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Editorial Comment

Rationale for drug combinations

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No reader of this journal needs to be reminded that real progress in the treatment of solid tumours is hard to achieve. The explosion of scientific knowledge about the metabolism of tumours and the genetic influences that promote or restrict growth will it is hoped lead to the more rationale design of therapeutics, which in future will be more selective and more beneficial than existing drugs. Studying the mechanism of action of anticancer drugs is not an intellectual exercise in its own right, but has value in optimising drug design for the generation of improved analogues, in understanding why different cancers respond differently to the same compound, and how to combine drugs most effectively together.

The concept of using drugs in combination, now 40 years old, is based on the premise that drugs with different mechanisms of action will cause a greater metabolic disruption if the tumour cell is exposed to simultaneous attack rather than is the case if used sequentially or on their own. The optimum deployment of this strategy requires true knowledge of the mechanism of action of the drugs and this is often incomplete.

In this issue, D'Incalci and colleagues present exciting results exploring this concept with the combination of a well-characterised drug cisplatin (DDP) combined with a new—partially characterised—natural compound, Yondelis (ET743) [1]. Yondelis is a tetrahydroisoquinoline alkaloid isolated from the marine ascidian *Ecteinascidia turbinata*. This natural product has attracted great interest recently as a result of a large phase I/II programme, where responses have been seen in a variety of solid tumours, most notably sarcomas and ovarian cancer [2,3]. Its mechanism of action includes formation of monoadducts of Yondelis at the N2 position of guanine, in the minor groove, whereas DDP binds at the N7 position of guanine, in the major groove of DNA. As with many DNA interacting drugs, Yondelis alters the cell cycle causing a delay in the transition from G_1 to G_2, inhibition of DNA synthesis and a marked blockade in G_2M which is p53-independent. An apparently unique feature of the cell cycle effects of Yondelis is the phase specificity, where cells in G_1 are the most sensitive [4]. Studies of drug resistance are often informative about the mechanism of action and it is of note that whilst cell lines deficient in mis-match repair are partially resistant to DDP, they are nevertheless sensitive to Yondelis [5]. Cell lines deficient in nucleotide excision repair are exquisitely sensitive to DDP, but partially resistant to Yondelis. This contrasting sensitivity of Yondelis and DDP in cells with different abilities to repair DNA damage was the starting point for hypothesising that the two drugs could be advantageously combined.

D'Incalci and his colleagues have investigated various combinations of these two drugs in a panel of human tumour xenografts including sarcomas, neuroblastoma, head and neck, lung, melanoma and ovarian carcinomas. The combination of Yondelis and DDP had a strongly synergistic activity in vivo and it was possible to use both drugs at full dosage with only a small increase in toxicity. Platinum-based therapy remains the basis of chemotherapy for ovarian cancer. Early clinical results with Yondelis in ovarian cancer are highly promising. At the ESMO Congress in 2002, Sessa and her colleagues presented data on the use of Yondelis as second-line treatment in patents previously treated with platinum and taxanes [6]. Partial responses of approximately 40% were seen in patients resistant to carboplatin, DDP and paclitaxel. These early results clearly deserve further investigations and phase I studies of the combination of Yondelis and cisplatin are now in progress.

It would be of interest to see the xenograft experiments extended to carboplatin as a more widely used platinum drug than DDP. The further evaluation of the combination of Yondelis with platinum drugs is awaited with great interest.

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