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Dose finding study of oral PSC 833 combined with weekly intravenous etoposide in children with relapsed or refractory solid tumours

F. Pein[a], *R. Pinkerton*[b,*], *P. Berthaud*[c], *K. Pritchard-Jones*[d], *G. Dick*[d], *G. Vassal*[e]

[a]*Institut Regional du Cancer Nantes Atlantique, Dept de Recherche Therapeutique, CLCC Rene Gauducheau, Nantes, France*
[b]*Queensland Childrens Cancer Centre, Royal Childrens and Mater Childrens Hospitals, Brisbane, Queensland 4101, Australia*
[c]*Novartis Pharma, Basel, Switzerland*
[d]*Department of Paediatrics, Royal Marsden NHS Trust and Institute of Cancer Research, Downs Road, Sutton, United Kingdom*
[e]*Institut Gustave Roussy, Department of Paediatric and Adolescent Oncology and UPRES-EA-2710, Parmacology and New Cancer Therapies, Villejuif, France*

ARTICLE INFO

Article history:
Received 3 October 2006
Received in revised form
25 June 2007
Accepted 4 July 2007
Available online 22 August 2007

Keywords:
PSC 833
Multi-drug resistance
Childhood cancer
Solid tumours
Phase 1
Ataxia

ABSTRACT

PSC 833 is an effective MDR1 reversal agent *in vitro*, including studies with paediatric cancer cell lines such as neuroblastoma and rhabdomyosarcoma. This study was performed to determine the safety profile, dose limiting toxicity (DLT) and maximum tolerated dose (MTD) in children with solid tumours and to determine the influence of PSC 833 on the pharmacokinetics of co-administered etoposide. Each patient received one cycle of intravenous etoposide (100 mg/m^2 daily for 3 days on three consecutive weeks) to document baseline pharmacokinetics, and subsequently the same schedule using a dose of 50 mg/m^2 was given combined with PSC 833 given orally every 6 h at a starting dose of 4 mg/kg. Thirty two eligible patients (23 male, median age 8.3 years) were enrolled. Neuroblastoma and rhabdomyosarcoma were the common disease types. Brain tumours were excluded. DLT was defined as any non-haematological grade 3–4 toxicity (common toxicity criteria) and using a specific toxicity scale for cerebellar toxicity. The MDT was defined as the first dose below which 2 or more patients per dose level experienced DLT. Grade 1–2 ataxia occurred in cohorts 2 and 3 (4 and 5 mg/kg, respectively). Three patients developed grade 3 neurotoxicity in the 6 mg/kg cohort and this defined the MTD. Six responses were observed (2 CR, 4 PR). Pharmacokinetic studies indicated that the clearance of etoposide was reduced by approximately 50% when combined with PSC 833. It is concluded that the toxicity profile and MDT is similar in both children and adults, as is the effect on etoposide metabolism. The study demonstrated the feasibility and safety of carrying out a paediatric phase 1 trial across European boundaries and acts as a model for future cooperative studies in rare cancers among children.

1. Introduction

Despite advances in the management of localised cancers in children the outcome in those with metastatic disease at presentation remains poor where, with the exception of nephroblastoma, hepatoblastoma and germ cell tumours, survival rarely exceeds 20%. Although the addition of drugs, dose intensification and consolidation with high dose chemoradio-

* *Corresponding author:* Tel.: +617 3840 3424; fax: +617 3840 8012.
E-mail address: Ross.pinkerton@mater.org.au (R. Pinkerton).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.07.003

therapy with haematopoietic stem cell rescue have all increased progression free survival time, there has been little improvement in overall survival.

