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Commentary

Improving the Therapeutic Index of Intra-arterial Cisplatin Chemotherapy

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(A COMMENT ON: Abe R, Akiyoski T, Koba F, Tsuji H, Baba T. 'Two-route chemotherapy' using intra-arterial cisplatin and intravenous sodium thiosulfate, its neutralizing agent, for hepatic malignancies. *Eur J Cancer Clin Oncol* 1988, **24**, 1671–1674.)

THE relative advantage (R_t) of an intra-arterial infusion, from the point of view of the tumor, is directly proportional to the plasma clearance of the drug used, and inversely proportional to the plasma flow to the tumor. This relationship is defined by Eq. (1) [1]

$$R_t = 1 + \frac{\text{(plasma clearance)}}{\text{(tumor plasma flow)}}. \qquad (1)$$

The greater the plasma clearance of the drug, and the smaller the tumor plasma flow, the larger the advantage of injecting the drug by the i.a. route. In the case of cisplatin infused into the common hepatic artery, R_t has been reported to average 1.9 ± 0.5 (± S.E.M.) [2]. In order to increase R_t one must either increase plasma clearance or decrease tumor blood flow.

In a previous issue of this Journal, Abe *et al.* report on a technique directed at the former of these two approaches. They infused 120 mg/m^2 of cisplatin over 3 min via the common hepatic artery into patients with tumors limited to the liver, and concurrently administered the cisplatin neutralizing agent sodium thiosulfate intravenously. The rationale for this approach has been outlined previously [2], and depends on the ability of thiosulfate to react covalently with cisplatin to form a product that is both non-toxic and devoid of antitumor activity [3]. All of the advantage of an i.a. infusion occurs with the first pass of the cisplatin through the tumor bed. Once the drug has entered the systemic circulation, it makes no difference whether it got there via the i.a. or the i.v. route. The hypothesis on which the approach of Abe *et al.* is based is that during the first 3 min the tumor will be exposed to an extraordinarily high cisplatin concentration (approx. 250 times higher than peak plasma concentration following standard i.v. dosing). However, once the cisplatin passes through the tumor and reaches the plasma it will be neutralized by the thiosulfate, and this will effectively increase the plasma clearance. Thus, the tumor will receive a very brief exposure to an extremely high concentration of cisplatin, and the exposure of the systemic circulation to active cisplatin will be reduced.

This approach is pharmacologically sound. Thiosulfate is a competitive antagonist of cisplatin, and its ability to neutralize cisplatin is a function of the concentration of both agents [3]. Thiosulfate is also not a very potent neutralizing agent, and thiosulfate/cisplatin molar ratios in excess of 10 are required before the reaction is fast enough to contribute significantly to the clearance of cisplatin [4]. Assuming that the tumor concentration of cisplatin was one eighth of the infused concentration during the 3 min injection, and that the thiosulfate concentration in the tumor was equivalent to the peak plasma concentration produced by a 9 g/m^2 injection (approximately 2.2 mM), the thiosulfate to cisplatin ratio in the tumor would be just 10:1, a ratio associated with a cisplatin neutralization half-life of just 60 min [4]. On the other hand, the ratio in the plasma shortly after injection would be expected to be greater than 250:1, a value associated with a neutralization half-life of 3.7 min [4]. Thus, even if thiosulfate were present in the tumor bed at the same concentration as in plasma during the first 3 min, the extremely high local concentration of cisplatin should result in little neutralization in the tumor relative to that taking place in

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the plasma. Likewise, it is clear that thiosulfate administration does in fact offer substantial protection to tissues in contact with the systemic circulation since the investigators were able to administer a total of 480 mg/m^2 in 4 weeks, whereas the maximum tolerated dose of cisplatin given weekly without thiosulfate is approx. 160 mg/m^2 in 4 weeks (or 120 mg/m^2 when given once in 3 weeks). Since there is little hepatic retention or inactivation of cisplatin [2], one can estimate that the thiosulfate protected the body against an amount equivalent to approximately two thirds of the administered cisplatin.

In fact, thiosulfate does not have to neutralize two thirds of the administered dose to achieve this degree of protection. Thiosulfate is extensively concentrated in the urine [5], so that the rate of inactivation in the kidneys can be expected to be substantially higher than that in the plasma. When the kidneys are protected against the toxicity of cisplatin, either with thiosulfate [6] or large volumes of saline [7], it turns out that the rest of the body will tolerate a doubling of cisplatin exposure. Thus the requirement that thiosulfate neutralize cisplatin in the plasma is reduced by virtue of the ability of thiosulfate to selectively protect the kidneys.

In principle, one could further improve the therapeutic index of this approach by increasing the dose of both cisplatin and thiosulfate even more. As long as sufficiently large doses of thiosulfate can be given to accomplish the needed systemic neutralization, the dose of cisplatin could be escalated to the limit of solubility. When 120 mg/m^2 of cisplatin is dissolved in 400 ml of saline, in a 1.7 m^2 patient the infused concentration of 0.51 mg/ml is approximately half the solubility limit of cisplatin. Thiosulfate can be administered in bolus doses exceeding 29 g/m^2 [8], and thus a doubling of both cisplatin and thiosulfate doses is potentially possible.

The report by Abe *et al.* establishes that the i.a. cisplatin/i.v. thiosulfate regimen can be administered on a weekly schedule, and that this schedule permits delivery of a very high cisplatin dose rate. It does not clearly define how long this weekly dosing regimen can be continued; it is difficult to determine from the data presented whether myelosuppression was cumulative with serial dosing. The report does not define the maximum tolerated dose, the dose-limiting toxicity, nor the reason why therapy was discontinued in responding patients. In addition, no conclusions can be drawn as to the efficacy of this regimen except to say that at least some antitumor activity was retained. The partial response rate of hepatocellular carcinoma to single agent cisplatin administered without thiosulfate has been reported to be 40% in a group of 10 patients [9], which is similar to the partial response rate of 45% observed in the Abe trial. Nevertheless, this approach does have the potential of substantially increasing the therapeutic index of i.a. cisplatin therapy, and in another report on the use of the i.a. cisplatin/i.v. thiosulfate regimen a partial response rate of 55% was found in a group of 33 patients with hepatocellular carcinoma [10]. These studies should serve to excite interest in conducting the phase I/pharmacologic studies necessary to define the maximum tolerated doses and extent of neutralization actually taking place.

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