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BRIEF REPORT
A Phase II Study to Determine the Efficacy and Safety of Oral Treosulfan in Patients With Advanced Pre-Treated Ewing Sarcoma ISRCTN11631773

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We report a prospective Phase II study of efficacy and toxicity for oral treosulfan in advanced Ewing sarcoma. Twenty patients, median age 19 years (range 7–39) from five UK sites, were treated with oral treosulfan 1 g/m^2 daily for 7 days in 28. Primary endpoint was objective response rate. Best response was stable disease in one patient. All patients died of progressive disease, after median 6.41 months. Median progression free survival was 1.8 months. Toxicity was minimal. No activity was demonstrated for treosulfan at this dose. Progression free survival data should be able to be used for comparison when planning future clinical trials. Pediatr Blood Cancer 2015;62:158–159. © 2014 Wiley Periodicals, Inc.

Key words: Ewing sarcoma; treosulfan

INTRODUCTION

Very few prospective trials of treatments for palliation of advanced recurrent Ewing sarcoma (ES) have been undertaken, despite its poor prognosis [1–4]. Patients have often received multiple individual cytotoxic agents as well as multiple courses of treatment including radiotherapy. Oral etoposide is frequently used in this setting when further low intensity and convenient treatment is desirable; however, response rates are reportedly low (approximately 10%) [5]. We investigated the efficacy of an alternative oral agent.

Treosulfan (dihydroxybusulfan) is a bi-functional alkylating agent. Its active metabolites monoepoxide and L-diepoxide are produced by non-enzymatic reactions under physiological conditions. These epoxides are responsible for producing DNA alkylation and inter-strand cross-linking. Efficacy of treosulfan in pre-clinical studies (*in-vitro* ES cell line inhibition and anti-tumour activity in mouse xenograft models) has been shown to be superior to busulfan [6,7]. Treosulfan is a prodrug structurally related to busulfan, an agent widely used in ES at high-doses [8]. One of the limitations to busulfan is concurrent use of radiotherapy, because of reported synergism causing demyelinating neurotoxicity [9]. High-dose treosulfan, appears to differ from busulfan, having a reduced toxicity profile and importantly does not appear to have the same adverse consequences when administered with radiotherapy [6]. Treosulfan given orally at lower doses has been widely used in the past for treatment of advanced ovarian cancer [10]. No data have been published to date on the clinical role of oral treosulfan in ES.

METHODS

The primary endpoint was best response and we hoped for a response rate (CR + PR + SD) of more than 30%. However, a response rate of more than 10% would have been considered clinically meaningful. We planned to recruit 25 patients (one-sided alpha level of 0.05 and 80% power) and if there were at least six responders then treosulfan would be worth investigating further.

Patients had advanced, refractory ES, had failed at least one course of chemotherapy, and had measurable disease. Eligible patients were aged 3–50 years with WHO performance status (PS) of 0–2 or Lansky PS > 30. All patients received oral treosulfan capsules 1 g/m^2 daily for 7 days, every 28 days until progression. Imaging was performed at baseline and then every two cycles. Response was assessed according to RECIST criteria [11]. Adverse events were graded according to CTCAE v4.0.

RESULTS

Twenty-one patients were recruited from five UK sites between February 2010 and June 2012 at which point the trial was stopped as, even if a response was seen in all remaining patients, the primary endpoint would not have been met. One patient did not receive treatment and was excluded from analysis. Median age was 19 years (range 7–39); 40% male, 60% female. All had a performance status above 50% (Lansky) or ≤ 2 (WHO).

Twelve (60%) patients had received two previous lines of chemotherapy; seven (35%) received three or more. Ninety percent had prior radiotherapy (4 patients to 1 site only and the others had between 2–6 sites treated). Seventy percent had previous surgery. Only 11 (55%) patients received > 1 treatment cycle. Best overall response (OR) was stable disease for one patient lasting approximately three months. Objective progressive disease (PD) was documented in 13 patients. Six patients were not assessable for OR, with all of them stopping treatment due to clinical deterioration.

