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Phase II study of temozolomide in combination with topotecan (TOTEM) in relapsed or refractory neuroblastoma: A European Innovative Therapies for Children with Cancer-SIOP-European Neuroblastoma study ☆,☆☆

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Abstract ***Purpose:*** To assess objective response rate (ORR) after two cycles of temozolomide in combination with topotecan (TOTEM) in children with refractory or relapsed neuroblastoma.

Patients and Methods: This multicenter, non-randomised, phase II study included children with neuroblastoma according to a two-stage Simon design. Eligibility criteria included relapsed or refractory, measurable or metaiodobenzylguanidine (mIBG) evaluable disease, no more than two lines of prior treatment. Temozolomide was administered orally at 150 mg/m^2 followed by topotecan at 0.75 mg/m^2 intravenously for five consecutive days every 28 days. Tumour response was assessed every two cycles according to International Neuroblastoma Response Criteria (INRC), and reviewed independently.

Results: Thirty-eight patients were enroled and treated in 15 European centres with a median age of 5.4 years. Partial tumour response after two cycles was observed in 7 out of 38 evaluable patients [ORR 18%, 95% confidence interval (CI) 8–34%]. The best ORR whatever the time of evaluation was 24% (95% CI, 11–40%) with a median response duration of 8.5 months. Tumour control rate (complete response (CR) + partial response (PR) + mixed response (MR) + stable disease (SD)) was 68% (95% CI, 63–90%). The 12-months Progression-Free and Overall Survival were 42% and 58% respectively. Among 213 treatment cycles (median 4, range 1–12 per patient) the most common treatment-related toxicities were haematologic. Grade 3/4 neutropenia occurred in 62% of courses in 89% of patients, grade 3/4 thrombocytopenia in 47% of courses in 71% of patients; three patients (8%) had febrile neutropenia.

Conclusion: Temozolomide–Topotecan combination results in very encouraging ORR and tumour control in children with heavily pretreated recurrent and refractory neuroblastoma with favourable toxicity profile.

1. Introduction

Neuroblastoma is the most common extracranial solid tumour of childhood [1]. Despite recent advances, children with relapsed and refractory neuroblastoma have a less than 50% response rate to second-line regimens and a poor long-term survival [2]. Therefore, new treatment strategies are needed for these patients.

Temozolomide is a methylating agent considered to exert its toxic effects primarily by generating O^6-methylguanine in DNA [3]. Temozolomide was attractive because of its activity in neuroblastoma xenografts [4], excellent oral bioavailability, absence of pharmacokinetic drug interaction, efficient penetration of the blood–brain barrier [5] and modest toxicity in paediatric phase I studies [6] Temozolomide has been approved for treatment of malignant glial tumours in adults and children [7,8] and has shown activity in relapsed or refractory high-risk neuroblastoma patients [9,10].

Topotecan is a semisynthetic camptothecin derivative capable to block DNA and RNA synthesis in inhibiting topoisomerase I. This drug demonstrated antitumour activity in pre-clinical models of neuroblastoma [11,12] and in paediatric phase I/II trials [13–16]. Phase I studies of topotecan showed a toxicity profile with dose-limiting myelosuppression [17,18].

A phase II trial of topotecan in patients with newly diagnosed neuroblastoma, using the 5-day schedule for two consecutive weeks, reported an objective response rate (ORR) of 60% in 28 children [19].

The rationale for the combination of temozolomide and topotecan is based on the synergistic activity of temozolomide in combination with topoisomerase I inhibitors observed in preclinical studies [20] due to their distinct mode of action [21]. The paediatric phase I study combining topotecan and temozolomide (TOTEM) showed absence of pharmacokinetic interaction between both drugs, mainly haematological toxicity and preliminary responses in neuroblastoma [22].

We explored the efficacy of TOTEM in a multicenter, non-randomised, phase II study. The trial included three disease strata, neuroblastoma, central nervous system (CNS) tumours and extracranial solid tumours; this current report presents the results of the neuroblastoma cohort.

2. Patients and methods

2.1. Eligibility

Eligibility criteria included: age between 6 months and $\leqslant$20 years; histological or cytological diagnosis of neuroblastoma; refractory or relapsed metastatic or localised disease; maximum two previous lines of chemotherapy; patients previously treated with only one of the two drugs were eligible; life expectancy $>$ 3 months; no concomitant anticancer or investigational drug; Eastern Cooperative

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