Classical multidrug resistance, due to overexpression of *p*-glycoprotein (Pgp), the product of the *MDR1* gene, has been shown to be modified *in vitro* by a wide range of compounds providing the possibility of either reversing or preventing drug resistance. A variety of childhood cancers have been shown to express high levels of Pgp which may be of prognostic significance in leukaemia; neuroblastoma; rhabdomysarcoma and retinoblastoma.[1]

In vitro studies have shown that compounds such as verapamil, cyclosporin, PSC 833 and VX710 can all, to variable degrees, sensitise neuroblastoma, rhabdomyosarcoma and osteosarcoma cells to a range of MDR associated drugs that are in common use in paediatric practice. These include doxorubicin, etoposide and vincristine.[2–4]

Phase 2 studies in children using verapamil or high dose cyclosporin in combination with etoposide, doxorubicin and vincristine have indicated some degree of chemosensitisation.[5–7] The only real test of this strategy is to perform a phase 3 randomised trial of standard chemotherapy with and without the reversal agent and evaluate both response rate and event free survival. Towards this end, it is important to identify a modulating agent that can be given safely in combination with multiagent chemotherapy and does not require the close monitoring that is necessary with verapamil or possess significant organ toxicity, as occuring with high dose cyclosporin. PSC 833 is an analogue of cyclosporin A which has *in vitro* activity and has recently entered Phase III trial in adults. Phase I studies of PSC 833 in adults have indicated that it is better tolerated than cyclosporin with regard to liver or renal toxicity with a dose limiting toxicity of cerebellar ataxia, occurring at doses above 6 mg/kg/day.[8–12]

Because of the possibility that children metabolise PSC 833 differently than adults, as is the case with cyclosporin A,[13] it was necessary to carry out a dose finding study specifically in this age group. Moreover, it was essential to document that PSC 833 had an effect on the pharmacokinetics of the agents with which it was likely to be combined. PSC 833 influences etoposide kinetics in the pre-clinical model[14] and in adults the dose of etoposide has to be reduced by 50% to achieve the same area under the concentration curve.[15]

The present study used the 'three by three' etoposide schedule (three days a week for 3 consecutive weeks every 28 days) which has been used both alone or in combination.[16,17] This rapid schedule also facilitated the administration of a single course of etoposide without PSC 833 in order to document baseline pharmacokinetic (PK) data. PK data were collected on both PSC 833 and etoposide individually and in combination to determine the influence of PSC 833 on etoposide kinetics.

2. Patients and methods

2.1. Study design

The primary objective was to determine the maximum tolerated dose (MTD) of the combination of PSC 833, given orally every 6 h and etoposide given by short infusion in a paediatric population with relapsing and/or refractory solid tumours. Dose limiting toxicity (DLT) was defined as any CTC Grade 3 or 4 toxicity and Grade 3 or 4 cerebellar toxicity using a specific, more detailed, grading system (Table 1). The maximum tolerated dose (MDT) was the dose of PSC 833 at which no more than 2 in 6 patients at any one dose level experience a DLT.

Secondary objectives were to study the pharmacokinetics (PK) of etoposide alone when given by short infusion and to determine the effects of oral PSC 833 on the PK of etoposide in order to recommend safe doses of PSC 833 in combination with etoposide for use in phase II/phase III paediatric trials, and to document any possible antitumour activity of etoposide in combination with PSC 833.

The dose of PSC 833 remained fixed for all subjects within a cohort. The dose of etoposide for all subjects was fixed at 100 mg/m^2/day in Cycle 1 (single-agent treatment) and at 50 mg/m^2/day in Cycle 2 (combination treatment) The PSC 833 dose escalation and in turn, subsequent cohort assignation were dependent on DLT. The starting doses of etoposide were chosen with the knowledge obtained from studies performed in children with single-agent etoposide and in adults using a combination of etoposide and PSC 833. The starting dose of PSC 833 was chosen from a knowledge of the maximum tolerated dose in adults.

Cycle 1 used etoposide alone rather than combination therapy with PSC 833 so that any subjects who obtained a complete response with etoposide alone would continue on that regimen without the addition of PSC. This also facilitated the study of the baseline pharmacokinetics of etoposide alone prior to the addition of PSC 833.

