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Phase I study of topotecan in combination with temozolomide (TOTEM) in relapsed or refractory paediatric solid tumours ☆

Hervé Rubie [a,*,l], *Birgit Geoerger* [b,l], *Didier Frappaz* [c,l], *Antonin Schmitt* [d,l], *Pierre Leblond* [e,l], *Anna Ndiaye* [b,l], *Isabelle Aerts* [f,l], *Marie-Cécile Le Deley* [b,l], *Jean-Claude Gentet* [g,l], *Angelo Paci* [b,l], *Pascal Chastagner* [h,l], *Nathalie Dias* [b,l], *Latifa Djafari* [i,l], *Marlène Pasquet* [d,l], *Etienne Chatelut* [d,l], *Judith Landman-Parker* [j,l], *Nadège Corradini* [k,l], *Gilles Vassal* [b,l]

[a] *Hôpital des Enfants, Toulouse, France*
[b] *Institut Gustave-Roussy, Villejuif, France*
[c] *Centre Léon Bérard, Lyon, France*
[d] *Institut Claudius Regaud, Toulouse, France*
[e] *Centre Oscar Lambret, Lille, France*
[f] *Institut Curie, Paris, France*
[g] *Hopital de la Timone, Marseille, France*
[h] *Hôpital Mère-Enfants, Nancy, France*
[i] *Schering-Plough France, France*
[j] *Hopital Trousseau, Paris, France*
[k] *Hôpital des Enfants, Nantes, France*

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ABSTRACT

Purpose: To evaluate maximum tolerated dose and recommended dose (RD) for phase II studies of topotecan (TPT) combined with temozolomide (TMZ) (TOTEM) in children and adolescents with relapsed or refractory solid malignancies.

Patients and methods: Multicentre, phase I study with a standard '3 + 3' design in five dose increments. Eligible patients: aged 6 months to 21 years, diagnosis of a solid malignancy failed at least 2 previous lines of therapy. TMZ was administered orally, starting at 100 mg/m^2/d, and TPT intravenously over 30 min, starting at 0.75 mg/m^2/d over 5 consecutive days every 28 d. A pharmacokinetics analysis was performed on Day 1 and Day 5 of cycle 1.

Results: Between February and October 2007, 16 patients were treated. The median age was 8.5 years (range, 3–19 years). Dose-limiting toxicity (grade 4 neutropenia and/or thrombocytopenia lasting more than 7 d) during the first cycle occurred in 2 of 3 patients at level 3 (TMZ 150 mg/m^2/d and TPT 1.0 mg/m^2/d) and was always manageable. Confirmed complete and partial responses were observed in 4 patients (25%), three with metastatic neuroblastoma and one with high-grade glioma. Seven patients had a stable disease. Pharmacokinetic data show a wide inter-individual variability. No significant differences were

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* *Corresponding author:* Address: Unité d'Hémato-Oncologie, Hôpital des Enfants, 330 avenue de Grande Bretagne, TSA 70034, 31059 Toulouse cedex 9, France. Tel.: +33 (0)5 34 55 86 11; fax: +33 (0)5 34 55 86.
E-mail address: rubie.h@chu-toulouse.fr (H. Rubie).

[l] On behalf of Société Française des Cancers et leucémies de l'Enfant et de l'adolescent (SFCE).

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observed between plasma TMZ and TPT concentrations on Day 1 and Day 5 indicating the absence of pharmacokinetic interaction between the drugs.

Conclusions: The RD for the combination is TMZ 150 mg/m^2/d and TPT 0.75 mg/m^2/d with dose-limiting haematological toxicity. The observed activity deserves further evaluation in paediatric malignancies.

1. Introduction

During the last decades, improvement in the treatment of childhood malignancies has been achieved with current cure rates attaining nearly 80% (http://seer.cancer.gov/). However, the prognosis of some malignant solid tumours such as those presenting with metastases or many central nervous tumours remains dismal. New innovative therapies or drug combinations are therefore strongly needed.

