Cancer Chemother Pharmacol (1988) 21: 355

Cancer Chemotherapy and Pharmacology

Letter to the editors

In response to Vriesendorp et al. Prediction of normal tissue damage by cancer chemotherapy

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Dear Sirs,

I read with interest the review by Vriesendorp et al. [5], who argued that the practice of dose calculation based on body surface area (BSA) should be re-evaluated particularly in those cases where the dose-limiting toxicity is hematological, as the authors showed the haematopoetic stem cell (HSC) content in man to be better correlated with kg body weight.

My comments on their article involve firstly a semantic point on their use of the term secondary "staging" for the quantitative evaluation of dose-limiting normal tissues. Stage is a term which is usually applied only to geographical localisation of tumours before or after therapy rather than a measure of all pre-treatment prognostic factors. The authors state that primary staging in most tumours correlates with both the anatomical distribution of clonogenic tumour cells and their number. While this may hold in Hodgkin's disease, where the disease spreads in an ordered, predictable fashion, in many solid tumours, such as FIGO stage III ovarian carcinoma, where the tumour cell burden may vary from 10^8–10^{11} cells, the clinico-pathological stage may bear no relation to the bulk of the tumour. The current limitations of stage are that it is a snapshot of a process that is continually evolving with time, that in many cases it insufficiently correlates with bulk as shown where markers are available to relate cell number to prognosis [2], and that it needs to be taken in conjunction with the histological type or sub-type of disease to predict for outcome. In broad terms, it requires a qualitative as well as a quantitative element to give a more coherent assessment of prognosis.

Secondly, the authors have oversimplified the problem of prediction of normal tissue toxicity in dosage selection; they have extrapolated from the inter-species correlations of dose with kg body weight and the gross differences between neonates, children and adults to apply the same techniques to fine tuning of dose in adults. Their assumption is that the extent of inter-individual variation in normal tissue toxicity is largely due to differences in HSC number. They have disregarded the effect that the route and rapidity of excretion may have on AUC in the case of a drug such as carboplatin, where the dose-limiting normal tissue toxicity is myelosuppression; however, elimination is acutely dependent on the glomerular filtration rate, which has been proposed as the optimum baseline parameter for dose calculation [3]. Similarly for drugs such as cyclophosphamide, mitomycin C and etoposide, where microsomal metabolism plays an important part in both activation and detoxification, genetic polymorphism in oxidation or the acquired variation in enzyme activity due to age, induction or inhibition could contribute to variation in the concentration/time parameters of the active metabolites [1, 4].

Individualisation of drug dose and schedule will depend on typing not only of the individual tumour but also of the normal tissues in the same patient, which may limit the achievable dose by a variety of genetic and acquired mechanisms. The dynamics of drug handling by the normal tissue as well as the volume/number of HSC or "target areas" will limit the effective dose that can be given. At present we rely on averaged data from in vivo/in vitro phase II studies and crude normal tissue toxicity indices to determine the dose and schedule at which drugs are first introduced, and on retrospective dose modification to achieve an acceptable therapeutic ratio in practice. The authors were right to knock the BSA from the pedestal it has occupied for too long, but were overzealous in their enthusiasm to replace it by kg body weight.

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Received September 23, 1987/Accepted March 14, 1988