Table 1 – Grading for cerebellar toxicity

Grade	Severity	Walking	Physical examination
1	Mild	Slight subjective sense of incoordination. No difficulty walking	Normal or equivocally normal
2	Moderate	Definite subjective incoordination on walking but able to walk without assistance	Broad-based gait and/or mild dysdiadochokinesias and difficulty walking heel-to-toe
3	Severe	Unable to walk without assistance from another person or a walker	Markedly abnormal gait and inability to walk heel–to-toe
4	Life threatening	Unable to walk because of incoordination even with assistance	

If a child who was not yet able to walk experienced cerebellar toxicity, specialist opinion was to be sought to assess the severity of the toxicity.

2.2. Patient selection

Children and adolescents aged $\geqslant$12 months and $\leqslant$18 years, of either sex, with solid tumours that had relapsed after, or were refractory to, conventional therapy including high-dose chemotherapy were eligible. Brain tumours were excluded because disease related neurodisability could lead to difficulty in defining drug related central nervous system (CNS) side effects.

Patients with disease that was stable or partially responding to the first study course of etoposide remained eligible to receive PSC 833, as were patients who had an initial transient response to etoposide alone in Cycle 1 but later developed progressive disease. Patients who had developed progressive disease on previous non-study treatment including the rapid schedule (3×3) of etoposide were ineligible for enrolment.

Other inclusion criteria were: Lansky performance scale >30, life expectancy of at least 12 weeks, WBC $\geqslant 1.5 \times 10^9$/L and granulocyte count $\geqslant 1.0 \times 10^9$/L and platelet count $\geqslant 75 \times 10^9$/L. Subjects with bone marrow disease causing myelosuppression could be included.

Non-inclusion criteria included impairment of hepatic or renal function and impairment of gastro-intestinal function which might significantly alter the absorption of PSC 833. Treatment with myelosuppressive chemotherapy or any new investigational drugs was not permitted within 4 weeks prior to study entry or within 6 weeks if nitroso-ureas had been administered. Patients could not have recently experienced seizures or neurotoxicity, particularly peripheral neurotoxicity of severity $\geqslant$2 on the NCI toxicity criteria. Concurrent therapy with drugs known to increase or decrease Cyclosporin A concentrations was not allowed.

Up to eight treatment cohorts were expected, each consisting of a minimum of four evaluable subjects and a maximum of six subjects (except the cohort containing the final recommended doses of the combination which was to be expanded to 10 subjects).

All study candidates or their parents were required to provide written informed consent as approved by local institutional review board/ethics committees before initiation of any study procedures. Consent was obtained at the time of disease relapse or progression prior to the administration of single agent etoposide.

3. Treatment plan

3.1. PSC 833 administration

Subjects received the PSC 833 dose level of the assigned cohort for the total duration of the treatment, given every 6 h on days 0–4, 7–11 and 14–18.

PSC 833 dosing was given on an empty stomach, i.e. at least 1 h before or 2 h after a meal. Any subject taking $\leqslant$50% of the total dose of PSC 833 for Cycle 2 was removed from study and replaced in order to make an accurate assessment of toxicity. If DLTs occurred in a subject who took $\leqslant$50% of the total dose of PSC 833 for Cycle 2, no replacement was necessary. In subsequent cohorts, the dose of PSC was escalated from 4 mg/kg q6h upwards in increments of 1 mg/kg q6h.

3.2. Etoposide administration

In the rapid schedule of etoposide, the drug was given on days 1–3, 8–10 and 15–17. A complete cycle of treatment was days 1–28, including the three above sequences.

In Cycle 1, etoposide 100 mg/m^2/day of etoposide was administered and 50 mg/m^2/day, according to the same schedule, in Cycle 2.

3.3. Patient evaluation

Before treatment, patients underwent medical history and physical examination, ECG, laboratory evaluation (blood cell count, serum chemistries, liver function tests, coagulation screen) and pregnancy test (if appropriate). These parameters were repeated prior to Cycle 2.