Temozolomide (TMZ) is a methylating agent used to treat malignant glial tumours in both adults and children. After oral administration, the drug is rapidly and completely absorbed and then is hydrolysed in monomethyl 5-triazeno imidazole carboxamide (MTIC), whose derivative methylates DNA mainly in O^6 position of guanine.[1] Several pre-clinical and clinical studies have investigated the efficacy of TMZ in different cancer cell types.[2] Paediatric phase I studies have determined the recommended dose (RD) as that indicated for adults, i.e. 200 mg/m^2/d over 5 consecutive days given every 4 weeks.[3,4] A phase II study failed to demonstrate significant activity of TMZ in malignant brainstem tumours and high-grade glioma in children.[5] However, anti-tumour effects have been observed in neuroblastoma (NB) xenograft models[6] and we recently confirmed its efficacy in children with heavily pre-treated NB with a 20% response rate (RR).[7] Some activity has also been suggested in other paediatric tumours.[8] In addition TMZ is effective when combined with other drugs such as etoposide,[9] procarbazine,[10] cisplatin[11] and particularly CPT11 the topoisomerase 1 inhibitor.[12–14]

Topotecan (TPT) is another camptothecin analogue acting as a topoisomerase 1 inhibitor. Pre-clinical studies in several paediatric xenograft tumour models demonstrated its activity in various histological subtypes, in particular NB.[15,16] The Paediatric Oncology Group phase I study determined an RD of 1.5 mg/m^2/d over 5 consecutive days.[17] The St. Jude's Children's Hospital reported a 60% RR in 28 children with NB using the 5-d schedule for 2 consecutive weeks.[18] TPT also proved to be active in children with medulloblastoma or supratentorial primitive neuroectodermal tumours[19] and Wilms' tumours.[20] Like TMZ, it was reported to be efficient when combined with other dugs such as cisplatin,[21] carboplatin[22] and vincristine and doxorubicin (TVD).[23] In the latter study, the Italian group reported a 64% RR in 25 children with refractory or relapsed NB. The German group reported a 41% RR in 54 patients with NB[24] after TPT combined with etoposide. The efficacy of TPT may be superior when combined with cyclophosphamide compared to TPT alone in children with sarcomas, NBs[25] and metastatic rhabdomyosarcomas.[26]

To our knowledge, this is the first paediatric phase I trial of intravenous (i.v.) TPT in combination with oral TMZ (TOTEM). As this combination has never been used in humans and due to the known myelosuppression of both agents, the main aim of this study was to determine the RD to be given in children and adolescents.

2. Patients and methods

2.1. Study design

This was a multicentre phase I trial adopting the standard '3 + 3' dose-escalation design with five dose increments to determine the RD of TOTEM to be given to children and adolescents with refractory or relapsed malignant solid tumours. The study was conducted in nine centres belonging to the Pharmacology Group of the Société Française des Cancers de l'Enfant.

2.2. Eligibility

Eligibility criteria included: age between 6 months and 21 years; histological or cytological diagnosis of solid malignancy; $\geqslant$2 previous lines of chemotherapy or no effective treatment available; life expectancy $\geqslant$8 weeks; no concomitant anticancer or investigational drug; Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant$2 or Lansky play score $\geqslant$50%; completion of anticancer therapy $\geqslant$4 weeks prior to study entry; adequate bone marrow reserve: neutrophils $>1.0\times10^9$/L – platelets $>100\times10^9$/L or neutrophils $>0.5\times10^9$/L – platelets $>75\times10^9$/L in case of bone marrow involvement; no organ toxicity $\geqslant$grade 2 according to NCI-CTCAEv 3.0, except for neurological symptoms due to the underlying disease; written informed consent signed by patient or parents/guardians.

The protocol (NCT00412503) was approved by the Institutional Review Board/independent Ethics Committee.

