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ORIGINAL ARTICLE

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A retrospective evaluation of the feasibility of intrapatient dose escalation as appropriate methodology for dose-ranging studies for combination cytotoxic regimens

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Abstract *Purpose*: To investigate the feasibility of intrapatient dose-escalation methodology for dose-ranging studies of conventional cytotoxics in combination. *Patients and methods*: Case records were identified for patients with ovarian cancer treated first-line with either single-agent carboplatin or carboplatin and paclitaxel in combination and routinely subjected to a 10% dose escalation in carboplatin at each cycle, towards a target day-22 neutrophil count in the range 1.0–1.5×10^9/l and a platelet count in the range 75–110×10^9/l, defining adequate dose. 'Entry level' carboplatin doses were in the range AUC 5.1 to AUC 7.4; paclitaxel was given at 175 mg/m^2 as a 3-h infusion throughout. All drugs were administered three-weekly. *Results*: The distribution of carboplatin maximum tolerated doses (MTDs) indicated a wide interpatient variation, ranging from AUC 5.4 to AUC 9.8. The median MTD in those receiving carboplatin alone (AUC 6.9) was significantly lower than in those treated with carboplatin and paclitaxel (AUC 7.6) ($P = 0.01$). Also, paclitaxel had both neutrophil- and platelet-protective effects. *Conclusions*: The median MTD documented here using intrapatient dose escalation for carboplatin combined with paclitaxel is remarkably similar to that derived from conventional phase I studies. Furthermore, the striking range of carboplatin MTDs recorded in previously untreated patients may have implications for the wider development of management strategies based on the adequacy of treatment, as defined by the modest levels of dose-limiting toxicity encountered. The ready availability of an expanded set of MTD data by this methodology may also provide more compelling evidence about potential pharmacodynamic drug interactions than may be available from conventional phase I combination studies. These retrospective findings clearly justify further prospective evaluation of intrapatient dose-escalation methodology in dose-ranging studies.

Keywords Intrapatient dose escalation · Carboplatin · Paclitaxel · Maximum tolerated dose · Ovarian cancer

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Introduction

The use of cytotoxic chemotherapy at doses close to the maximum tolerated (MTD) is an established tenet of conventional oncological practice and the determination of MTD remains the primary objective of early phase clinical evaluation [20]. For conventional agents at least, the rationale of this approach is predicated on a relatively steep dose response curve gradient at dose values below the MTD and it represents a pragmatic approach to negotiating their poor therapeutic index. Interpatient dose escalation, based on successive three-patient cohorts treated at increasing dose levels, has historically been considered the standard phase I trial design as it provides the means to distinguish acute from cumulative dose-limiting toxicities. However, the MTD as typically thus defined inevitably reflects relatively few toxic events in just a small number of patients. Furthermore, many patients are taken off-study following just two or three cycles of treatment because of disease progression at a dose which may be lower than their MTD. Such studies therefore provide only preliminary evidence, at best, of any cumulative toxic effects.

Drugs which subsequently show single-agent activity in phase II trials are typically investigated further within combination regimens. Decisions about doses used in combination regimens are conventionally made

either intuitively, which is risky, or through additional interpatient dose-escalation dose-ranging studies, which are time consuming. With so many new drugs currently in development, there is an urgent need for a streamlined but safe dose-ranging methodology for combination regimens.

There is thus increasing interest in intrapatient dose-escalation dose-ranging designs and several studies using this approach have now been reported [16, 19, 22, 29, 34]. Advantages might include: faster definition of MTD than allowed by intercohort designs; less concern about the potentially adverse implications of delivering a suboptimal dose of an existing standard agent at entry level, given that this may be preferentially escalated; and greater likelihood of providing more representative data about the extent of variation of individual MTDs, with potential to provide MTD data points for most patients entered. This approach may also provide a better perspective on the recently documented problem of discrepancies arising between the dose at first recorded dose-limiting toxicity, and the ultimately defined MTD [28]. Similarly the expanded MTD dataset provided by this methodology may allow better identification of pharmacodynamic interactions between individual drugs, thus having specific advantages in combination therapy dose-ranging studies.

