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Comments and Critique

Clinical Reversal of the Multidrug Resistance Phenotype: True Tumour Modulation or Pharmacokinetic Interaction?

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INTRODUCTION

THE MULTIDRUG resistance (MDR)-1/p-glycoprotein story is one of the most elegant in cancer research. Identification of a membrane protein which confers resistance to cytotoxic effects of a number of structurally unrelated natural products has led to great activity in anticancer pharmacology and therapeutics. The *in vitro* evidence from human tumour cell lines and MDR-1 gene transfection studies displays the increased drug efflux and decreased sensitivity resulting from p-glycoprotein expression [1]. In addition, retrospective clinical studies have shown an association between tumour expression of p-glycoprotein and a poor prognosis [1]. The mechanism of resistance, i.e. altered drug efflux resulting in decreased intracellular drug concentrations, and the apparent prognostic influence then led to strategies for reversing the effects of p-glycoprotein.

A large number of compounds are able to reverse the multi drug-resistant (MDR) phenotype *in vitro* through competitive inhibition of drug efflux. These include calcium channel antagonists, cyclosporin, calmodulin inhibitors, antimalarials, steroids and miscellaneous other drugs (as reviewed in [2, 3]). The *in vitro* data with such inhibitors demonstrate alteration of anticancer drug efflux, surrogate dye accumulation (e.g. rhodamine-123) and photo-affinity binding to p-glycoprotein. Modulation of drug activity has also been observed in p-glycoprotein-expressing xenograft models [4, 5], leading to enthusiastic support of clinical trials in humans.

The clinical experience with reversal of multidrug resistance is now beginning to accumulate for calcium channel antagonists (e.g. verapamil, bepridil, dexniguldipine), cyclosporin and its analogues (e.g. SDZ PSC 833) and other miscellaneous agents (e.g. tamoxifen, progesterone, cefoperazone, fluphenazine, quinine). Initial phase I/II trials, combining conventional chemotherapy with a MDR reversing agent, have had mixed results, with some responses noted in refractory patients with leukaemia, myeloma and soft tissue sarcomas [2]. While these clinical trials of MDR reversing agents have shown activity, the basis for this effect has come into question.

A series of elegant studies, performed by Sikic, Lum and colleagues at Stanford University, U.S.A. [5], has given insights into the mechanisms behind the activity observed in these clinical trials. In their trials, patients first received single agent chemotherapy, without MDR modulation, until clinical resistance was confirmed. The patients then received the same agent with simultaneous cyclosporin. This design assured 'resistant' tumour and determined modulator-induced changes in chemotherapy pharmacokinetics and pharmacodynamics within an individual patient. Cyclosporin increased etoposide area under the plasma concentration–time curve (AUC) 1.8-fold, doxorubicin AUC 1.55-fold, and its metabolite doxorubicinol 3.5-fold [6, 7]. Both renal and non-renal (e.g. hepatic) elimination of both drugs was altered by cyclosporin. As increased haematological toxicity was observed when cyclosporin was added to both etoposide and doxorubicin therapy, pharmacodynamic analysis was used to determine whether a change in bone marrow sensitivity had occurred or if a pharmacokinetic interaction had taken place. Sigmoidal maximum effect and exponential models were used to find the relationship between cytotoxic systemic exposure (e.g. AUC) and effect (e.g. % change in WBC). While the decrease in WBC was inversely related to the AUC of etoposide and doxorubicin, neither drug displayed a shift in the systemic exposure–response curve when combined with cyclosporin therapy [7, 8], demonstrating that the increased effect was secondary to an increased AUC and not 'modulated' response. Pharmacokinetic alterations have also been observed in further cyclosporin MDR modulation trials with decreased anthracycline clearance and increased systemic exposure, compared with previous literature values for patients, in patients receiving non-modulated therapy [9–11]. Preliminary mouse and human studies with a non-immunosuppressive cyclosporin SDZ PSC 833, show similar alterations in etoposide and doxorubicin disposition [4, 12, 13]. Although modulation trials utilising verapamil or other calcium channel antagonists have also been performed, few have included pharmacological evaluation. Verapamil has been shown to increase daunomycin and vincristine systemic exposure in the rat and mouse, respectively

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[14, 15], and lead to a 2-fold increase in doxorubicin AUC in a small human series [16]. Information on pharmacokinetic interactions with other MDR modulators is currently not well developed.

MORE IS BETTER VERSUS ALTERED TUMOUR RESPONSE

Possible mechanisms for the activity of modulator therapy in early clinical trials include pharmacokinetic modulation and tumour modulation (Figure 1). If true tumour modulation occurs, the level of effect (toxicity, tumour regression) will increase at a given level of systemic exposure, secondary to a shift in the effect curve (e.g. response rate will increase from 20% for drug alone to 80% for drug plus modulator, with no change in the plasma AUC; Figure 1b). This is in contrast to the observed data from Stanford University for cyclosporin plus etoposide or doxorubicin, where systemic exposure increased but no change in the response curve occurred (e.g. plasma AUC increased from 2 for drug alone to 4 for drug plus modulator, leading to an increase in effect; Figure 1a).