2.3. Dose escalation, study treatment and stopping rules

Dose-limiting toxicity (DLT) during the first treatment cycle was the basis for determining the maximum tolerated dose (MTD) and RD. Treatment cohorts were dosed in escalating order. At least 3 patients were to be treated at a given dose level (DL). If at least 1 patient developed a DLT, 3 additional patients were to be treated at the same dose. Dose escalation was stopped if 2 or more patients of the cohort developed a DLT. The following patients were to be treated at the lower DL. The MTD and RD were defined as the DL below the DL at which at least 2 patients within the cohort experienced DLT. At least 10 patients were to be treated at the defined RD. Five DL were planned with alternating dose increments of each

drug. The starting DL corresponded to 50% of the RD of each drug administered as a single drug treatment. The doses of TMZ and TPT were, respectively, level 1: 100–0.75, level 2: 150–0.75, level 3: 150–1.0, level 4: 200–1.0 and level 5: 200–1.5 mg/m^2/d. No intra-patient dose escalation was allowed. TMZ was given in the morning after a fasting overnight, and TPT was administered in a 30-min infusion 1 h after TMZ. The combination was administered over 5 consecutive days, repeated every 28 d. Anti-emetic prophylaxis was recommended. Treatment was to be continued until disease progression, unacceptable toxicity, patient's or parental refusal or treatment delay of >3 weeks.

2.4. Dose-limiting toxicity

Toxicity was assessed according to NCI-CTCAEv 3.0 (see http://ctep.info.nih.gov).

DLT was assessed over the first 28-d cycle and was defined as: grade 4 neutropenia lasting >7 d, grade 3–4 thrombocytopenia lasting or necessitating platelet transfusion for >7 d; documented infection during grade 4 neutropenia; any non-haematological ⩾grade 3 toxicity (except grade 3 nausea/vomiting, transient AST/ALT elevation and fever). The next cycle began at Day 29 after recovery to ⩽grade 2 neutropenia and thrombocytopenia or ⩽grade 1 non-haematological toxicity. Doses that were reduced due to toxicity were not re-escalated. If grade 4 toxicity persisted despite dose reduction, treatment was to be discontinued.

2.5. Pharmacokinetic methods

2.5.1. Blood sampling and drug measurement

Heparinised blood samples were collected before the TMZ intake, 1, 1.5 (corresponding to 5 min before the end of TPT infusion), 2, 2.5, 4.5, 7.5 h after TMZ intake at Day 1; before the TMZ intake, 1, 1.5 (corresponding to 5 min before the end of TPT infusion), 4.5, 7.5 h after TMZ intake at Day 5. Samples were immediately centrifuged at –4 °C and the plasma was stored at –20 °C until analysis. TPT plasma concentrations were determined using high-performance liquid chromatography as previously described.[27] TMZ plasma concentrations were determined within 30 d using high-performance liquid chromatography coupled to a UV detection adapted from Kim et al.[28]

2.5.2. Pharmacokinetic analysis

Plasma TMZ and TPT concentrations were analysed according to a non-linear mixed effects ('population') approach, using NONMEM program (version VI, level 1.0) running on a PC (Intel Xeon) using a FOCE Interaction method for TMZ and FOCE for TPT data. A proportional error model was used for both inter-patient and residual variability. Inter-occasion variability (corresponding to intra-patient variability between Day 1 and Day 5) was used for clearance. The area under the curve (AUC) was calculated for each drug using individual POSTHOC clearance (CL; corresponding to apparent oral clearance for TMZ): AUC = dose/CL. A one-compartment and zero-order absorption model was used for TMZ data; a two-compartment model was used for TPT data.

2.6. Tumour response

Patients were assessed by World Health Organization (WHO) criteria every 2 cycles. Objective responses were to be confirmed 4–6 weeks later. Efficacy parameters included complete (CR) or partial response (PR), its duration and progression-free survival (PFS, time from first treatment to disease progression, death or cut-off date).

3. Results

3.1. Patient characteristics

Between February and October 2007, 16 patients were enrolled in the study. Patient's characteristics are shown in Table 1. Briefly, the median age at inclusion was 8.5 years (range 3–19); 8 patients were diagnosed with NB. Most children had metastatic disease (87.5%), refractory to conventional treat-

Table 1 – Patient characteristics.

