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Phase I clinical and pharmacokinetic study of trabectedin and cisplatin in solid tumours

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ABSTRACT

Aim of the study: To define the maximum tolerated dose (MTD) and toxicity of trabectedin (T) and cisplatin (C) given on days 1 and 8 every 3 weeks to adult patients with advanced solid tumours. Plasma pharmacokinetics at cycle 1 and a preliminary anti-tumour activity assessment in ovarian and non-small cell lung cancer (OC, NSCLC) were secondary objectives.

Methods: In the dose finding part (DFP) of the study the dose of T given at each administration was escalated by 100 μg/m^2 increments from 300 μg/m^2 up to the MTD, with a fixed dose of C of 40 mg/m^2. The recommended dose (RD) was assessed in the previously treated and untreated OC and NSCLC patients in the expansion of the RD (ERD) part of the study.
T was administered with corticosteroids pre-medication as 3-h infusion and C as 30-min infusion.

Results: Thirty-nine patients were treated in the DFP and 10 in the ERD. The MTD of T was 700 μg/m^2 due to dose-limiting neutropaenia and the RDs in the previously treated/untreated patients were 500 and 600 μg/m^2, respectively. Most common toxicities were nausea/vomiting (67%), asthenia/fatigue (55%) and reversible ASAT/ALAT elevation (51%). Time to recovery from myelosuppression was dose-dependent and treatment could be repeated after $\geqslant$4 weeks in the majority of patients at 600 μg/m^2. Confirmed partial responses were observed in 4 of 13 evaluable OC patients and in 1 with uterine leiomyosarcoma. No pharmacokinetic interaction was observed.

Conclusion: The administration of T and C on days 1 and 8 resulted in prolonged neutropaenia requiring treatment delay. The evaluation of a single every 3 week schedule is worthwhile because of the hints of anti-tumour activity observed in OC.

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1. Introduction

Trabectedin (T) is a marine alkaloid isolated from the tunicate Ecteinascidia turbinata that has shown striking anti-tumour activity in a variety of preclinical models, including some that were unsensitive to conventional chemotherapeutics. Clinical investigations have shown that T was effective against a variety of tumours, especially in patients with soft tissue sarcomas (STS) resistant to Doxorubicin and Ifosfamide and with ovarian cancer pre-treated with platinum compounds, paclitaxel and other drugs.[1] It was approved by the EU regulators as therapy for patients with advanced STS resistant to or relapsed after anthracyclines and ifosfamide or for those cases not suitable for conventional chemotherapy.

Most of DNA directed anticancer agents, e.g. cisplatin (C), bind in the major groove of DNA, alkylating mainly N7 of guanine and forming DNA–DNA and DNA–protein cross-links. Instead T binds in the minor groove of DNA forming monoadducts at the N2 position of guanine. The structural DNA alterations cause an impairment of the transcription regulation, with modulation of the promoter activity of inducible genes, e.g. heat shock proteins,[2] or cell cycle regulators.[3] In addition, the different DNA damage induced by T compared to other DNA-interacting agents explains why the pattern of sensitivity of T in cells deficient in different mechanisms of DNA repair is peculiar. In particular, it has been reported[4] that Nucleotide Excision Repair (NER) deficient cells, that are more susceptible to conventional alkylators, are resistant to T. On the other hand, cells that are deficient in Homologous Recombination, e.g. for the mutations of BRCA1 or BRCA2, are much more sensitive to T as well as to many other DNA-damaging agents.[5–7]

The mechanistic differences between T and C prompted pre-clinical studies to assess the combination of the two drugs.[7] Although in the majority of cancer cells in culture the effects of the combination were additive or slightly synergic, when the two drugs were combined *in vivo* they had a synergistic anti-tumour effect. In one human ovarian cancer xenograft poorly responsive to C and moderately sensitive to T, the combination produced a striking and long-lasting tumour remission with some cures.[8]

