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# Phase I study of temozolomide combined with oral etoposide in children with recurrent or progressive medulloblastoma

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ABSTRACT

*Background:* The prognosis of recurrent or progressive medulloblastoma (MB) is still poor. This study was designed to investigate the potential therapeutic benefit of combination therapy with temozolomide (TMZ) and oral etoposide (VP-16) in children with progressive or relapsed MB. Given the oral administration of both drugs the regimen was administered outpatient.

*Methods:* A phase I trial was conducted to establish the maximum tolerated dose (MTD) of TMZ and oral VP-16. This orally administered combination was investigated by classical 3 + 3 design. Cohorts of patients were enrolled at four different levels: (1) TMZ 120 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–8; (2) TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–8; (3) TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–10; (4) TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–12. Therapy was administered in 28-d courses. A total of 66 courses were administered to 14 patients with a median age of 5.7 years.

*Results:* None of the 3 patients at dose levels 1 and 2 had dose-limiting toxicity (DLT). Of the 6 patients at dose level 3, 1 patient had DLT. At dose level 4, grade 4 thrombocytopaenia and neutropaenia were observed in the first 2 patients enrolled. Therefore, the MTD was established at dose level 3.

*Conclusion:* The recommended phase II dose in children is TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–10 every 28 d. The combination was well tolerated and demonstrated antitumour activity.



## 1. Introduction

Medulloblastoma (MB) is one of the most common malignant brain tumours in children, accounting for 20–25% of all brain tumours in the paediatric population.[1] Patients were divided into stratification groups on the basis of age, degree of resection and disease dissemination. Currently, multimodality treatment, comprising surgery, chemotherapy (CT) and depending on the age of the patient, radiotherapy (RT), is considered the most effective strategy against these malignant cerebellar tumours of childhood. The 5-year survival rate is 55–76% for high-risk patients and 70–80% for standard-risk

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patients.[2] Surgery alone is not an effective treatment for MB because this disease tends to recur both locally in the posterior fossa and in the whole central nervous system through leptomeningeal dissemination. In the 1950 adjuvant RT had been proposed as a possible treatment to reduce the risk of recurrence and the prognosis improved substantially.[3,4] Unfortunately, many of the patients treated develop severe late toxicity that heavily impacts their quality of life. RT has a devastating effect on the intellect; furthermore, children's growth could be impaired as a result of growth hormone deficiency, early puberty development and compromised spinal growth.[2,5] Since 1980 many investigators have tried to optimise adjuvant treatment, modifying radiation fractionation schedules, lowering radiation total doses and/or introducing CT, in an attempt to further improve survival and to reduce late toxicity. In particular, in children less than 3 years of age many aggressive CT schemes have been employed in order to delay RT or to avoid it completely.[6–11] Currently, vincristine, lomustine, cyclophosphamide, CCNU, platinum derivatives, methotrexate and etoposide (VP-16) are those in most common use. High-dose CT with stem cell rescue has been employed with promising results but its role remains to be defined.[12–14] Randomised studies have reported that CT in combination with radiation therapy improves the survival rate in patients with MB compared with radiation therapy alone.[15,16] Although many of the developments in the management of children with MB are the result of well-performed, prospective multi-institutional randomised trials, many issues are still open. Optimal CT drugs and schedules have not yet been identified, in particular, in children with recurrent or progressive MB. About 30–50% of children with MB still relapse with an almost inevitably fatal disease.[1,17] Relapses occur earlier in children; nearly 75% of relapses in children are observed within 2 years. The prognosis at relapse of MBs is grim, especially when it occurs after conventional RT, and only few long-term survivors are reported.

Clinical studies have reported some activities of single agent temozolomide (TMZ) and oral VP-16 in children with progressive or relapsed MB.[18–21] Pre-clinical data and adult experience suggest a synergistic effect when an alkylator and a topoisomerase inhibitor are used together.[22–24]

A phase I study of TMZ and escalating doses of oral VP-16 for adults with recurrent malignant glioma has recently been published.[24] The maximum tolerated dose (MTD) of TMZ and VP-16 in this group was TMZ 150 mg/m$^2$/d for 5 d and VP-16 50 mg/m$^2$/d for 12 d.

To our knowledge until now, phase I studies have not been reported in paediatric patients. In order to assess the potential therapeutic benefit of combination therapy with TMZ and oral VP-16 also in children with progressive or relapsed MB, this phase I study was designed to establish the toxicity and MTD. The starting dose was about 80% of the MTD established in adults phase I trials.

## 2. Patients and methods

### 2.1. *Eligibility*

Patients aged between 3 and 18 years with histologically confirmed supratentorial PNET/MB, including patients with metastatic disease, were eligible for this study. Metastatic disease was defined as unequivocal evidence on magnetic resonance imaging (MRI) scan of supratentorial metastases and/or spinal metastases. Patients were required to have a recurrent or progressive disease refractory to conventional therapy. Other eligibility criteria included disease measurable by conventional MRI criteria; life expectancy of at least 8 weeks; adequate performance status (Karnofsky or Lansky score > 30); ability to swallow capsules; a minimum of 6 weeks from prior RT and a minimum of 4 weeks after any CT (6 weeks since nitrosoureas); adequate laboratory values, including an absolute neutrophil count $\geqslant 1 \times 10^9$/l, a platelet count $\geqslant 100 \times 10^9$/l, total bilirubin levels $\leqslant 1.5 \times$ the upper limit of normal, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels $\leqslant 2.5 \times$ the upper normal limit. A clinically appropriate daily dose of steroids was determined for each patient before beginning the first cycle of therapy. The dose was required to have been stable for at least 7 d before treatment initiation, and efforts were made to maintain the same dose until the radiographic tumour measurement was performed after completing the second cycle. Patients with the following conditions were excluded from the study: previous treatment with single TMZ or oral VP-16; concomitant investigation of treatment for PNET/MB; severe or threatening infection; pregnant or lactating females. Written informed consent to participate in the study was obtained from either patients or their parents or both.

### 2.2. *Study design and treatment plan*

The aim of this multicentre prospective study was to assess the toxicity and to determine the MTD of oral TMZ in combination with oral VP-16 administered as a single dose in patients with relapsed or refractory supratentorial PNET/MB. The combination therapy with TMZ and oral VP-16 once daily was investigated in cohorts of 3–6 patients by escalating either the dose of TMZ or the number of days of VP-16 treatment given at a fixed dose. Cohorts of patients were enrolled at four different levels: (1) TMZ 120 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–8; (2) TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–8; (3) TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–10; (4) TMZ 150 mg/m$^2$ on days 1–5 and VP-16 50 mg/m$^2$ on days 1–12. TMZ and VP-16 were administered orally in a fasting state, in the morning and late afternoon, respectively. Capsules of VP-16 and TMZ had to be swallowed whole with a glass of water. Cycles were repeated every 28 d and a maximum of 12 cycles were given. Intrapatient dose escalating was not permitted.

Dose escalation was performed according to the classical 3 + 3 design. If none of the first 3 patients enrolled at a given dose level developed dose-limiting toxicity (DLT), subsequent patients were enrolled at the next higher dose level. If 2 or 3 of the first 3 patients experienced DLT, then the dose was considered to be too high, and the dose was decreased to the previous level. If DLT occurred in 1 of 3 patients, 3 additional patients were enrolled at that level. If 1 of 6 patients experienced DLT, the dose could be escalated. If 2 or more of 6 patients had DLT at a given level, the MTD was exceeded. The MTD was defined as one level below the level at which 2 or more of 6 patients developed DLT. Given the risk of infection