Tumour size was assessed prior to Cycle 1 (etoposide alone) by X-ray ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) as appropriate. The same technique was used prior to and following Cycle 2 (etoposide plus PSC 833).

Tumour response was assessed according to the standard definition. Complete response equals complete disappearance of all measurable disease, partial response equals reduction in measurement of disease by $\geqslant$50%. Progressive disease was a $\geqslant$50% increase to the evaluation of a lesion or the appearance of a new lesion. Stable disease was disease not meeting any of the above criteria. Complete or partial response must last at least 4 weeks.

Combination treatment could be administered until disease progression, unacceptable toxicity or death occurred. Safety was assessed in all cycles with physical examination, vital signs, performance status and laboratory examination. Tumour response was assessed after every 2 subsequent cycles.

3.4. Treatment modification in relation to toxicity

The start of the next cycle of treatment could be delayed for up to 20 days and/or the start of sequence within a cycle could be delayed for up to 10 days from its projected beginning to allow the WBC to reach a level of 1.5×10^9/L (granulocytes 1.0×10^9/L) and the platelets a level of 75×10^9/L. These criteria did not apply to subjects with bone marrow involvement causing myelosuppression.

The subject discontinued immediately if grade 4 neurotoxicity occurred. If lesser degrees of toxicity resolved within 10 days of the start of the next projected cycle, or sequence within a cycle, to $\leqslant$grade 2, the subject was allowed to continue on treatment.

If a grade 3 or 4 hyperbilirubinemia had not returned to baseline within 10 days of the projected start of the next cycle or sequence within a cycle, the subject had to be discontinued.

If the ALT and/or AST values increased to $\geqslant 5 \times$IU/L, the subject discontinued the study immediately. If the raised values decreased to $\leqslant 2.5 \times$IU/L within 10 days of the projected start of the next cycle or sequence within a cycle, the subject was allowed to continue on the study.

For all other grade 3/4 toxicities or other reasons, a maximum of 10 days delay in the start of the next cycle or

sequence of cycle, was allowed. A delay longer than this led to discontinuation of the subject.

The severity of adverse events was graded (except for cerebellar toxicities) using the expanded NCIC CTC.

3.5. *Pharmacokinetic evaluation*

Etoposide plasma pharmacokinetics were studied during the third weekly sequence in Cycle 1 (without PSC 833) and Cycle 2 (with PSC 833). Blood samples were collected at the following times:

Day 15 – prior to the second infusion.
Day 16 – prior to the third infusion, at the end of infusion, and at 2, 3, 4, 6, 8, 10 and 12 h after the start of infusion.
Day 17 – 24 and 36 h after the start of the third infusion.

Samples were centrifuged immediately after collection and plasma was frozen and stored at −20 °C until analysis. Plasma levels for etoposide were assayed by HPLC with UV detection. The lower limit of quantification was 0.2 μg/ml.

Model-independent analysis was performed using the Winnonlin Software (Scientific Consulting, Inc., Cary, NC). The area under the plasma concentration-versus-time curve (AUC) was measured after the third etoposide infusion, using a log-linear trapezoidal rule and extrapolated to infinity according to the linear regression of the elimination phase. Clearance was calculated by dividing the administered dose of etoposide by the measured $AUC_{0-\infty}$.

The difference between etoposide clearance observed in Cycles 1 and 2 (with PSC 833) was analysed by a match-pair non-parametric Wilcoxon test.

3.6. *Pharmacokinetic/parmacodynamic analysis*

The relationship of PSC 833 dose to the proportion of patients who experienced the two major adverse events related to PSC 833 treatment, namely ataxia and hyperbilirubinemia, was examined in an exploratory manner.