The striking anti-tumour activity of the combination of T and C in preclinical models was the rationale to perform a phase Ib study in adult patients with potentially sensitive solid tumours, such as NSCLC and OC. A day 1–8 schedule was selected to avoid the prolonged neutropaenia observed with T given in combination with doxorubicin every 3 weeks[9] and to decrease the acute subjective and liver toxicities. The use of a weekly regimen was supported by the clinical results achieved with taxanes and platinum compounds, for which weekly treatment is an effective option in patients partially sensitive to the same agents given intermittently.[10]

2. Patients and methods

2.1. Eligibility

The study consisted of two parts; in the first part (dose finding-DFP), which aimed to define the maximum tolerated dose (MTD) and the recommended dose (RD) of the combination of T and C, were entered patients with advanced solid tumours, who had failed a maximum of 2 prior lines of chemotherapy (3 in the case of breast cancer) and for whom treatment with C was indicated; in the second part (expansion of the RD – ERD) were entered patients with a diagnosis of non-small cell lung cancer (NSCLC) or ovarian cancer (OC) and no prior treatment.

Other eligibility criteria were <70 years of age, expected survival of $\geqslant 3$ months, ECOG Performance Status (PS) $\leqslant 1$, adequate haematological, renal and liver function (alkaline phosphatase (AP) $\leqslant 1.5 \times$ upper normal limits (UNL), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) within normal limits, $\leqslant 2.5 \times$ UNL in the case of liver metastases, normal total serum bilirubin, albumin $\geqslant 2.5$ g/dl.

Exclusion criteria were a pre-existing symptomatic hearing impairment, peripheral neuropathy > grade 1, significant liver disease, >500 mg/m^2 prior cumulative dose of C or platinum equivalent, prior radiotherapy to >30% bone marrow reserve. At least one measurable lesion according to RECIST[11] was requested in the ERD.

2.2. Ethics

The protocol was approved by the local Ethics Committee of each participating centre and patients had to sign a written informed consent.

2.3. Treatment and study design

In the DFP patients received increasing doses of T in combination with 40 mg/m^2 of C, both administered on days 1 and 8 every 21 d; 3–6 patients per dose level were treated according to toxicity. The starting dose of T was 300 μg/m^2, to be increased by 100 μg/m^2 increments up to the MTD, which was defined as the dose at which at least one-third of the patients experienced a dose-limiting toxicity (DLT) at cycle 1. The RD was fixed one dose level below and its tolerability was to be confirmed by expanding the dose cohort in the expansion of recommended dose (ERD) part in which chemo-naïve NSCL and ovarian cancer (OC) patients were treated. A total of 19 untreated patients were originally planned to be entered.

DLTs were the occurrence at cycle 1 of febrile neutropaenia (NCI-CTC definition), grade 4 neutropaenia lasting for >5 d, grade 3 thrombocytopaenia, lack of recovery from haematological toxicity by day 35, any grade increase of AP, ASAT, ALAT and bilirubin, any other grade $\geqslant 3$ non-haematological toxicity, failure to deliver treatment on day 8 due to grade 2 haematological toxicity, or grade > 1 liver toxicity.

The dose of T was decreased by 1 dose level in the case of a DLT or delayed recovery from haematological toxicity between days 35 and 42. T was supplied by PharmaMar (Madrid, Spain) as a lyophilised powder concentrate for solution for infusion in two strengths of 0.25 and 1 mg, to be reconstituted with 5 ml or, respectively, 20 ml sterile water for injection. The calculated amount of T was given through a free flowing intravenous (IV) line as a 3-h infusion; commercially available C was administered as a 30-min infusion 30 min after the end of T. Pre–post hydration IV fluids were administered with C according to institutional policies. Steroids premedication before the start of T with dexamethasone and antiemetic pro-

phylaxis with IV 5HT 3 antagonists and metoclopramide up to 48 h after C were mandatory.

During treatment weekly clinical controls with full chemistry and haematological blood counts were performed; tumour assessment by radiological imaging had to be done within 4 weeks before starting and repeated every 2 cycles; total protein, albumin and urinalysis were performed at the end of each cycle.

Responders or patients with stable disease (SD) continued treatment for 4 cycles; treatment could be then continued at the discretion of the investigator or until progressive disease (PD) was documented.

