patients a dose double that received by the Mito patients.

"The present study confirms these findings and, furthermore, shows that mitoxantrone is probably less cardiotoxic than 4'-epidoxorubicin at a therapeutic dose range when given for longer than 3 months."

The published study does not give any grounds at all for the above conclusion, which has now been tested in this analysis. A correct analysis on these data would reveal that farmorubicin is much less markedly cardiotoxic than mitoxantrone.

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Offprint requests to: O. Elison

Reply

Sir,

Thank you for the opportunity to reply to Dr Ove Elisson's comment on our publication "Assessment of ventricular function by radionuclide angiography in patients receiving 4'-epidoxorubicin and mitoxantrone" [6].

Nowhere in the article did we postulate "that the cardiotoxicity of mitoxantrone and epirubicin should be the same". Furthermore our report never stated that it was a randomized study. It was in fact first submitted as two separate articles, and it was on the suggestion of the jour-

nal reviewers that the two reports were combined, as both drugs were given at their optimal therapeutic doses. The conclusions drawn relative to cardiotoxicity are, we contend, valid in this context. Using the same criteria a major decrease (> 15% to a final level of ≤ 45%) in the LVEF values determined by radionuclide angiocardiography occurred in two patients receiving *m*-AMSA at doses > 580 mg/m^2, while a minor decrease was evident in one patient (who had previously been treated with doxorubicin) at a dose of 375 mg/m^2. On these data it was concluded that radionuclide ventriculography was of value in monitoring cardiac change in patients receiving *m*-AMSA [5]. In a series of patients with colon cancer treated with 4'-deoxydoxorubicin (esorubicin), 8 of 19 patients showed a fall of ≥ 10% in their LVEF [2].

Hematological toxicity is the usual dose-limiting toxicity for 4'-epidoxorubicin and mitoxantrone. It is of no practical value to compare equimolar doses of the agents [1]. At the usual full therapeutic dose, namely 90 mg/m^2 3-weekly, 4'-epidoxorubicin has caused greater changes in cardiac function, as measured by LVEF, than has mitoxantrone given at the dose of 9–14 mg/m^2 3-weekly in this series. It is clearly stated that dose modification in subsequent treatments was based on the measured white cell and/or platelet count nadirs.

Risk factors enhance the chances of cardiotoxicity [3]. None of the 4'-epidoxorubin-treated patients who had a significant fall in LVEF had risk factors, so that cardiotoxic effects can only be attributed to this drug. All the patients receiving mitoxantrone who had a significant fall in LVEF had risk factors. We never stated that there was a function of linearity in the fall of LVEF in patients receiving cardiotoxic drugs. We would like to refer Dr. Elisson to the review on the computer methodology for evaluating radionuclide ventricular function studies by Reiber [4]. There is no doubt that a fall from 100% to 90% is different from a fall from 20% to 10%, nor did we even imply any doubt.

No conclusions were drawn in our article about therapeutic range or therapeutic index, as our intention was simply to draw attention to the cardiotoxicity that we could document in patients receiving either of the two newer therapeutic agents. Cardiotoxicity has been shown to occur with treatment continued for longer than 3 months with either drug, and in our series this was more marked among patients receiving 4'-epidoxorubicin. The conclusions that we drew are not therefore invalidated in the proposed arithmetic solution, especially as this is based on an assumption that dose of a drug converted to the equivalent dose of another drug can be added to the converted "equivalent" dose of a third drug.

References

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