4. Results

4.1. *Patients studied*

Thirty-two patients with refractory solid tumours were enrolled into this study between 1996 and 1998. The tumour types included 11 neuroblastoma, 8 rhabdomysarcoma, 6 Wilms' tumour, 2 osteosarcoma, 1 Ewing's sarcoma, 1 thoracic sarcoma, 1 desmoplastic small round cell sarcoma, 1 synovial sarcoma and 1 sacrococcygeal teratoma.

The mean age was 8.3 years (range: 1–18 years). Twenty-three were male and 9 were female. Twenty-five patients were Caucasian in origin, 2 were black, 3 were oriental and 2 were classed as others.

The mean time since first diagnosis was 25.1 months ranging from 5 to 95 months. A total of 27/32 patients had experienced a remission or a period of stable disease; the mean time since this occurrence was 13.1 months ranging from 2 to 33 months. These figures are similar between cohorts.

A total of 8/24 (33%) of patients had bone marrow involvement. At baseline, 12 patients had a Lansky performance status of 100%, 10 of 90%, 4 of 80%, 1 of 70%, 2 of 60% and 3 of 50%.

4.2. *Dose escalation and toxicity*

Five patients were enrolled in the first cohort (PSC 833 dose 4 mg/kg q6h), one of whom was considered non-evaluable due to the incorrect dose administration of etoposide in the second cycle. No DLTs were observed in 4 evaluable patients in the first cohort, so the dose of PSC was increased to 5 mg/kg q6h. Eleven patients were initially enrolled in the second cohort, in order to obtain 6 evaluable patients, as the first patient of this cohort experienced a DLT. Five patients were considered non-evaluable for DLT evaluation as none completed the first 2 cycles of therapy. Two DLTs were observed in the evaluable patients; prolonged grade 4 thrombocytopenia and neutropenia and grade 3 hyperbilirubinemia in one and grade 3 ataxia in the other. In accordance with the protocol, the dose of PSC 833 was escalated to 6 mg/kg q6h in cohort 3.

Eight patients were enrolled in cohort 3. Two patients were considered non-evaluable for DLT as neither completed cycles 1 and 2. DLT was observed in the second evaluable patient enrolled in cohort 3 (grade 4 hyperbilirubinemia), therefore, the cohort was expanded to include 6 patients. Two further DLTs were observed; grade 3 ataxia in one and grade 4 hyperbilirubinemia in the other. As 3 DLTs had occurred in 6 patients, the MTD of PSC 833 in children was determined to be 5 mg/kg q6h. It was decided to enrol further 5 patients at the dose used in cohort 2 (5 mg/kg q6h). One DLT was observed; neurotoxicity grade 3 Overall, 6 of the 21 evaluable patients experienced a DLT (1 haematological toxicity, 2 neurotoxicity, 3 hyperbilirubinemia). Six patients (19%) stopped treatment during or after Cycle 1 and 15 patients (47%) during or after Cycle 2. Six patients completed 6 or more cycles (5 cycles of PSC 833 as per protocol). Of those, 1 patient completed 7 cycles, 2 completed 8 cycles, 1 patient completed 9 cycles and 1 patient completed 12 cycles. All the non-evaluable patients were withdrawn from the study due to disease progression rather than treatment toxicity or the inability to tolerate oral etoposide.

4.3. *Pharmacokinetic data*

PK data for PSC 833 were obtained in 5 patients at 4 mg/kg, 11 patients at 5 mg/kg and 7 at 6 mg/kg. Mean PSC 833 trough blood concentrations are given in Fig. 1. With the exception of day 1 in the low dose group, at all times at which etoposide was administered, the mean trough concentrations of PSC 833 were above the target of 1000 ng/ml which has been shown in studies *in vitro* to be necessary for reversal of MDR. There was a general increase in mean C_{max} and $AUC_{(0-6h)}$ with increase in dose (Fig. 2), however, there are insufficient data to make any definitive statements on linearity and proportionality.