NCI-CTC version 2 criteria for toxicity and modified RECIST criteria for the definition of response were applied.[11]

2.4. *Sample collection and pharmacokinetic analysis*

Blood samples (5 ml) were collected in Li-heparin for the measurement of C before the start of the infusion, at the end of the infusion, and 0.5, 1, 2, 3.5, 5 and 24 h after the end of the infusion. T PK samples were collected before the start of the infusion, 30 min after the start of the infusion, at the end of the infusion and 0.5, 1, 2, 5, 7 and 24 h after the end of the infusion. Blood samples were immediately centrifuged at 2500*g* for 10 min at 4 °C and plasma was transferred in polypropylene tubes and stored frozen at –30 °C until analyses. At each time point specified for collection, 1 ml of plasma was frozen at –70 °C; in parallel, 1 ml of plasma was ultrafiltered using Centrifree 30.000 D ultrafiltration devices (millipore, Centrifree YM – 30 catalogue N04104) at 4 °C for 20 min at 2000*g*. Plasma ultrafiltrate (PUF) was separated into cryotubes and was immediately frozen at –70 °C. T was measured in plasma by a liquid chromatography coupled with electrospray ionisation tandem mass spectrometry (LC–MS/MS) method.[12] Platinum levels in plasma and PUF were determined by inductively coupled-mass spectrometry (ICP-MS). PK parameters were calculated using standard non-compartmental methods.

3. Results

3.1. *Patient characteristics*

Forty-nine patients were treated in three centres: 39 in the DFP and 10 in the ERD; all were evaluable for safety, 36 were evaluable for DLT in the DFP (tumour-related infection with inadequate evaluation of toxicity: 1 patient; no treatment administration on day 8 due to tumour-related conditions: 2 patients) and 43 for efficacy (only 1 cycle administered: 3 patients; lack of measurable lesions, no tumour re-evaluation after 2 cycles and inconsistent assessment methods: 1 case each).

Table 1 reports the main characteristics of the patients. Seventeen patients had epithelial OC, 16 were pre-treated with platinum combinations, of whom 8 recurred after >6 months from the last administration (defined platinum-sensitive) and 8 during or within 6 months from last therapy (platinum-refractory/resistant).

Table 2 reports per dose level the number of patients treated and the DLTs observed. The median number of cycles per patient was 3 (range: 1–10). The dose of T was increased from 300 μg/m^2 (dose level 1) to 400 and 500 μg/m^2 (dose level 3), where 1 DLT was observed among 7 patients. At 600 μg/m^2 (dose level 4), a total of 15 patients were treated in the DFP with 4 DLTs: grade 3 ALAT in 3 cases (in 1 case not recovered by day 35 and in another associated with grade 1 increase of bilirubin leading to skip the day 8 dose) and recovery from grade 3 neutropaenia beyond day 35 in 1.

At 700 μg/m^2 (dose level 5) 9 patients were treated, 7 were evaluable and 3 had a DLT (grade 4 neutropaenia lasting >5 d: 2 patients; grade 3 neutropaenia not recovering by day 35: 1 patient). In pre-treated patients the MTD was T 700 μg/m^2 and the RD was 600 μg/m^2 but in view of the cumulation of myelotoxicity observed along the study, a dose of 500 μg/m^2 was selected for clinical development. In fact the overall incidence of neutropaenia by patient was 67% at cycle 1 versus

Table 1 – Patient characteristics.

	Study part		
	Dose findingpart	Expansion recommended dose	Total
No. of patients	39	10	49
Performance status			
0	34	10	44
1	5	–	5
Previous chemotherapy for advanced disease			
1 line	24*	–	24*
2 lines	13*	–	13*
Tumour type			
Ovary	16	1	17
Uterine leiomyosarcoma	7	–	7
Endometrium	6	–	6
NSCLC	–	9	9
Other	10	–	10

NSCLC = non-small cell lung cancer.

* Two patients with uterine leiomyosarcoma received adjuvant chemotherapy only.