This paper presents a retrospective investigation of an intrapatient dose-escalation approach, employed in routine standard practice, where only one of the constituents (carboplatin) in a drug combination (carboplatin plus paclitaxel) was escalated, and where dose-limiting toxicity was largely haematological. The ICON-3 ovarian cancer trial protocol for first-line chemotherapy in ovarian cancer specified a minimum carboplatin dose both as a single agent (control arm) and in combination with paclitaxel (research arm), providing scope for either escalation or adoption of a higher dose at the clinician's discretion [14]. At this centre we employed the same dose-escalation scheme for carboplatin, whether as single agent or in combination with paclitaxel, namely successive 10% dose increments with each cycle until modest myelosuppression supervened. Here we compare the range and distribution of carboplatin MTDs encountered, both as a single agent and in combination, and with that recorded in the literature using standard interpatient dose-escalation designs.

Patients and methods

Patient selection

Case reports for newly diagnosed patients with ovarian cancer treated at City Hospital, Birmingham, with either single-agent carboplatin or carboplatin and paclitaxel in combination were retrospectively examined. Patients whose carboplatin dose was escalated either within the ICON-3 study or with an identical regimen off-study were identified.

Chemotherapy

All patients commenced carboplatin at a minimum targeted area under the concentration-time curve (AUC, mg·min/ml) of 5.1, maximum 7.4, using the Cockcroft formula for calculated creatinine clearance, based on weight, age and serum creatinine as a surrogate for glomerular filtration rate (GFR) [6, 9]. The serum creatinine was measured using Vitros slide technology. Subsequent carboplatin doses were increased by 10% at each cycle with the aim of achieving a target neutrophil count in the range $1.0–1.5\times10^9$/l and a platelet count in the range $75–110\times10^9$/l on day 22 of each treatment cycle (i.e. day 1 of the next cycle). Paclitaxel was given at 175 mg/m^2 over 3 h throughout. Chemotherapy was administered three-weekly, with treatment delayed if necessary until the neutrophil count was 1.0×10^9/l or more and the platelet count 75×10^9/l or more. The full blood count was measured on day 22 of each cycle, with the exception of the final cycle.

Maximum tolerated dose

The carboplatin MTD was defined as the first dose delivered which achieved a day-22 count for neutrophils or platelets in the target range. For each patient, the MTD AUC was retrospectively calculated using the Cockcroft formula for calculated creatinine clearance, based on weight, age and serum creatinine measured prior to the commencement of this treatment cycle. If the highest dose level given failed to achieved an MTD, then the MTD was censored at this dose level.

Statistical methods

The frequency distribution of the MTD AUC values for the patients who reached MTD was plotted for each treatment group. Differences in the carboplatin MTD AUC values across treatments (carboplatin vs carboplatin plus paclitaxel) were assessed using a Wilcoxon two-sample test. A chi-squared test was used to analyse the dose-limiting toxicity between treatments.

Results

Patient characteristics

A total of 90 patients with previously untreated ovarian cancer, who commenced chemotherapy between 17 August 1995 and 23 November 2001 (54 who had been entered into ICON-3 and 36 who followed the same treatment regimen off-study) were included in this analysis. In total, 45 patients had been treated with single-agent carboplatin (39 in ICON-3 and 6 off-study) and 45 received combination carboplatin and paclitaxel (15 in ICON-3 and 30 off-study).

Baseline characteristics were balanced across the two treatment arms (Table 1). The median age of the patients was 58 years in both treatment groups. The FIGO stages were distributed similarly with a total of 44/90 patients (49%) being stage III. The renal function of both groups at the start of their treatment was similar with a median GFR of 80 ml/min for those receiving carboplatin and 73 ml/min for those receiving carboplatin plus paclitaxel. The median starting carboplatin AUC was 6.1 for both regimens.

Table 1 Baseline characteristics

	Carboplatin alone	Carboplatin plus paclitaxel
Total no. of patients	45	45
Stage		
I	8 (18%)	10 (22%)
II	7 (16%)	5 (11%)
III	22 (49%)	22 (49%)
IV	6 (13%)	6 (13%)
IIc/IV	0 (0%)	1 (0%)
IIIc/IV	2 (0%)	1 (0%)
Age (years)		
Median (range)	58 (35–79)	58 (36–75)
Weight (kg)		
Median (range)	62 (45–93)	62 (45–86)
Serum creatinine (μmol/l)		
Median (range)	67 (50–103)	71 (50–105)
GFR (ml/min)		
Median (range)	80 (44–112)	73 (36–173)
Starting carboplatin dose (AUC)		
Median (range)	6.1 (5.8–7.4)	6.1 (5.1–7.1)