	N = 16
Age at diagnosis (years)	
Median [Min–Max]	8.5 (3–19)
Gender	
Male/female	11/5
Performance status: Lansky play score/ECOG	
90–100%/0	11 (69%)
70–80%/1	5 (31%)
Underlying disease	
Neuroblastoma	8
Osteosarcoma	2
Ependymoma	1
High grade glioma	1
Rhabdomyosarcoma	1
Undifferentiated carcinoma of the nasopharyngeal tract (UCNT)	1
Granulosa cell tumour	1
Peritoneal carcinomatosis, primary unknown	1
Delay after initial diagnosis (months)	
Median	2.8 (0.4–7.4)
Tumour stage at inclusion	
Metastatic	14 (87.5%)
Non-metastatic	2 (12.5%)
Disease status at registration	
Refractory disease	5 (31%)
Relapse	2 (13%)
Refractory and relapsing disease	9 (56%)
Number of relapses (including the present one) n = 11	
1	7 (64%)
2	1 (9%)
3	2 (18%)
4	1 (9%)
Prior anticancer therapies	
Chemotherapy	15
High-dose chemotherapy regimen	6
Radiation therapy	7
Surgical resection	11

Table 2 – Dose levels and dose-limiting toxicities (DLT).

Dose level	Temozolomide ($mg/m^2/d$)	Topotecan ($mg/m^2/d$)	Treated patients	DLTs/evaluable patients	DLT during cycle 1	Cycles/patient median (Min–Max)	Total cycles evaluable for toxicity
1	100	0.75	3	0/3	None	2 (2–3)	7
2	150	0.75	10	2[a]/10 (1/6 + 1/4)	Gr 3 thrombocytopenia >7 d Gr 3 thrombocytopenia >7 d requiring transfusions	4 (2–12[b])	61
3	150	1.0	3	2/3	Gr 3–4 thrombocytopenia >7 d Gr 4 neutropenia + Gr 3 thrombocytopenia >7 d	2 (2–11[a])	16
Total			16			3 (2–12)	84

[a] Dose escalation: 1 out of 6 patients experienced DLT during dose escalation and 1 of 4 additional patients during the extension at the defined RD.

[b] Treatment ongoing for 1 patient at 16 months; another patient is ongoing with TMZ alone after 12 cycles of TOTEM.

Table 3 – Pharmacokinetic parameters of temozolomide and topotecan: mean (coefficient of variation %).

	Dose level (mg/m^2)	No of patients (Day 1/Day 5)	AUC (mg h/L) Day 1	AUC (mg h/L) Day 5	CL ($L/h/m^2$) Day 1	CL ($L/h/m^2$) Day 5
Topotecan	0.75	13/13	0.089 (79%)	0.079 (33%)	11.1 (40%)	10.6 (33%)
	1	3/2	0.083 (34%)	0.054–0.143	13.0 (34%)	7.0–18.5
Temozolomide	100	3/3	42.9 (6%)	42.4 (17%)	2.31 (5%)	2.40 (17%)
	150	12/11	43.2 (21%)	41.5 (26%)	3.70 (21%)	4.02 (27%)

ment and had been heavily pre-treated including high-dose chemotherapy (HDC) regimens in six of them.

3.2. *Treatment and toxicity*

All patients were evaluable for DLT at cycle 1 (Table 2). All doses were administered according to the protocol except one with a body surface area (BSA) of 2.27 m^2 who was treated with doses calculated on a BSA of 2 m^2. At DL 1, none of the 3 patients experienced DLT. At DL 2, one of the first 3 patients experienced a dose-limiting grade 3 thrombocytopenia lasting more than 7 d. Consequently, 3 additional patients were treated at the same level, and no DLT was observed. At DL 3, grade 3 thrombocytopenia lasting for more than 7 d was observed in 2 of 3 patients, associated with grade 4 neutropenia in one. Four more patients were then treated at DL 2; one of these patients experienced a dose-limiting grade 4 thrombocytopenia requiring platelets transfusions during more than 7 d, leading to two DLTs in 10 patients at this DL (20%, 95% CI, 2.5–56). Thus, the RD for the TOTEM phase II study was established as 150 $mg/m^2/d$ for TMZ and 0.75 $mg/m^2/d$ for TPT administered every 28 d.