Complete sets of plasma pharmacokinetic data for etoposide including information on etoposide alone or in combination with PSC were available in 11 patients. Four at PSC dose

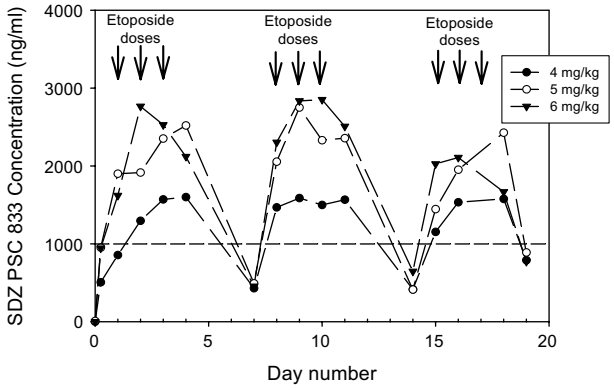

Fig. 1 – Mean trough blood concentrations of PSC 833 during the second cycle of etoposide showing maintenance of concentrations above the 1000 ng/ml target concentration during etoposide treatment.

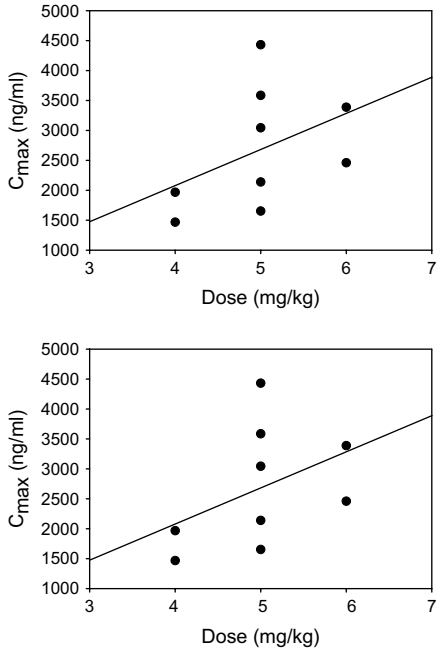

Fig. 2 – Linear regression of PSC 833 blood C_{max} and AUC (0–6 h) versus dose.

of 4 mg/kg, 4 at 5 mg/kg and 3 at 6 mg/kg. Details of the AUC, α and β half life, C_{max} and clearance are given in Table 2.

The etoposide clearance was significantly reduced ($p < 0.0001$) during Cycle 2 with a means ± SD difference of 53 ± 10% The individual reduction in etoposide clearance between Cycles 1 and 2 ranged from 27% to 65%. No effect of the PSC 833 dose was observed on the magnitude of the clearance reduction. In addition, no correlation was found between clearance reduction and PSC 833 plasma levels (data not shown).

4.4. *Pharmacokinetic/pharmacodynamic relationship*

Although a positive correlation was observed between PSC dose and occurrence of both ataxia and hyperbilirubinemia,

Table 2 – VP16 Plasma Pharmacokinetics as single agent (dose 1) and combined with PSC (dose 2)

	Dose 1 VP (mg)	Dose 2 VP (mg)	AUCinf1 (μg h/ml)	AUCinf2 (μg h /ml)	α-HL1 (h)	α-HL2 (h)	β-HL1 (h)	β-HL2 (h)	C_{max1} (μg/ml)	C_{max2} (μg/ml)	Cl1 (ml/h)	Cl2 (ml/h)	V_{ss1} (ml)	V_{ss2} (ml)
Median	70	38	98.5	96.9	1.98	2.17	8.82	8.1	23.60	13.01	788.2	407.5	4075	3409
Mean	83	42	96.2	107.5	1.92	2.17	10.10	8.2	22.65	13.65	868.4	404.0	4932	3742
SD	42	21	14.7	25.4	0.19	0.73	4.68	2.67	2.67	2.06	383.3	169	2500	2050
Min	53	27	74.6	76.2	1.5	0.71	5.69	4.69	18.20	10.45	480.3	192.0	2736	1894
Max	200	100	118.7	156.3	2.13	2.95	20.48	12.02	25.90	17.07	1805.5	748.6	11,281	9470

HL, half life; AUC, area under concentration curve; C_{max}, maximum concentration; Cl, clearance; V_{ss}, steady state volume.

there were insufficient data to determine how this was related to C_{max} and $AUC_{(0-6h)}$.

