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Phase II Study of Liposomal Muramyl Tripeptide Phosphatidylethanolamine (MTP/PE) in Advanced Soft Tissue Sarcomas of the Adult. An EORTC Soft Tissue and Bone Sarcoma Group Study

J. Verweij, I. Judson, W. Steward, R. Coleman, P. Woll, C. van Pottelsberghe, M. van Glabbeke and H. Mouridsen

The EORTC Soft Tissue and Bone Sarcoma Group conducted a phase II study with intravenous muramyl tripeptide phosphatidylethanolamine (MTP/PE) at a dose of 4 mg once weekly in 20 patients with metastatic soft tissue sarcomas. Responses were not seen in 19 evaluable patients. Toxicity consisted mainly of a mild flu-like syndrome after 62% of drug administrations. It is concluded that MTP/PE at this dose and schedule has no activity in metastatic soft tissue sarcoma.

Key words: MTP/PE, soft tissue sarcomas, phase II
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INTRODUCTION

BECAUSE THE number of active drugs in the treatment of metastatic soft tissue sarcomas is limited, new active drugs are urgently needed. The current first-line agents (doxorubicin, ifosfamide and DTIC) were found to be active when tested in second-line chemotherapy, and thus it seems appropriate to test new drugs in patients after failure to first-line chemotherapy [1]. Liposomal muramyl tripeptide phosphatidylethanolamine (MTP/PE) is a new compound exerting antitumour activity in several *in vitro* [2–4] and *in vivo* models [5, 6], among others, antitumour effects and prolonged survival were observed in Danish dogs with spontaneous osteosarcoma [6]. The drug has been shown to activate macrophages [7]. A stable, reproducible preparation of liposomal MTP/PE has recently been produced and was shown to induce increased serum levels of ceruloplasmin, C-reactive protein and IL-1β (interleukin-1β) [8–12]. Phase I studies have shown chills and fever to be the main side-effects; the recommended dose for phase II studies is 4 mg once daily, given as a 30–60 min infusion [8–12]. In osteosarcoma patients with pulmonary metastases, fibrotic changes and a change to a more benign phenotype have been reported in resected tumour nodules [13]. We performed a phase II study with MTP/PE given in second- or third-line therapy to patients with soft tissue sarcomas.

Correspondence to J. Verweij at the Department of Medical Oncology, Rotterdam Cancer Institute, P.O. Box 5201, 3008 AE Rotterdam, The Netherlands; I. Judson is at the Department of Medical Oncology, Royal Marsden Hospital, London; W. Steward is at the Department of Medical Oncology, Beatson Oncology Center, Glasgow; R. Coleman is at the Department of Medical Oncology, Weston Park Hospital, Sheffield; P. Woll are at the Department of Medical Oncology, Christie Hospital, Manchester, U.K.; C. van Pottelsberghe is at the EORTC Data Center, Brussels, Belgium; and H. Mouridsen is at the Department of Oncology, Rigshospitalet, Copenhagen, Denmark.
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MATERIALS AND METHODS

For eligibility, patients were required to have a histologically confirmed diagnosis of locally advanced or metastatic progressive soft tissue sarcoma with at least one measurable lesion, WHO performance score of ≤ 2, age ≤ 75 years, WBC ≥ 3.0×10^9/l, platelets count ≥ 100×10^9/l, serum creatinine ≤ 140 μmol/l and bilirubin ≤ 20 μmol/l. Previous chemotherapy was allowed. MTP/PE (CIBA-GEIGY, Basel, Switzerland) was supplied in a pack which contained the lyophilisate and the necessary suspension medium (isotonic aqueous saline phosphate buffer), a transferring needle, and an infusion set with 10 μm filter. The drug was supplied in 50 ml glass vials containing either 1 or 4 mg of MTP/PE. The solution for infusion was prepared fresh before each administration.

Before administration the content of a vial containing 1 or 4 mg of MTP/PE was constituted with 50 ml of the provided suspension medium. The vials of lyophilisate and suspension medium were warmed to room temperature after removal from the refrigerator before constitution commenced. After transferring the suspension medium to the lyophilisate, the suspension was left undisturbed for 1 min to ensure thorough hydration of the phospholipids. To complete the liposome formation process, the suspension was then shaken vigorously by hand for 1 min. The entire preparation procedure was performed under aseptic conditions. The resulting suspension is stable for 24 h if stored at 4°C, but was used within 6 h.

Table 1. Patients' characteristics

Number of patients	20
Sex (males/females)	9/10
Age (years)	
Median	42
Range	20–65
WHO performance	
Median	1
Range	0–2
Prior chemotherapy	20
Prior radiotherapy	10
Cell type	
Leiomyosarcoma	5
Malignant fibrous histiocytoma	3
Neurogenic sarcoma	2
Rhabdomyosarcoma	2
Synovial sarcoma	2
Miscellaneous	6

The liposome suspension was infused at a dose of 4 mg intravenously over 30 min using an infusion set with built-in 10 μm filter and an infusion pump. Treatment was repeated weekly. Prophylactic use of paracetamol up to a dose of 1 000 mg was allowed to prevent or reduce fever and chills. Except for fever/chills, nausea/vomiting and alopecia, in case of any other grade III–IV toxicity, subsequent doses were to be reduced by 1 mg. If a patient could not tolerate a dose of 1 mg, then that patient was taken off the study.

During treatment there was a weekly assessment of haemoglobin, WBC and platelet count, and 4-weekly assessment of blood chemistry.

Response to treatment was assessed after 8 weeks using the common WHO criteria. Toxicity was assessed weekly and also graded according to the WHO criteria.

RESULTS

20 eligible patients were entered to the study. 1 never started treatment and 1 died after only five drug doses, due to a rapidly progressive disease as proven at autopsy. This patient was classified as having a progressive disease. The other 18 patients could be evaluated for response. Characteristics of all patients are given in Table 1. The median duration of treatment was 8 weeks (range 3–25). Intercurrent dose reductions were not needed. 19 patients were considered evaluable for toxicity. There were no haematological side-effects. Side-effects related to a flu-like syndrome, consisting of fever, chills, myalgia and headache, were most predominant and were present in 14 patients (70%), following 103 of 156 drug administrations (66%). Most of these symptoms were mild to moderate in severity. The other side-effects were infrequent. From the 18 patients considered evaluable for response, only 2 patients had no change for 20 and 23 weeks, respectively, all other patients progressed.

DISCUSSION

Previous studies have indicated that drugs with even moderate activity against soft tissue sarcomas can be discovered in second-line studies [1]. MTP/PE, tested in this situation, did not yield any activity. Toxicity in this short-term study was manageable and apparently tolerable. MTP/PE at this dose and schedule is not an active drug in metastatic soft tissue sarcomas. In view of *in vitro* and animal data, however, MTP/PE might still be an interesting drug for use as an adjuvant after surgery.

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