All 16 patients received at least 2 cycles of treatment (maximum 14, median 3.5). Among the 4 patients having experienced a DLT, 2 (1 at DL 2, 1 at DL 3) received the second cycle at the lower DL and 2 at the same DL because haematological toxicity was considered as easily manageable. None stopped treatment because of toxicity. Overall, 84 cycles were evaluable for toxicity. A total of 46 clinical non-dose-limiting adverse events observed in 14 patients were recorded. All were grade 1 or 2 except 2: 1 grade 3 vomiting and 1 grade 3 febrile neutropenia without documented infection which resolved after empirical antibiotic therapy. The most frequent adverse events were asthenia (8), vomiting (8), nausea (6), abdominal pain (4), anorexia (3) and diarrhoea (3). Haematological toxicity was frequent: grade 3 or 4 neutropenia and thrombocytopenia occurred in 12 and 11 patients, respectively. These haematological toxicities were manageable and never life-threatening, allowing treatment to be given on an outpatient basis and did not increase with prolonged treatment.

Concerning the patients treated at the RD, the actual dose intensity of the whole treatment was equal to or greater than 94% of the theoretical dose for both drugs in all but 1 patient. That patient had a metastatic NB with bone marrow involvement and experienced repeated episodes of thrombocytopenia, requiring delays in treatment administration.

3.3. *Pharmacokinetics (Table 3)*

Plasma samples for TMZ analysis were available in 15 patients. There was no significant difference between apparent clearance at Day 1 and Day 5 (Fig. 1A). The inter-individual variability in clearance was partly explained by BSA with a decrease from 45% (Day 1) or 53% (Day 5) to 26% (Day 1) or 32% (Day 5) when CL was expressed per m^2. The mean CL was higher for patients at 150 mg ($n = 12$) than that of the 3 patients treated with 100 mg (3.70 versus 2.31 $L/h/m^2$) resulting in similar AUC between the two dose levels (i.e. 43 mg h/L).

Plasma TPT samples were evaluable in all 16 patients. There was no significant difference between clearance at Day 1 and Day 5 (Fig. 1B). The inter-individual variability in