All patients died from sarcoma. Median progression free survival was 1.8 months (55 days) and median overall survival was 6.4 months (175 days) (Figs. 1 and 2).

Thirty three cycles of treosulfan were evaluable for toxicity. Five patients experienced grade 3/4 myelosuppression. One patient

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Conflict of interest: Nothing to report.

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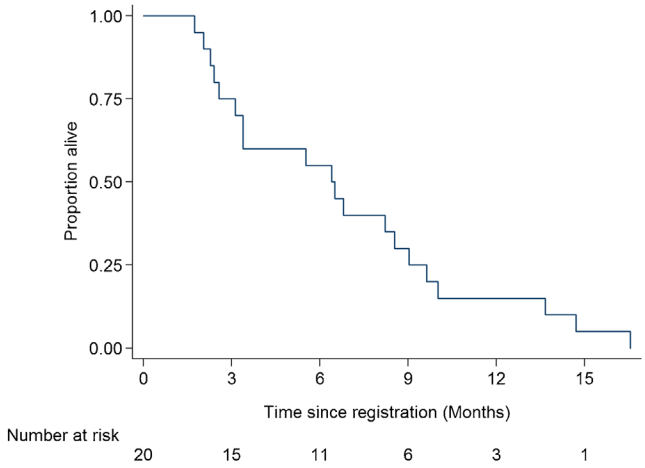

Fig. 1. Median overall survival: 6.41 (175 days).

developed febrile neutropenia and one a grade 3 infection. Both had planned treatment delays, but both subsequently had confirmed progressive disease and were withdrawn from treatment. These were the only treatment-related grade 3/4 adverse events and no treatment reductions were recorded.

DISCUSSION

No efficacy for this dose and schedule of treosulfan was demonstrated in this prospective phase II study. Little toxicity was apparent and one explanation for lack of efficacy may be relative under dosing. The study was conceived to explore options in an under-researched sub-group of patients with ES. Dosing and schedule were therefore selected from previous studies in adults with advanced carcinoma in the absence of specific dose finding studies in children. This was also felt to be reasonable as the median age of patients with recurrent ES is between 15 and 19 years [12]. It has since been noted that a randomised phase II study in adult ovarian cancer comparing oral treosulfan with carboplatin, closed prematurely because of a lack of efficacy at similar dose levels [13].

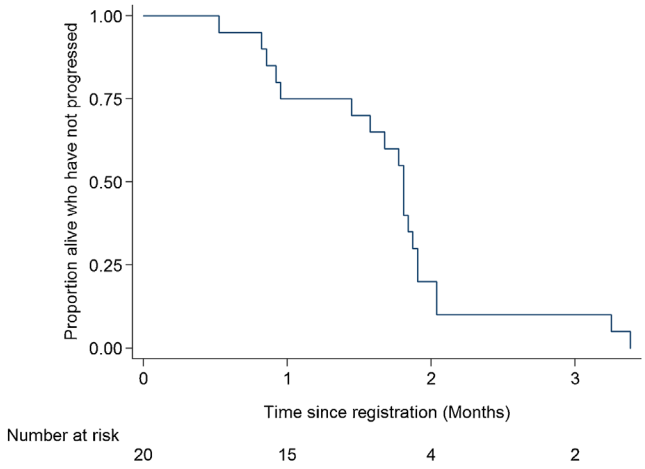

Fig. 2. Median progression free survival time: 1.81 months (55 days).

It is also worth noting the absence of efficacy data for high-dose treosulfan as a single agent despite its widespread adoption for use in stem cell supported high-dose therapy for ES [14].

New treatments are required for advanced refractory ES. Although not the subject of extensive prospective evaluation, oral etoposide is a convenient, well tolerated and commonly used treatment [5]. Alopecia and occasional profound myelosuppression are disadvantages but we recommend it remain a standard against which future treatments can be tested in a group of patients often excluded from clinical trials. The progression free survival data reported here should be valuable for the planning of future trials in this population.

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