Table 2 – Number of patients and occurrence of dose-limiting toxicity per dose level.

Dose level no.	T dose ($\mu g/m^2$/ dose)	Dose finding part (pre-treated pts)				Expansion recommended dose (untreated pts)			
		No. treated/ evaluable pts	No. pts with DLT	DLT description per patient		No. treated/ evaluable Pts	No. pts with DLT	DLT description per patient	
1	300	3/3	–	–		–	–	–	
2	400	4/4	–	–		–	–	–	
3	500	7/7	1	– Lack of recovery from G3 neutropaenia by D35 (1 pt)	→RD	–	–	–	
4	600	15/15	4	– G3 ALAT (3 pts) – Lack of recovery from G3 neutropaenia by day 35 (1 pt)		5/5	1	– G2 ALAT/ASAT causing day 8 dose skip	→RD
5	700	9/7	3	– G4 neutropaenia for >5 d, G4 thrombocytopaenia, lack of recovery from G3 ALAT by day 35 – G4 neutropaenia for >5 d – Lack of recovery from G3 neutropaenia by day 35		5/5	3	– Febrile neutropaenia (1 pt) – G4 neutropaenia for >5 d (1 pt) – Lack of recovery from G3 ALAT by D35 (1 pt)	

T = trabectedin; Pts = patients; DLT = dose-limiting toxicity; G = CTCAE grade; D = day; RD = recommended dose.

Table 3 – Number of patients and non-haematological toxicity at cycle 1 per dose level.

	Dose finding part (pre-treated pts)																Expansion recommended dose (untreated pts)				
	300 (*N* = 3)		400 (*N* = 5)			500 (*N* = 7)		600 (*N* = 15)			700 (*N* = 9)			All levels (*N* = 39)			600 (*N* = 5)		700 (*N* = 5)		
	G1–2	G3–4	G1–2	G3	G4	G1–2	G3–4	G1–2	G3	G4	G1–2	G3	G4	G1–2	G3	G4	G1–2	G3–4	G1–2	G3	G4
Asthenia/fatigue (%)	2 (67)	–	2 (40)	–	–	5 (71)	–	7 (47)	–	–	5 (56)	–	–	21 (54)	–	–	2 (40)	–	3 (60)	–	–
Nausea/vomiting (%)	–	–	3 (60)	–	–	4 (57)	–	12 (80)	–	–	6 (67)	1 (11)	–	25 (64)	1 (3)	–	3 (60)	–	4 (80)	–	–
ASAT/ALAT increase (%)	1 (33)	–	2 (40)	1 (20)	–	3 (43)	–	4 (27)	4 (27)	–	2 (22)	2 (22)	–	12 (31)	7 (18)	–	3 (60)	–	1 (20)	2 (40)	–

N = number of patients; pts = patients; G = CTCAE grade.

Table 4 – Number of patients and haematological toxicity at cycle 1 per dose level.

	Dose finding part (pre-treated pts)																Expansion recommended dose (untreated pts)				
	300 (*N* = 3)	400 (*N* = 5)		500 (*N* = 7)			600 (*N* = 15)			700 (*N* = 9)			All levels (*N* = 39)			600 (*N* = 5)		700 (*N* = 5)		
	Any G	G1–2	G3–4	G1–2	G3	G4	G1–2	G3	G4	G1–2	G3	G4	G1–2	G3	G4	G1–2	G3–4	G1–2	G3	G4
Neutropaenia (%)	–	1 (20)	–	4 (57)	2 (29)	–	5 (33)	8 (53)	–	–	4 (44)	2 (22)	10 (26)	14 (36)	2 (5)	3 (60)	–	–	–	4 (80)
Thrombocytopaenia (%)	–	2 (40)	–	2 (29)	–	–	5 (33)	–	–	4 (44)	–	1 (11)	13 (33%)	–	1 (3)	1 (20)	–	3 (60)	–	–

N = number of patients; pts = patients; G = CTCAE grade.

88% at subsequent cycles and this increase in frequency was associated with an increase in severity. Also thrombocytopaenia was more frequent at subsequent cycles (37% of patients at cycle 1 versus 64% at subsequent cycles) without difference in severity.