Table 2 Frequency of MTD attainment

	Carboplatin alone	Carboplatin plus paclitaxel	Total
Total attaining MTD	39 (87%)	34 (76%)	73 (81%)
No escalation after MTD	16	16	32
Escalated after MTD	15	9	24
Overshoot	8	9	17
No MTD attained	6 (13%)	11 (24%)	17 (19%)
Total	45	45	90

Treatment received

The majority of patients received six cycles of treatment (87%), although four patients (4%) received seven cycles and eight (9%) had eight cycles. Treatment was delayed for 47/90 patients (52%) (24 with carboplatin and 23 with carboplatin plus paclitaxel) until their neutrophils were 1.0×10^9/l or more and platelets 75×10^9/l or more. The median duration of delays was 7 days. Treatment delays were followed by a dose reduction in 22/47 patients (47%).

Maximum tolerated dose

The MTD was achieved in 73 patients (81%) (39 with carboplatin, 34 with carboplatin plus paclitaxel; Table 2). In 17 of the 73 patients who reached the MTD (8 with carboplatin, 9 with carboplatin plus paclitaxel), the day-22 neutrophil count was less than 1.0×10^9/l, or the platelet count less than 75×10^9/l, without the target range having been previously reached. In these cases of 'overshoot' the MTD was taken as the previous dose level. In 24 of 73 patients achieving the MTD (15 with carboplatin, 9 with carboplatin plus paclitaxel) higher doses were given after the MTD was reached; 11 of these achieved myelosuppression within the target range, giving a 'second' MTD. For this analysis, only the first MTD was included.

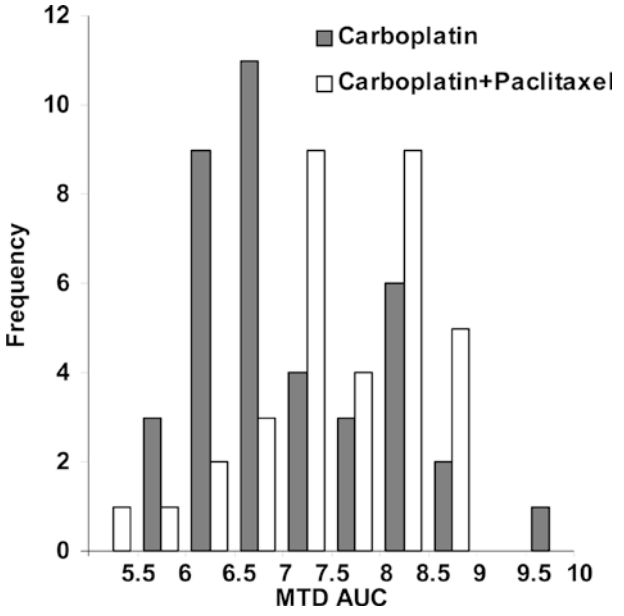

Fig. 1 Frequency distributions of MTD AUC

The MTD was not attained in 17/90 patients (19%) (6 with carboplatin, 11 with carboplatin plus paclitaxel) although the dose was escalated at least once. In 6 of these 17 patients (2 with carboplatin, 4 with carboplatin plus paclitaxel), the dose was escalated at each cycle and the highest dose given failed to achieve a value for neutrophils or platelets in (or below) the target range. The censored MTDs for these six patients ranged from AUC 7.7 to AUC 9.4. In 11 of the 17 patients (4 with carboplatin, 7 with carboplatin plus paclitaxel), the highest dose given failed to achieve a value in (or below) the target range, but due to fatigue or administrative reasons the dose had not been escalated when permissible haematologically. These censored MTDs ranged from AUC 6.1 to AUC 8.2.

Differences in MTD between the two regimens

The distribution of the attained MTDs, as shown in Fig. 1, indicated a wide interpatient variation with MTD values ranging from AUC 5.4 to AUC 9.8. It also demonstrated that patients having carboplatin alone had a significantly lower median MTD AUC of 6.9 (range 5.7–9.8) compared to 7.6 (range 5.4–9.0) for those having carboplatin plus paclitaxel ($Z=2.56$, $P=0.01$). As this was a parallel rather than a randomized study there was the possibility of selection bias. However, the baseline characteristics in the two groups were similar (Table 1) and the contribution to the study from the 54/90 patients (60%) randomized into ICON-3 went

