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Letter/Reply to the editors

Letter in response to paper by Abratt et al., Cancer Chemother Pharmacol (1992) 30: 495

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Sir,

In their study evaluating concurrent irradiation and cisplatin in non-small-cell lung cancer, Abratt et al. [1] elected to administer cisplatin 24 h before irradiation in order to exploit any possible differences in the repair capacity of normal and tumour tissue. In doing so, they ignored extensive preclinical data (available before their study commenced) which strongly suggested that the supra-additive effect of combined cisplatin and irradiation is schedule dependant [2, 6, 11, 14]. The clinical importance of scheduling has been confirmed in a large EORTC study where significant survival improvements over that achieved by radiotherapy alone were seen only when daily cisplatin was administered immediately before irradiation [13].

Whilst the exact mechanism of interaction remains unclear, impairment of repair processes by cisplatin is unlikely to be of major significance. Cisplatin administered half an hour before a course of fractionated radiotherapy has been shown to potentiate tumour cell kill in vivo in the absence of any repair inhibition [3]. Recent work, however, suggests that tumour reoxygenation may play a more important role in cisplatin-induced enhanced tumour cell kill.

Acutely developing hypoxia has been shown to develop in tumours as a result of dynamic fluctuations in tumour blood flow [4] and radiation-induced cell kill is decreased by a factor of between 2–3 in hypoxic tissue [12]. Nicotinamide has been shown to decrease acute hypoxia in tumours by decreasing transient fluctuations in blood flow [9]. If administered to tumour-bearing mice between 30 min and 2 hours before radiation, nicotinamide increases radiation cell kill by up to a factor of 1.7 [10]. Nicotinamide does not kill or chemically radiosensitize tumour or normal tissue in vitro [9] and no sensitization is seen if in vivo administration occurs after irradiation [10].

There are interesting similarities between the actions of nicotinamide and cisplatin. In human tumour cell lines showing varying sensitivity to cisplatin, combined treatment produced only additive effects and no sequence-dependant difference in efficacy [8]. Indirect evidence for a cisplatin-induced increase in tumour oxygenation has come from 2 studies. The greatest dose enhancement during combined treatment was seen when drug exposure preceded irradiation of tumour-bearing animals breathing a reduced oxygen atmosphere [15]. In addition, paired survival curve data showed the hypoxic fraction of cisplatin treated tumours to be lowest at between half to 2 h post treatment [7]. More direct evidence for reoxygenation is the increase in tumour blood flow observed in murine sarcomas which persists for 30 min after cisplatin [5].

These findings suggest that the combination of irradiation with agents which increase tumour blood flow can result in improved local tumour control. The timing of tumour reoxygenation varies with different chemotherapeutic agents [7] and this needs to be studied further and taken into account in the scheduling of treatments with concommitant irradiation.

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Reply to letter by Dr. S. Senan

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Sir,

Dr. Senan has raised some interesting points and I thank him for them. He is concerned that earlier work was ignored but I would note that the studies to which he refers, were cited in the article.

He may have misinterpreted the purpose of our study which was to investigate in humans with lung cancer, whether a therapeutic advantage could be obtained on the basis that repair of damage induced by either of the cytotoxic agents may be slower in tumours. This has been well documented. In 1 study of various regimens, the weekly administration of cisplatin 24 h prior fractionated radiation was found to be optimal [1].

Dr. Senan's interesting suggestion that increased tumour reoxygenation can result in improved local tumour control should be treated with caution. The data refers to in vitro and mouse work and it has recently been pointed out in reference to carbogen and nicotinamide, the clinical experience is unlikely to be as dramatic as that seen with rodant tumour [2].

The interaction of cisplatin and radiation is complex and there are many avenues of valid research.

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