Initially in the ERD 5 untreated patients were treated at 700 μg/m^2, with 3 DLTs. Five patients were then treated at 600 μg/m^2 with 1 DLT, defining the RD.

3.2. Safety and toxicity

Table 3 reports the number of patients treated per dose level and the number of patients with the most frequent non-haematological drug-related toxicities observed at cycle 1. In the DFP the most common toxicities were nausea/vomiting (67%), asthenia/fatigue (54%) and ASAT/ALAT increase (49%). Liver toxicity recovered in all cases but 5 by day 35 (1 patient at 500 μg/m^2, 2 at 600 μg/m^2 and 2 at 700 μg/m^2). Table 4 reports the number of patients per dose level with haematological toxicity at cycle 1. Neutropaenia was the most frequent and dose-dependent; at the RD of 500 μg/m^2 in pre-treated patients it reached maximum grade 3 in 29%, while only grades 1–2 neutropaenia was observed at the RD of 600 μg/m^2 in the previously untreated patients.

The occurrence of treatment delays (Table 5) and dose reductions at cycle 2 was analysed per dose level. Both types of treatment modifications were mainly due to neutropaenia (which caused 54% of all treatment delays, 78% of toxicity-related delays and 93% of dose reductions). A dose-dependent delay of recovery was observed in pre-treated patients from 600 μg/m^2 with 36% of patients who could re-cycle only after 4 and 43% after 5 weeks. All five untreated patients at 600 μg/m^2 could recycle by day 35. The dose of T had to be decreased at cycle 2 in 17% of pre-treated patients at 500 and in none of the untreated patients at 600 μg/m^2 (data not shown). C was discontinued in two patients, at cycle 2 due to creatinine increase and at cycle 7 due to neurological toxicity. Overall, 13 patients discontinued treatment because of toxicity: 14%, 40% and 22% at 500, 600 and 700 μg/m^2 in the DFP, respectively, all due to haematological toxicity.

3.3. Anti-tumour activity

Four of 13 evaluable patients with OC achieved a partial response: 2 of 6 platinum-sensitive, treated with 400 and 600 μg/m^2, with a time to progression (TTP) of 8 and 11.6 months; 1 of 6 platinum-resistant treated at 600 μg/m^2, with a TTP of 22.6 months and 1 previously untreated with a TTP censored at 3.4 months, when a new anticancer therapy was started with PR still maintained. One partial response with a TTP of 14.8 months was observed in uterine leiomyosarcoma treated with adjuvant epirubicin and ifosfamide and gemcitabine for metastatic disease, and in one chemonaïve NSCLC with a TTP of 10.6 months. Four of 6 responders received 6 cycles or more, while 1 pre-treated and 1 untreated OC patient, both treated at 600 μg/m^2, were withdrawn, respectively, at cycles 4 and 3 due to neutropaenia, in the first case associated with liver toxicity.

3.4. Pharmacokinetics

The pharmacokinetic profiles of T and C were analysed in 21 patients. The pharmacokinetics of T was linear with AUC correlated to the dose (AUC_{inf} R^2 = 0.9513). The means of CL_{TB} were not significantly different between doses being of 50.9 ± 28.6, 42.7 ± 16.6, 48.9 ± 22.5 and 66.7±45.2 L/h/m^2, respectively.

Increasing doses of T do not change the plasma disposition of the platinum species, so that the mean clearance values of total and free platinum had a low variability being 1.6 ± 0.5 L/h/m^2 (CV 31%) and 18.0 ± 3.6 L/h/m^2 (CV 20%), respectively.