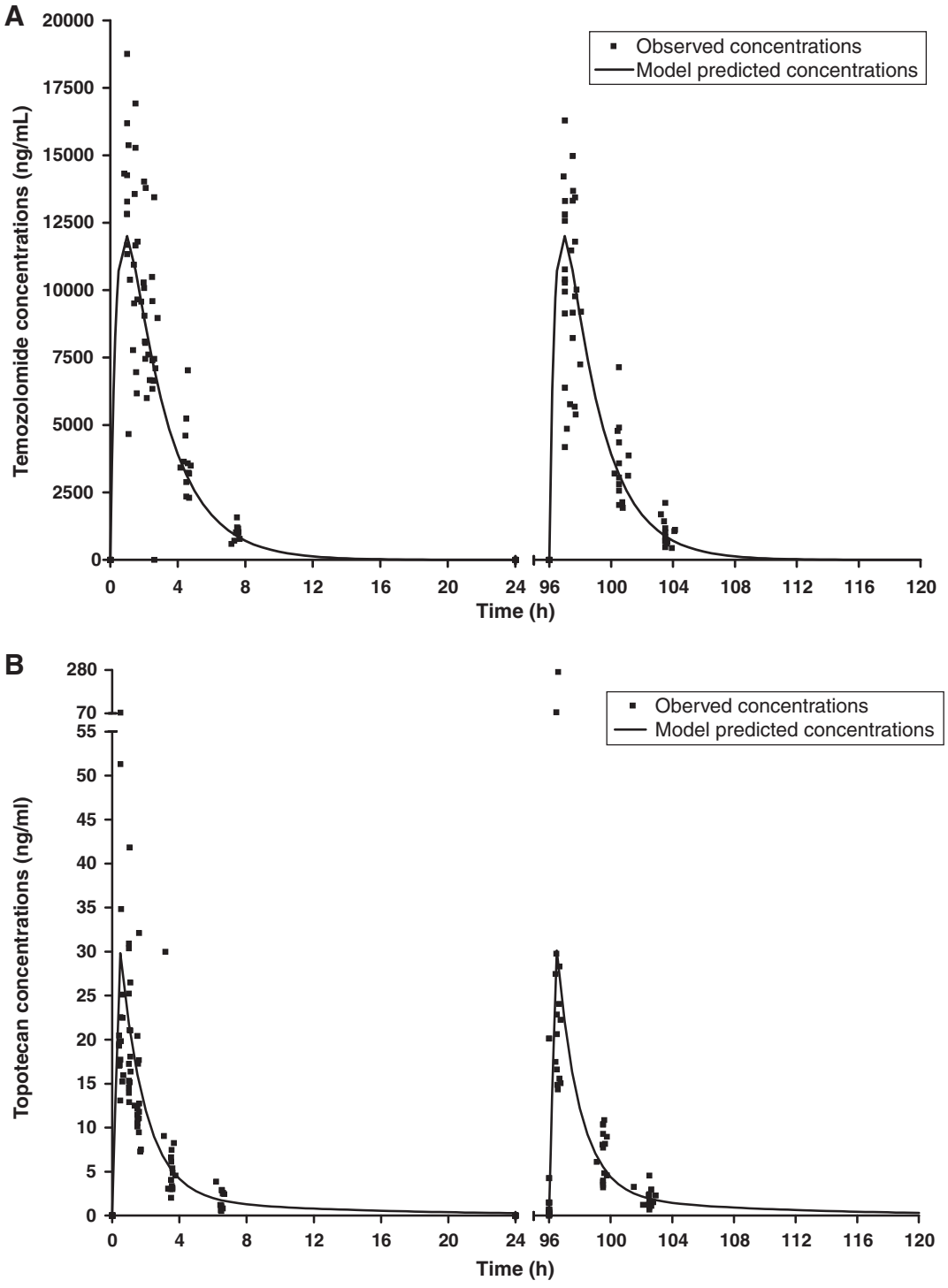

Fig. 1 – Temozolomide (A) and topotecan (B) plasma concentrations at Day 1 and Day 5.

clearance was poorly explained by BSA with a decrease from 54% (Day 1) or 44% (Day 5) to 39% (Day 1) or 36% (Day 5) when CL was expressed in m^2 per BSA.

3.4. *Efficacy*

All 16 patients had received at least 2 cycles of treatment and were evaluable for efficacy. Confirmed objective tumour responses were observed in 4 patients at DL 2, leading to the best observed response rate of 25% (95% CI, 7–52). One child with a metastatic relapsed NB had previously received 3 lines of chemotherapy including HDC 3 years prior and achieved a PR after 2 cycles and a confirmed CR after 10 and 12 cycles. He continued with TMZ alone until disease progression 4 months later and was still alive 18 months later. Another child had a third metastatic relapse of a localised NB and a confirmed PR was observed after 3 cycles. Local residue was surgically resected leading to CR and the

patient received 9 additional months of a TMZ–irinotecan combination before disease progression 11 months later. A 5-year-old girl, with a metastatic NB relapsing during retinoic acid-containing maintenance treatment following intensive chemotherapy including HDC, achieved a metastatic PR after 4 cycles that was confirmed after the sixth cycle. PR of the primary calcified site (49%) was obtained after 14 cycles, although new concomitant metastatic progression occured. The fourth patient had presented with a relapsed high-grade glioma (HGG) 10 months after cranial irradiation. A PR was observed after 2 cycles which lasted 10 additional months. All responders received full doses of each drug at DL 2, except one who received the second cycle at DL 1 and subsequent cycles ($n = 10$) at DL 2. Prolonged stable disease was observed in 7 patients: 5 NBs (during 5, 12, 15 and 18 months in 2), 1 rhabdomyosarcoma (7 months) and 1 osteosarcoma (6 months).