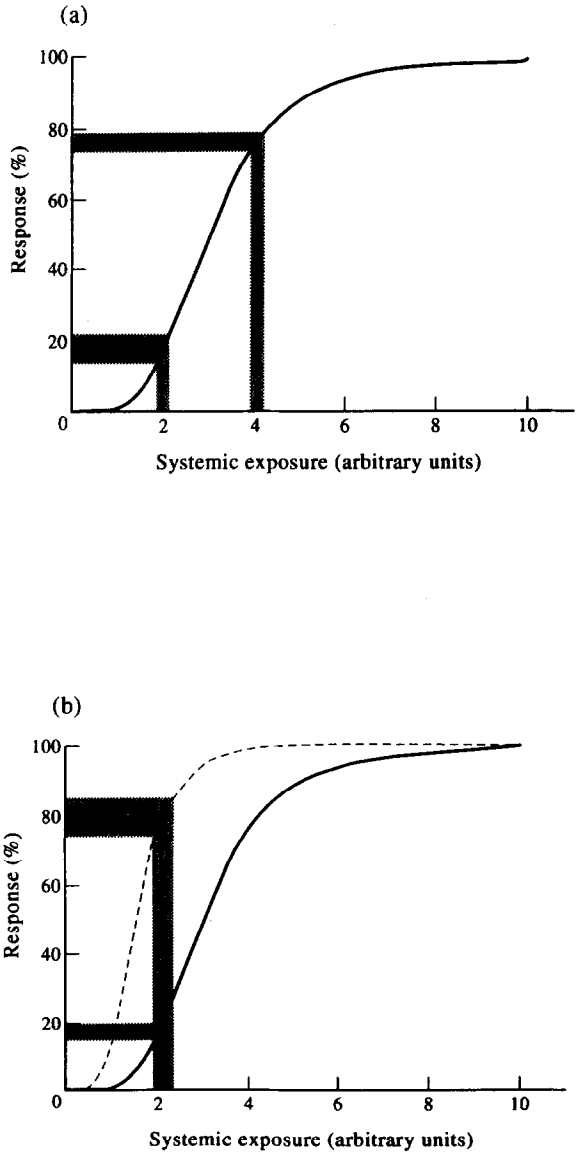

Figure 1. Effect of MDR modulators on chemotherapy. (a) Pharmacokinetic modulation: the MDR modulator produces an increase in systemic exposure, with resulting increase in effect (toxicity, tumour regression). There is no modulator-induced shift in the effect curve, but rather a shift to a higher point on the existing curve. (b) Tumour modulation: the MDR modulator produces an increase in effect, without alterations in systemic exposure, by inducing a new, steeper effect curve (-----).

WHO CARES ABOUT THE MECHANISM BEHIND ALTERED DRUG EFFECT?

The most important reason for defining the *in vivo* mechanism(s) for drug activity is the future design of agents and rational clinical trials to overcome MDR. If MDR modulators confer increased activity by an increase in drug exposure through a simple pharmacokinetic interaction, then more emphasis must be placed on achieving maximum tolerated systemic exposure in each individual patient. Prospective individualisation of anticancer chemotherapy based on patient systemic clearance has already been successfully performed for methotrexate, teniposide, cytarabine and carboplatin [17–20]. The therapeutic rationale for individualisation of many anticancer drugs, including MDR substrates (e.g. etoposide, teniposide, doxorubicin, paclitaxel) has also been established [21, 22]. It must be recognised that pharmacodynamic correlations have not been found for all anticancer drugs. In addition, other measures of systemic exposure, such as steady-state concentration or time above a threshold concentration, may provide a stronger correlation with effect than AUC. Future phase II/III trials will need to determine if the systemic exposure–response relationship present for toxicity also exists for tumour response. This would allow administration of the 'optimal' quantity of anticancer drug necessary to achieve a favourable effect/toxicity ratio for individual patients, and no further modulation would be required or of benefit.

Modulation with cyclosporins alter both systemic drug clearance and apparent volume of distribution of etoposide and doxorubicin [7, 8]. This suggests two independent interactions; increased volume of distribution, due to prolonged retention of intracellular drug via blockade of p-glycoprotein efflux in tissues (including, tumour, kidney and biliary tract) and altered liver metabolism perhaps via direct action of cyclosporin on cytochrome P450s. The influence of pharmacokinetics on drug effect depends on the pharmacodynamic relationship. Volume of distribution does not effect AUC, but will alter the shape of the concentration–time curve (e.g. time above a threshold concentration). Decreased drug clearance will directly increase all measures of drug exposure. Therefore, if MDR modulation is independent of altered metabolism, more emphasis must be placed on identifying modulators devoid of this drug interaction. This should lessen the portion of systemic toxicity induced by an elevated AUC, but will not effect modulation of p-glycoprotein in normal versus tumour tissue. Many preclinical and clinical trials of MDR reversal have noted an increase in gastrointestinal and biliary toxicity, tissues with high expression of p-glycoprotein [23]. As no structural or substrate differences in p-glycoprotein have been identified between normal and tumour tissues, it is unlikely that toxicity secondary to enhanced retention of anticancer drug in normal tissues can be avoided [23].

Future trials of MDR modulation need to evaluate equal potency and not equal dose. For example, Sikic and colleagues recommend a 50% reduction in etoposide and doxorubicin dose when either agent is combined with cyclosporin [5]. A randomised comparison of cyclosporin plus a 50% reduced dose

of etoposide with a 50% reduced dose of etoposide alone could possibly show greater effect of the combined therapy and successful modulation would be claimed. However, the true effect will be increased drug exposure, as the etoposide AUC will be twice as great with the combined therapy. A more useful trial would compare activity for the maximum tolerated dose of etoposide alone with the maximum tolerated dose of etoposide plus cyclosporin. This could be achieved with the conventional mg/m^2 maximum tolerated dose or through individualisation of drug dosage using adaptive control with feedback. This strategy, evaluating equal potency, will define the usefulness of clinical tumour modulation, while minimising other confounding factors. It is only with a greater understanding of *in vivo* drug action that the laboratory successes of MDR modulation can be turned into a clinical reality.

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