4.5. *Efficacy*

In the three cohorts at 4.5 and 6 mg/m^2 there were 2/5, 3/19 and 1/8 responses, respectively. The overall response rate was 19% including 2 complete responses – 1 Wilms tumour and 1 neuroblastoma which lasted >240 days and 90 days, respectively. There were 4 partial responses; 2 neuroblastoma and 2 rhabdomyosarcoma. Stable disease was documented in 4 patients; 1 Wilms, 1 neuroblastoma, 1 Ewings sarcoma and 1 rhabdomyosarcoma.

5. Toxicity

A range of symptoms unrelated to PSC 833 were documented. These included fever (50%), sepsis (23%) or other infections or pain (both 13%). Many were anticipated and associated with etoposide. Gastrointestinal disorders were observed in 21 (66%) patients and consisted mainly of vomiting (44%), abdominal pain (31%), nausea (22%), constipation and diarrhoea (19% each). Alopecia was seen in 10 (31%) patients.

The incidence of ataxia was 16% overall, however, this was not observed in cohort 1 at the 4 mg/kg q6h. Three (16%) events of ataxia were noted in cohort 2 and two (25%) in cohort 3 which implies a dose effect relationship although the numbers are much too small to be of significance. Three patients experienced neurological dose limiting toxicities; one patient experienced grade 3 ataxia during the first sequence of Cycle 2 and had the PSC 933 dose reduced from 5 mg/kg q6h to 4 mg/kg q6h. During the second sequence of the same cycle, grade 3 ataxia was noted again and the patient was discontinued from the study. A second patient had grade 3 ataxia during Cycle 2 and the PSC 833 dose reduced from 6 mg/kg q6h to 5 mg/kg q6h and continued on study at this dose for 9 cycles. A third patient experienced a neurotoxicity grade 3 and had the PSC 833 dose reduced from 5 mg/kg q6h to 4 mg/kg q6h then subsequently continued on study for 8 cycles.

6. Discussion

The maximum tolerated dose (MTD) of PSC 833 given orally in combination with etoposide was determined to be 5 mg/kg q6h. At this level 3 DLTs were observed in 10 evaluable patients. All PSC 833 related toxicities were immediately reversed on stopping the drug. It has been demonstrated that the PK profile after 50% dose of etoposide when given in combination with PSC 833 is equivalent to that after a full dose. It was not possible to associate the level of PSC 833 with the related toxicities which occurred, however, there appeared to be a relationship between the dose level and the incidence of ataxia and hyperbilirubinemia.

Although the study was not designed to study efficacy in this population, many of the patients had prolonged episodes of stable disease or partial responses and two achieved a complete response.

At the time the etoposide was administered, mean trough concentrations of PSC 833 were maintained above the target of 1000 ng/ml except in the low dose group on day 1. Thus it appears that in all the dose groups the blood concentrations of PSC 833 were sufficiently high to maintain the theoretical effective minimum concentration. Increases in the dose of PSC 833 result in increases in systematic exposure. However, in the present study it was not possible to determine definitely if the systematic exposure and C_{max} rise linearly and in proportion to dose. There was a higher incidence of ataxia and hyperbilirubinemia in the higher dose groups and this is consistent with dose proportional rises in C_{max} and AUC.

