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Editorial Comment

Dose-adjusting epirubicin in patients with altered liver function: when classical pharmacology makes good practical sense

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At a time when the field of new drugs for cancer patients has never been more abundantly endowed of opportunities and resonant promises for targeted and tailored therapies, it is reassuring to read that classical pharmacology, far from being the mascot of old-fashioned laboratory zealots, is there alive and capable of improving our way of administering classical and still very fashionable chemotherapy. In an elegant work that today appears in the *European Journal of Cancer*, Dobbs and coworkers describe that the anthracycline epirubicin can be delivered to patients with liver dysfunction according to a novel scheme of dose adjustment that is based on considerations of drug disposition, route of elimination and relationship between plasma concentrations and side-effects [1].

The starting point of the systematic approach by Dobbs and coworkers is simple and reasonable. The liver is the organ mainly responsible for eliminating anthracyclines, so that liver dysfunction is associated with reduced drug clearance, increased plasma concentrations and increased toxicity. In view of this, the current recommendation that also appears in the data sheet of the manufacturer calls for adapting the dose of epirubicin to serum bilirubin that is taken as the most relevant indicator of altered drug excretion. Such recommendation for the classic anthracycline doxorubicin [2] and the newer analogue epirubicin [3] stems from work that goes back more than 20 years, but the issue on how best should doses of anthracyclines be adapted in patients with liver dysfunction remains unsettled and leads to variable prescribing attitudes in daily practice. Indeed, serum bilirubin is only weakly associated with epirubicin clearance and, in the past, Dobbs and coworkers had already clearly shown that a much better correlation exists between the drug elimination and the serum aspartate aminotransferase (AST) [4], suggesting that liver necrosis predicts better than cholestasis for impaired drug elimination from the body. The obvious subsequent step was that of using such information to devise a scheme for dose adjustment based on AST levels, and validating it in an independent cohort of patients. That is what Dobbs and coworkers did and they report their results in today's article [1].

Using prior pharmacokinetic information, they defined a target plasma exposure to epirubicin that would correspond to that expected after administration of standard doses of 60 or 90 mg/m^2 to patients without AST alterations. In a group of women with altered liver function, they defined the correspondence between AST levels and plasma exposure to epirubicin, and built a simple nomogram from which doses can be selected based on the serum transaminase level. After these two preliminary steps, they showed in a third group of patients with altered AST that the nomogram could be successfully applied to individually tailor the dose of epirubicin so that plasma exposure to the drug was consistently in the range of safe and active concentrations achievable with standard doses in patients with normal liver function. In this respect, the approach is very simple and analogous to that applied for dose adjustments of aminoglycoside antibiotics or, to stay within the field of anticancer chemotherapy, of carboplatin according to renal function [5]. Importantly, in the work of Dobbs and colleagues [1], none of the patients with liver dysfunction whose dose was adjusted based on AST levels experienced excessive toxicity, especially myelosuppression. This aspect pinpoints the

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major expected achievement of the strategy, because it is well established that a relationship exists between plasma epirubicin concentration and bone marrow toxicity [6]. The only serious reported event was an episode of myocardial infarction, a potential sub-acute toxicity of epirubicin that is unpredictable based on plasma concentrations. A second important aspect is that liver dysfunction was due to liver metastases in many patients. In some of them, the therapeutic effect of the first dose of epirubicin also caused an amelioration of AST levels. The nomogram was again used to adjust the dose to the new status of the liver function, resulting in dose increases in subsequent cycles capable of maintaining the drug concentrations at the desired level and avoiding under-dosing.

Should we change our habits, neglect the manufacturer's recommendations, and in view of its successful application adopt the new method of dose adjustment to all patients with liver dysfunction? The data of Dobbs and coworkers are convincing and based on sound background, but they also deserve some critical consideration and a word of caution. The authors stress the point that they could safely treat patients with AST alterations administering epirubicin every 3 weeks while achieving results similar to those described by other investigators with weekly low dose epirubicin in patients with similar liver alterations [7]. However, the authors themselves were concerned observing that the weekly dose intensity possible with their method was lower than that achieved by the empirical administration of a weekly dose, and view this as an indicator that their approach needs refinement. While the concern of improving their approach is understandable, the reason they offer is unclear, because the actual goal of dose tailoring that they propose is not that of achieving higher dose intensities, but uniform concentrations in spite of individual differences of drug disposition. In this respect, the problem is not that of achieving a lower or higher dose intensity than would empirically be possible, but that of consistently reaching optimal concentrations in terms of tolerability and therapeutic effect. The nomogram developed by Dobbs and coworkers can indeed only be as good as the data from which it was generated, and as generally applicable as those same data were representative of the overall population of patients with cancer and AST alterations. As such, the effort presented in this issue of *EJC* can be considered as a work in progress, but not because of dose intensity. The target exposure of their AST-based method was deduced from less than 20 'normal' patients receiving doses in the range of 25–120 mg/m^2 of epirubicin, and the nomogram was derived from only 16 women with altered AST who had received the drug weekly. In spite of such limitations, the scheme for dose adjustment was feasible and safe. Now that the approach has shown its validity, a more comprehensive and larger pharmacokinetic database should be used to propose a more robust and widely applicable nomogram for dose selection in patients with liver dysfunction. Dobbs and coworkers should be commended for having appraised the need for such improvements of their approach to give it a broad applicability.

The point will remain whether such an approach will also allow for obtaining better therapeutic results by eliminating a source of variability of plasma concentrations. A number of studies indicate that a relationship exists between anthracycline concentration and response [8]. In principle, there is little doubt that plasma exposure to adequate drug concentrations should be a determinant of antitumour activity. However, many confounding factors contribute to obscure such a relationship. Dobbs and coworkers propose that, after refinement, their scheme for dose adjustment should be tested in a randomised trial to measure the benefits of dosing modified by AST. The real limitation to this plan is that we have very little clue as to the 'optimal' concentration of epirubicin for antitumour activity. For that matter, knowledge of that kind is missing for almost all chemotherapeutic drugs commonly used in oncology, because the achievement of uniform plasma concentrations is only one of the many factors eventually determining the success of drug therapy, especially when the narrow therapeutic window of the agents forces their use at doses that are most likely sub-optimal for efficacy. Since epirubicin is already used at doses consistent with efficacy, the possible therapeutic advantage of a decreased variability of plasma concentrations may be too small to be proved in any randomised study of a reasonable sample size. However, definition of a final scheme for dose adjustment that was based on a larger database of patients and on additional variables, as Dobbs and coworkers are planning to do, should be immediately applicable and have the advantage to allow for safely administering epirubicin to patients every 3 weeks in the presence of liver alterations without the risks of occasional severe toxicity and possible inadequate exposure to the drug that are inherent to any empirical approach such as those currently available. Such an achievement is not of minor consequence because in the foreseeable future anthracyclines are here to stay as key drugs for treating cancer patients.

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