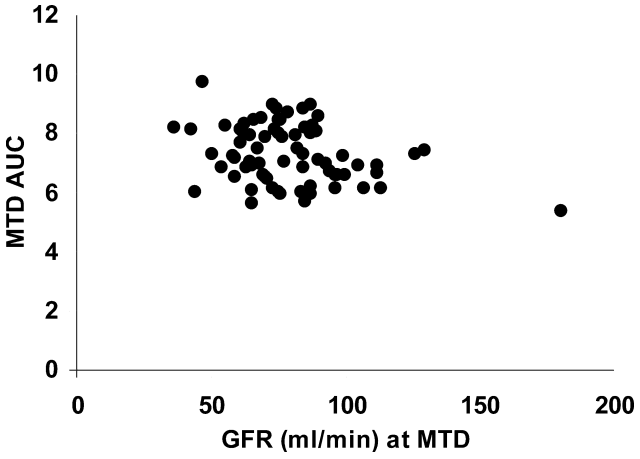

Fig. 2 MTD AUC vs GFR at MTD

Table 3 Dose-limiting myelotoxicity

	Carboplatin alone	Carboplatin plus paclitaxel
Number attaining MTD	39	34
Neutropenia	23 (58%)	12 (35%)
Thrombocytopenia	8 (21%)	18 (53%)
Neutropenia and thrombocytopenia together	8 (21%)	4 (12%)

some way towards avoiding this. The patient with the highest MTD of AUC 9.8 received carboplatin alone, and had the fourth lowest GFR at MTD in our series of 47 ml/min, reflecting a weight of 44 kg, serum creatinine of 64 μmol/l and age 75 years. Conversely, the patient with the lowest MTD (AUC 5.4) had by far the highest GFR at MTD of 180 ml/min after receiving carboplatin and paclitaxel. The MTD did not appear to be related to the GFR calculated at the MTD (Fig. 2).

There were 23/39 patients (59%) who received carboplatin alone who achieved a MTD less than AUC 7, compared with 7/34 patients (21%) who had carboplatin and paclitaxel. This suggests that paclitaxel may have protective properties against myelosuppression. There was a significant difference in the relative proportions of patients encountering dose-limiting neutropenia, dose-limiting thrombocytopenia, or both together, for carboplatin alone compared with carboplatin plus paclitaxel ($\chi^2 = 8.33$, $P = 0.02$; Table 3). The addition of paclitaxel increased the proportion of patients for whom the dose-limiting toxicity was thrombocytopenia only from 21% to 53%. Reciprocally, it reduced the proportion of patients for whom neutropenia only was dose limiting from 59% to 35%.

An exploratory analysis including the second MTD showed that eight patients with single-agent carboplatin had a second or even third (i.e. higher) MTD compared with only three patients with combination carboplatin and paclitaxel. Including values for these MTDs increased the median MTD to AUC 7.2 for single-agent carboplatin compared to 7.6 for carboplatin plus paclitaxel, reducing the difference between the two regimens.

Evidence of cumulative toxicity

Some patients on both treatment arms encountered cumulative toxicity. Of the 32 patients whose dose was not further escalated after reaching MTD, 16 (50%) experienced delays due to neutrophils $< 1.0 \times 10^9$/l or platelets $< 75 \times 10^9$/l on day 22 of subsequent cycles. Seven of these (22%) received dose reductions. In contrast, 6 patients (19%) continued at MTD for several cycles with no delays or dose reductions.

Discussion

In 34 patients who received the combination of carboplatin and paclitaxel 175 mg/m^2 every 3 weeks, the median carboplatin MTD was AUC 7.6 (range 5.4–9.0) and at least AUC 7.7 in a further four patients whose dose of carboplatin was escalated each cycle but who did not reach MTD. These data are comparable with those defined in conventional dose-escalation strategies [3, 12, 26] and justify further prospective studies to evaluate the feasibility of intrapatient dose-escalation designs as a means to define the optimal dose of components in novel combinations. Hybrid methodologies, involving intrapatient dose escalation, and intercohort escalation in the same design potentially offer the most attractive means of differentiating acute and cumulative dose-limiting toxicities. This approach has recently been pursued in a prospective dose-ranging study of gemcitabine, carboplatin and paclitaxel in combination [24].

These data also suggest a trend towards a 10% higher median MTD for carboplatin combined with paclitaxel (AUC 7.6) than for carboplatin alone (AUC 6.9). This is an interesting finding alongside the suggestion, made elsewhere, that paclitaxel may moderate carboplatin-induced thrombocytopenia in the absence of any pharmacokinetic interaction [5, 7, 18, 30, 31]. However, our data also suggest a possible neutrophil-protective effect, and this appears to be a new finding. Although our analysis utilized retrospective data, the carboplatin and carboplatin plus paclitaxel MTDs were derived contemporaneously, thus addressing questions previously posed by Kearns and Egorin as to whether such observations were historical artefact [18].