This study has demonstrated the suitability for oral PSC 833 to be taken into further clinical trials in children. The MTD is similar to that in adults and in combination with etoposide, the main non-haematopoietic toxicity is also similar, namely cerebellar ataxia and obstructive jaundice. Hepatic toxicity is likely to share the same aetiology as with high dose cyclosporin and may be due to the inhibition by PSC 833 of biliary canalicular *p*-glycoprotein mediated bile excretion.[18,19] As with cyclosporin this is invariably transient. The mechanism of the cerebellar ataxia is unclear. Plasma levels that are shown *in vitro* to be effective at modulating pgp are readily achieved at doses below the MTD, but if these are to be maintained for a prolonged period, 6 hourly dose scheduling is required. This is obviously inconvenient for child and parents. The necessity for prolonged unbroken exposure to MDR modulators is unproven. In paediatric tumour cell lines the most important factor appeared to be an adequate period of prior exposure (loading period) and then maintaining levels during the peak exposure to cytotoxic agent (2).

The influence of PSC on the PK of etoposide mirrors that reported in adults (15) and that previously described in children with high dose cyclosporin (7). The mean 54% decrease of the etoposide clearance rate indicated that a dose reduction to 50% is required in subsequent studies if potential increased efficacy due to higher drug levels rather than MDR modulation is to be avoided. A similar increase in AUC for doxorubicin has been described in adults and it is reasonable to assume that this will also be the case in children.[20] It is unfortunate that there are no clear data for vincristine as this drug stands out in preclinical studies as one with which high levels of sensitisation can be achieved. In a series of neuroblastoma and rhabdomyosarcoma cell lines, a range of MDR modulators have been shown to increase sensitivity to vincristine by up to 16-fold.[3] In view of the potentially disabling nature of vincristine neurotoxicity it is wise to proceed with caution in the absence of any paediatric data. With high dose cyclosporin, a 50% reduction of vincristine dose appeared to avoid any significant exacerbation of toxicity.[21]

Having determined the MTD, the next step would be to proceed to further studies in children. The only reliable method of confirming that PSC 833 is effective is either a randomised phase 2 study where a novel combination with and without modulator is used or a phase 3 trial with and without modulator. It is essential that both response rate and event-free survival (EFS) are used as endpoints. In the initially highly chemosensitive paediatric cancers it may be difficult to demonstrate an improvement in response rates. A more important effect may be the elimination of resistant tumour clones that would otherwise remain despite apparent complete remission. PSC 833 could also prevent the development of secondary drug resistant clones following exposure to MDR

associated chemotherapy.[3,22,23] Both these beneficial effects might only be apparent in an EFS advantage in the absence of any change in initial CR rate.

Randomised trials in relapsed and untreated AML in elderly patients have failed to show any benefit.[24,25] In younger patients there was, however, an increase in disease free and overall survival.[26] Unfortunately, the unavailability of intravenous PSC 833 lead to the premature closure of a study to confirm this observation.[24] Recent studies in adults have focused on novel drug combinations such as with liposomal daunorubicin.[27,28]

The lack of any consistent benefit from the addition of MDR modulators highlights the multifactorial nature of drug resistance. Several mechanisms may be present *de novo* or may develop during therapy which will reduce any impact of modifying a single mechanism. Moreover, in some studies the agent is used in the absence of any demonstration of MDR phenotype which is likely to dilute any benefit. Finally, it remains unclear what blood levels are required in different tumour types to maximise the effect. All modulators studied to date have significant toxicities – renal, hepatic and CNS which limit dose escalation.

This study demonstrated the feasibility of carrying out a complex phase 1 dose finding study in children in a multicentre and international setting. The study was pharma sponsored and carried out in a number of UK and French centres. It was not a formal UKCCSG/SFOP study. Nonetheless, it acts as a model for the current European initiative (ITTC network) to try and increase the earlier evaluation and introduction of novel agents in children with cancer.

Conflict of interest statement

None of the main authors (F.P., R.P., K.P.J., G.D., G.V.) had any potential conflict of interest in the performance of this study.

P. Berthaud was at the time of the study in the employment of Novartis Ltd, the manufacturer of PSC833. He had no role in the execution or monitoring of the study or in the evaluation of patents and his position had no influence on the outcome of the trial.

Acknowledgement

PSC 833 was provided for the study by Novartis.

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