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

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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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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