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Questions and Answers

Question: It appears that multiple mechanisms of resistance may operate in any given system; on this basis, combination therapy obviously has potential (and is already used clinically). Are there any relevant preclinical studies of combination therapy as a means of overcoming resistance? If so, has additive or synergistic activity been demonstrated for combination therapy versus monotherapy?

Dr L.R. Kelland: Synergy is acknowledged to occur between platinum analogues and both etoposide and 5-fluorouracil. In addition, a different type of synergy has been discovered between carboplatin and paclitaxel in that the latter drug appears to ameliorate the thrombocytopenia that is normally dose-limiting for carboplatin such that the combination can be given at full dose every 3 weeks instead of every 4 weeks in the case of single agent carboplatin. Preclinically, synergy has also been demonstrated between cisplatin and gemcitabine. Tumour xenograft studies in mice (and, to a much lesser extent, *in vitro* studies using cell lines) may be useful in guiding clinical combination studies.

Question: Is anything known about the structure of the adducts formed by some of the newer drugs designed to overcome resistance (i.e. are they similar to or different from those formed by cisplatin or carboplatin)?

Dr Kelland: The preferred DNA sequences associated with the binding of ZD0473 are different from those of cisplatin and carboplatin. In the case of BBR3464, the adducts themselves are structurally different in that they span a greater length of DNA and do not cause the same degree of distortion in the DNA molecule, a factor that may lead to a reduced ability to recognise and remove such adducts.

Question: Cisplatin, carboplatin and oxaliplatin may be the established drugs, but would you envisage a scenario (similar to that in HIV infection) where there will eventually be numerous clinically available platinum drugs with varying mechanisms of action and means of overcoming resistance, and where patients will switch regimens relatively frequently as resistance develops?

Prof. G. Giaccone: Theoretically, it is possible to envisage several different platinum analogues with different mechanisms of action and resistance which do not result in cross-resistance. This is so far partially true for oxaliplatin compared with cisplatin and carboplatin, but the latter 2 compounds have very similar activities and mechanisms of drug resistance. If a lower potential for cross-resistance can be demonstrated with newer platinum derivatives, it may become attractive to switch these drugs in order to prevent development of drug resistance or when progression occurs. One could also envisage their use in combination, especially in the case of non-overlapping toxicity profiles.

Question: You have indicated that high dose regimens have been used in a number of settings, but the clinical evidence regarding a dose-response relationship appears limited and equivocal; can you comment on this (is there any definitive evidence from preclinical or clinical studies that higher doses are generally more effective?)

Prof. Giaccone: In preclinical models there is a clear dose-response relationship for most anticancer agents, including the platinum compounds and the alkylators. However, the dose-response relationship is followed by a plateau at which an increased dose does not correspond to an increased benefit. For platinum compounds this may well be the case at the doses commonly used in the clinic.

However, the major limitation to increasing the dose of drugs such as the platinum compounds, even in the presence of bone marrow rescue, is the development of life-threatening nonhaematological toxicities, which seriously limits the escalation of doses to only 2- to 3-fold.

Question: Which of the issues highlighted in your article do you think may be most significant from clinical and patient perspectives (e.g. tolerability issues, oral administration, combination regimens)?

Dr I. Judson: The altered spectrum of antitumour activity as exemplified by oxaliplatin is probably the most important advance. It is possible that ZD0473 and BBR3464 may also display similar properties. Oral delivery appears possible but has yet to be of proven value.

Question: The new approaches and developments of recent years are described in your article; can you speculate on possible future research directions?

Dr Judson: The trinuclear molecule BBR3464 may represent a new type of agent with different binding properties and reduced susceptibility to resistance. If this drug is successful in clinical trials, further developments are likely.