Recent years have seen renewed interest in intrapatient dose-escalation designs for dose-ranging studies [16, 19, 22, 29, 34]. Their application to combination regimens whose individual components have shown no marked evidence of a tendency towards cumulative toxicity seems particularly appropriate. Such designs allow better scope for defining the range of MTDs in a typical treatment population. This retrospective study provides some indication of the range of interpatient

variation in the MTD of carboplatin and carboplatin combined with paclitaxel, but the relatively small number of patients involved behoves caution in any comment as to the nature of its frequency distribution (whether normal or bimodal). The breadth of the range of MTDs is particularly striking and surprising in the context of the pharmacokinetically modelled dosing formula applied here for carboplatin. This might be expected to minimize one important source of interpatient variation, namely differences in drug clearance, and perhaps reduce the range [8]. For other drugs, such as the anthracyclines, interpatient differences in clearance are harder to model, and the range of MTDs might be wider. Thus this methodology might have even greater applicability there [2]. However, our own observations are clearly specific to the case of carboplatin.

Our documentation of such wide interpatient variation in carboplatin MTD seems particularly relevant to developing interest in dose individualization. Retrospective analyses across a number of tumour types have shown that patients who incur modest haematological toxicity have done better than those suffering no myelosuppression [2, 11, 23, 25, 27]. Thus an adequate dose is increasingly seen as one associated with mild to moderate toxicity. These observations are consistent with both the failure of randomized controlled trials of high-dose therapy to achieve improved relapse-free or overall survival [1, 10], as well as others testing more modestly increased doses [13, 15, 32]. These and other data have led to the acceptance of the generality of sigmoid dose response curves in conventional cytotoxic chemotherapy. In the majority of cases where modest toxicity seems associated with better outcome, it is often presumed that such toxicity is a pharmacodynamic surrogate for some unmeasured pharmacokinetic parameter. Notably, these observations were first made in the cases of carboplatin and anthracyclines, drugs which have marked patient to patient variation in clearance, and thus AUC, following a dose specified in milligrams per metre squared. This view is sustained by studies documenting the relationship of carboplatin AUC to myelosuppression [4] and to carboplatin AUC and response rate in ovarian cancer [17]. In the latter case, there is a sigmoid AUC/response relationship, again consistent with a threshold effect and notions of dose adequacy. However, we showed here a marked interpatient variation in carboplatin MTD despite utilizing pharmacokinetically guided dosing. Our data would therefore appear to indicate that there might be a case for investigating the potential benefits of carboplatin dose individualization by myelotoxicity incurred, in the treatment of ovarian cancer, as an adjunct to dosing by AUC.

Whilst we argue that interpatient pharmacodynamic differences must account for the breadth of the range of MTDs recorded in our own observations with single-agent carboplatin, others have more recently drawn attention to the limitations of the Cockcroft formula employed here to calculate renal clearance, in particular at the extreme ranges of renal function [7, 33]. We thus analysed our data to examine whether the range of MTD recorded here might have been an artefact of these inadequacies. The results of this are reassuring. Ironically, in the population under study, the patient with the highest MTD received carboplatin alone but had the fourth lowest calculated creatinine clearance in our series. Moreover, the patient with the lowest MTD had the highest calculated creatinine clearance and received carboplatin and paclitaxel. Furthermore, there was no overall relationship evident between calculated creatinine clearance and MTD, specified as carboplatin AUC (Fig. 2). Were this approach to dose individualization using pharmacodynamic surrogates to be supported by other data, then one means of eliminating the necessity for repeated incremental dose adjustments might be to determine the distribution of MTDs, and prospectively evaluate a candidate dose, one dose level above the lowest value MTD. This would minimize the number of steps required to reach MTD, and simultaneously provide a margin of reassurance, in so far as an excessive entry level dose would never be more that one dose level from safety. Systematic analysis of patient characteristics associated with lower MTD might also help in this respect. However, in the case of paclitaxel and carboplatin this might be too cautious, as there is now considerable evidence that the use of carboplatin AUC 7.5 in combination with paclitaxel 175 mg/m^2 over 3 h can be safely used in a large multicentre randomized trial [21].

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