4. Discussion

This phase I trial assessed the phase II RD for the TOTEM combination at 0.75 mg/m^2/d for i.v. TPT and 150 mg/m^2/d for oral TMZ and administered every 28 d. As expected, based on the dose-finding studies exploring TMZ and TPT as single agents in adults and children, the toxicity of this combination was mainly haematological.[2,4,16] The RD for TMZ and TPT as single agents was 200 and 1.5 mg/m^2, respectively, for 5 consecutive days. Due to the similar toxicity profile of these agents, this current combination trial was designed to start with the first DL at half doses of each drug and alternate dose increments of each drug. This approach proved to be safe and valid since all observed haematological DLTs were manageable on an outpatient basis and were never life threatening. Although prolonged thrombocytopenia and/or neutropenia occurred frequently, haemorrhagic events or documented febrile infections were rare. Remarkably, this was observed in heavily pre-treated patients who may be the target population for this treatment. Indeed, among the 4 children who experienced dose-limiting neutropenia and thromobocytopenia, 2 had received HDC 10 and 36 months before TOTEM administration, and the other 2 patients had received multiple prior lines of treatment. Moreover, the two of them with a metastatic NB might have had a massive bone marrow involvement, but such an assessment was not mandatory at enrollment in the trial although it was suggested by the rapid myelosuppression prior to study inclusion in one. Furthermore, 15 patients had a normal platelet count at the beginning of treatment, suggesting that possible bone marrow involvement in some of them was minimal. Interestingly, no cumulative toxicity was noted with prolonged treatment up to 14 cycles. No haematological disorder was reported during the study and subsequent follow-up. Consistent with the single agent toxicity profile, no other significant toxicity was observed with this combination, as they were all either grade 1 or 2, mainly digestive (nausea/vomiting) or tumour-related (hydrocephalus, abdominal or bone pain).

Regarding pharmacokinetics data, the inter-individual variability of TMZ clearance was limited when expressed according to the BSA (coefficient of variation of 26%). The inter-patient variability for TPT clearance was greater (coefficient of variation of 39% for clearance expressed in L/h/m^2). It is noteworthy that there was no significant difference between plasma concentrations observed at Day 1 and Day 5 confirming the absence of pharmacokinetic interaction between the two drugs. The mean TMZ single-day AUC observed at the RD (i.e. 43.2 mg h/L) was slightly but not significantly below the mean value observed at the RD of single drug administration (1000 mg/m^2 per cycle) (i.e. 48 mg h/L).[3] However, the mean TPT single-day AUC (i.e. 0.089 mg h/L) represents about the half of the mean value (i.e. 0.187 mg h/L) observed after the RD of single drug administration (i.e. 7.5 mg/m^2 per cycle).[17] These observations confirm that pharmacokinetic results were consistent between the different schedules of administration (combination versus single drug therapy), the difference (TPT) or similarity (TMZ) being exclusively due to the respective doses.

Despite the reduced single agent doses used in this combination, we observed interesting confirmed responses in 4 patients with metastatic relapsed or refractory and heavily pre-treated disease (1 CR and 2 PR in NB and 1 PR in HGG) as well as prolonged tumour stabilisations in nearly half of the patients. To our knowledge, this is the first study suggesting the efficacy of this drugs combination. To date, such an efficiency has been reported for single agent treatment in a variety of paediatric tumours[18–20] or suggested for TMZ in combination with etoposide,[9] procarbazine,[10] cisplatin[11] and irinotecan.[12–14] TPT was also found to be efficient when combined with platinum compounds,[21,22] vincristine–doxorubicin,[23] etoposide[24] and cyclophosphamide.[25,26] Concerning the combination with topoisomerase inhibitors, a recent clinical phase II study failed to demonstrate single agent activity of irinotecan in NB when administered on a 3 weeks schedule.[29] However, the American New Approach in Neuroblastoma Treatment Group recently reported the results of a phase I trial with a 50% RR or disease stabilisation in 14 evaluable children with NB after the administration of oral irinotecan during 2 consecutive weeks and combined with TMZ.[30] Due to the interesting activity observed with the topoisomerase 1 inhibitor TPT in combination with other anticancer drugs, as well as our finding in this phase I study, we are interested in evaluating the efficacy of TOTEM particularly in children with NB.

In conclusion, the TPT–TMZ combination is well tolerated and demonstrated remarkable activity in a paediatric phase I population with heavily pre-treated relapsed or refractory neuroblastoma and high-grade glioma. Further investigations are warranted to establish its potential in the treatment of these childhood malignancies and a phase II study is currently ongoing.

Conflict of interest statement

Although all authors completed the disclosure declaration, the following author indicated a financial or other interest that is relevant to the subject matter under consideration in this article.

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