Eur J Cancer Clin Oncol, Vol. 22, No. 8, pp. 905–907, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Perspectives and Commentaries

Minimising the Organ Toxic Effects of Chemotherapy

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(A COMMENT ON: Jones MS, Murrell RD, Shaw IC. Excretion of sodium 2-mercaptoethanesulphonic acid (MESNA) in the urine of volunteers after oral dosing. *Eur J Cancer Clin Oncol* 1985, **21**, 553–555.)

SUCCESSFUL chemotherapeutic approaches to cancer rely predominantly on the ability of antitumour drugs to destroy all cancer cells in the host. This has been achieved for certain types of cancer, but at doses which are also highly toxic to normal tissues. Some host toxicities such as myelosuppression and nausea and vomiting are clinically acceptable as they can be manageable. However, cumulative and irreversible damage to certain vital organs, such as the liver, kidney, heart or lung, raises concern and hinders chemotherapy. Continual therapy with bleomycin, adriamycin or cisplatin, for instance, results in life-threatening pulmonary, cardiac or renal failure respectively, and treatment may discontinue despite favourable antitumour response.

To reduce or obviate host toxicity, a variety of manoeuvres has been explored. The success of these manoeuvres, however, depends largely on exploiting the drug's known chemical, biochemical or pharmacokinetic property which is specifically responsible for the side-effect and which preferably is unrelated to the mode of antitumour action of the compound. Where reduction in host toxicity has been possible, this has been achieved mainly through developing less toxic analogues, optimising the treatment schedule or including in the treatment protocol compounds (antidotes, 'rescue' agents, etc.) which protect the target organ.

Analogue development necessitates structural changes to the parent molecule and, through structure-activity studies, analogues with reduced toxicities in the animal model are selected for preclinical and clinical developments. Although predictions of lower toxicity, such as myelosuppression of marcellomycin [1], may not be borne out clinically, this strategy has, nevertheless, identified a limited number of clinically viable analogues. These include Carboplatin [2], epirubicin [3] and trihydroxymethyl-trimethylmelamine [4], which are respectively less toxic analogues of the nephrotoxic cisplatin, cardiotoxic adriamycin and the highly emetic pentamethylmelamine. Animal studies indicate that the differential nephrotoxicity between cisplatin and Carboplatin may be directly related to the extent of active tubular involvement in their renal clearances [5]. The attenuated cardiotoxicity of epirubicin, on the other hand, has been ascribed to reduced formation of free radicals in the myocardium [6], whilst the reduced emetic activity of the pentamethylmelamine analogue has been attributed to the lower brain penetration of this new compound [4].

A distinct disadvantage of analogue development is the extremely long time taken between synthesis and clinical evaluation. Taking Carboplatin as an example, this antitumour agent was initially synthesised in 1971 (Cleare MJ, personal communication) but it was not until 1980 that its potential was first identified by Harrap and his co-workers [7]. Thus, the need to improve therapeutic indices of existing antitumour drugs by reducing or abolishing their toxicity is unequivocal. This provides an important basis for determining pharmacokinetics during phase I studies, as an understanding of this property together with the pharmacodynamic property of the drug may prove useful in minimising the side-effects by optimising the treatment schedule. Such understandings have indeed been critical in successful clinical applications of adriamycin. Thus, decreasing peak plasma levels of adriamycin by switching from single bolus schedules to ones incorporating split doses or continuous infusion of the drug has markedly reduced the incidence of cardiotoxicity and, significantly, without compromising the antitumour activity [8]. Similar avoidance of high

Accepted 18 November 1985.

plasma 5-fluorouracil concentrations has also resulted in a decreased incidence of its toxicity, namely myelosuppression [8].

Further illustrations of improvements in therapeutic indices through modifications of treatment schedules can be made with cisplatin and with a combination schedule for Hodgkin's disease. In the case of cisplatin, incorporating a hydration scheme in the treatment protocol has substantially reduced severe drug-induced nephrotoxicity and, thereby, has enabled the clinical use of cisplatin to flourish [9]. Combining hydration with continuous infusion further reduces the toxicity of this drug, without affecting the response rate [9]. In the treatment of Hodgkin's disease, the curative combination of mustine, vincristine, procarbazine and prednisone has been radically modified by replacing mustine and vincristine with chlorambucil and vinblastine, without any loss of treatment benefits [10]. The advantage of the new combination, however, is a clear reduction in nausea and vomiting, phlebitis and neurotoxicity.

Although optimal scheduling is a main pillar of cancer chemotherapy, it may cause great inconvenience when daily, weekly or continuous infusion schedules are considered. The continual aim, therefore, is to reduce the duration and frequency of drug administration especially when response rates appear to be schedule independent. Toxicity considerations, however, may prevent clinicians from achieving this aim. In some cases, life-threatening toxicity of the drug may prevent its clinical acceptance altogether. These considerations have led to identification of compounds, the so-called antidotes, which prevent or reverse the toxic effects and have, at the most, minimal effects on the antitumour activity of the cytotoxic drug. This is the main strategy in using mesna, for instance, to prevent both haemorrhagic cystitis and bladder tumours following oxazaphosphorine administration [11]. Mesna protects by inactivating acrolein, a product of oxazaphosphorine metabolism. Although haemorrhagic cystitis is prevented with concurrent use of mesna intravenously, this route of administration on a long-term basis to prevent any possible appearance of bladder tumours is not practicable. Oral administration of mesna, on the other hand, may make this feasible if its pharmacokinetics appear suitable. This forms the basis for the paper by Jones *et al.*, who conclude that "oral administration of mesna might find application in the prophylaxis of the putative bladder damage associated with oxazaphosphorine metabolites". Clinical demonstration of protection of the bladder by oral mesna, however, was not discussed by these authors, but has been documented elsewhere [12]. This 'antidote' approach is not restricted to mesna and oxazaphosphorine combinations. Indeed, another thiol derivative, *N*-acetylcysteine, has also been effective, possibly through a mechanism similar to mesna, in preventing the urotoxicity of ifosfamide [13]. The strong chemical interaction between thiosulphate and cisplatin has been exploited recently to provide protection from cisplatin-induced systemic toxicity following intraperitoneal administration of the oncolytic agent [9]. The nephrotoxicity of cisplatin has also been controlled through concurrent use of diuretics, such as mannitol and furosemide [9].

The use of high dose methotrexate in the clinic emphasises the value of antidotes, or 'rescue' agents. Leucovorin (5-formyltetrahydrofolate), for instance, can selectively reverse the toxicity of methotrexate in normal cells and reduce the side-effects [14]. The mechanism of this selectivity is not entirely clear and may involve a combination of pharmacological and biochemical events.

Perhaps the most widely used protective agents are the anti-emetics in attempts to minimise the gastrointestinal toxicity. Emesis is common with anticancer agents and, in some cases, results in patients refusing further courses of chemotherapy. Anti-emetics, such as metoclopramide and prochlorperazine, have significantly increased patient compliance and, therefore, have been invaluable in cancer chemotherapy [15].

This commentary has focused on examples which are clinically proven in terms of reducing the toxic effects of anticancer compounds. However, many other attempts to reduce the toxicity of a wide range of antitumour drugs have failed despite sound rationale and successful preclinical testing. Nevertheless, efforts continue to be directed toward identifying more potent and less toxic alternatives to existing chemotherapeutic approaches, and thereby provide oncologists with opportunities for greater success in cancer chemotherapy.

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