A comparison with the published data suggests that the plasma disposition of T does not appear to be altered by the concomitant administration of C.[13]

4. Discussion

The clinical development of the combination of T and C appeared particularly promising because both agents interact with DNA but are involved in different mechanisms of DNA repair; in addition, pre-clinical studies showed an anti-tumour synergism in one ovarian cancer xenograft resistant to C.[8] A day 1 and 8 schedule of administration was selected in the present study to avoid the prolonged myelotoxicity, mostly neutropaenia, we observed with T given in combination with doxorubicin on a 3-week schedule.[9]

In the present study, the MTD in patients with prior chemotherapy was 600 μg/m^2 T and 40 mg/m^2 C; the RDs for patients with/without prior chemotherapy were 500 and 600 μg/m^2 T, respectively, combined with 40 mg/m^2 C; the two RDs were selected on the basis of the limited number of dose reductions at cycle 2 (17% at 500 μg/m^2, none at 600 μg/

Table 5 – Number of patients and delay of cycle 2 per dose level.

	Dose finding part (pre-treated pts)					Expansion recommended dose (untreated pts)	
	300 (*N* = 3)	400 (*N* = 3)	500 (*N* = 6)	600 (*N* = 14)	700 (*N* = 6)	600 (*N* = 5)	700 (*N* = 4)
Re-cycle day 23–27 (%)	2 (67)	1 (33)	4 (67)	1 (7)	1 (17)	–	–
Re-cycle day 28–34 (%)	–	–	–	5 (36)	1 (17)	4 (80)	2 (50)
Re-cycle ⩾ day 35 (%)	–	–	1 (17)	6 (43)	3 (50)	–	2 (50)
Total number of cycle 2 delays (%)	2 (67)	1 (33)	5 (83)	12 (86)	5 (83)	4 (80)	4 (100)

Note: 30% of delays were due to reasons unrelated to toxicity (e.g., logistic issues).
N = number of patients receiving at least 2 cycles; pts = patients.

m^2) and time to re-treatment (which was about 4 weeks in pre-treated patients receiving 500 μg/m^2 T and between 4 and 5 weeks in untreated patients receiving 600 μg/m^2 T) reported with these two doses in the two groups of patients. One DLT was observed at 500 μg/m^2 and consisted of a delayed recovery (>35 d) of neutropaenia; from the dose of 600 μg/m^2 it appeared that treatment could be repeated only every 4 weeks in 36% of patients and every 5 weeks in a further 43% due to a delay in the recovery from neutropaenia and – to a lower extent – from ASAT and ALAT increase.

The delayed recovery from myelotoxicity, likely to be due to a repeated exposure to DNA-interacting agents, required, according to protocol, a reduction of the dose in 50% of pre-treated patients at 600 μg/m^2. Splitting the dose of T on days 1 and 8, however, decreased the acute liver toxicity, which became DLT in only two cases due to a delayed recovery. Nausea, vomiting and asthenia were moderate.

In this study epithelial OC was the most represented tumour type; the results achieved, however, were lower than expected, mainly in the sub-group of platinum-sensitive patients, with 2 partial responses of 8 and 11.6 months of 6 evaluable patients. We cannot exclude that the low dose intensity of T, due to treatment delay caused by a delayed recovery from haematological toxicity, might have impaired the anti-tumour effect. It is likely that, because both T and C cause damage of DNA and were given twice per cycle, neutropaenia and – to a much lesser extent – thrombocytopaenia were prolonged and the optimum time interval for re-treatment was at least 4 weeks. For those reasons, and also considering the limited number of patients, definitive conclusions cannot be drawn on the anti-tumour efficacy of the combination in OC, which should be assessed only when a more adequate treatment schedule has been defined.

PK studies did not show any pharmacokinetic interaction between the two drugs.

The weekly schedule, as also observed with T and gemcitabine,[14] is not suitable for the clinical development of the combination of T and C; however, the very promising preclinical data and the sound rationale of a potential synergistic effect on DNA repair, support further clinical evaluations to refine the schedule. A phase I study testing a single dosing of T and C given every 3 weeks will start soon, based on the acceptable degree of neutropaenia of T single agent and on the working hypothesis that delayed myelotoxicity, preventing a regular weekly administration of treatment, might be due to a repeated prolonged total DNA block with an impairment of haematopoietic stem cells.

Conflict of interest statement

C. Sessa, S. Cresta, C. Noberasco, G. Capri, E. Gallerani, F. De Braud, M. Zucchetti: none declared.

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