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A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: The TRUSTS trial ☆

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Abstract ***Purpose:*** To evaluate whether trabectedin as first-line chemotherapy for advanced/metastatic soft tissue sarcoma prolongs progression-free survival (PFS), compared to doxorubicin and, in the phase IIb part here, to select the most appropriate trabectedin treatment schedule (3-hour or 24-hour infusion) in terms of safety, convenience and efficacy.
Patients and methods: In this randomised multicentre prospective dose-selection phase IIb superiority trial, 133 patients were randomised between doxorubicin ($n = 43$), trabectedin (3-hour infusion, T3h) ($n = 47$) and trabectedin (24-hour infusion, T24h) ($n = 43$). PFS was

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defined as time from random assignment until objective progression by response evaluation criteria in solid tumours (RECIST 1.1), a global deterioration of the health status requiring discontinuation of the treatment, or death from any cause.

Results: The study was terminated due to lack of superiority in both trabectedin treatment arms as compared to the doxorubicin control arm. Median PFS was 2.8 months in the T3h arm, 3.1 months in the T24h arm and 5.5 months in the doxorubicin arm. No significant improvements in PFS were observed in the trabectedin arms as compared to the doxorubicin arm (T24h versus doxorubicin: hazard ratio (HR) 1.13, 95% confidence interval (CI) 0.67–1.90, $P = .675$; T3h versus doxorubicin: HR 1.50, 95% CI 0.91–2.48, $P = .944$). Only one toxic death occurred in the T3h arm, but treatment had to be stopped due to toxicity in 7 (15.2%) (T3h), 8 (19.5%) (T24h) and 1 (2.5%) doxorubicin patients.

Conclusion: Doxorubicin continues to be the standard treatment in eligible patients with advanced/metastatic soft-tissue sarcoma (STS). Trabectedin 1.5 mg/m^2/24-hour infusion is the overall proven approach to delivering this agent in the second-line setting for patients with advanced or metastatic STS.

1. Introduction

Currently, for the first line treatment of metastatic soft-tissue sarcoma (STS), no drug or drug association offers an overall survival (OS) advantage over doxorubicin alone [1] However, the benefits of this treatment are limited, with reported response rates of 10–25% [2], median progression-free survival (PFS) of 6 months and OS of 12 months.

Several clinical trials have investigated the activity of the single agent tetrahydroisoquinoline alkaloid trabectedin (YONDELIS®, PharmaMar) in STS [3–6], with three phase II studies in metastatic/advanced STS [4,5,7]. In a small series of chemotherapy-naive patients [4], a 17.1% response rate with 16.5-month median PFS was reported. Response rates were low but prolonged tumour stabilisations were achieved, and the Van Glabekke et al. [8] criteria for efficacy were met. Side-effects were manageable, independent of cumulative dose, and consisted mainly of uncomplicated neutropenia and uncomplicated hepatotoxicity, consisting essentially of liver test alterations.

The standard trabectedin delivery schedule in STS is 24-hour intravenous infusion/3 weeks/1.5 mg/m^2. A weekly trabectedin schedule of 3-hour infusion/0.58 mg/m^2 was tested against the standard infusion in a randomised phase II study, resulting in lower efficacy [7]. A clinically more convenient 3-hour infusion of 1.3 mg/m^2/3 weeks has been shown to be feasible, with limited but encouraging results in STS [9].

This randomised phase IIb/III trial was designed to evaluate whether trabectedin as first-line treatment prolongs PFS compared with doxorubicin in advanced/metastatic STS patients. The objective of the phase IIb step was to select the most appropriate trabectedin arm (3-hour (T3h) or 24-hour (T24h) infusion schedule) in terms of safety, convenience and efficacy (stopping the trial in case of futility). The objective of the second step (phase III) was to investigate whether PFS for the selected trabectedin arm was superior to doxorubicin. The results of the planned interim analysis at the end of the first step were reviewed by an independent data monitoring committee on 4th July 2013. They recommended discontinuation of the trial since none of the experimental arms fulfilled the conditions for continuation specified in the trial protocol. In this report we present the results of the phase IIb part of the study.

2. Methods

2.1. Patient selection

Eligible patients were $\geqslant 18$ years old, with one of the following histologically-confirmed advanced and/or metastatic STS of grades II/III and with progressive disease as assessed by the local investigator. All types were eligible (excluding well-differentiated liposarcoma, embryonal rhabdomyosarcoma, Ewing tumours, gastro-intestinal stromal tumours and dermatofibrosarcoma protuberans). Patients had not previously received chemotherapy. Other inclusion criteria included the presence of measurable disease according to response evaluation criteria in solid tumours (RECIST 1.1), World Health Organisation (WHO) performance status (PS) 0 or 1, adequate bone marrow (absolute neutrophils count (ANC) $\geqslant 1.5 \times 10^9$/L, hemoglobin (HB) $\geqslant 9$ g/dL or HB $\geqslant 5.6$ mmol/L, platelets (PLT) $\geqslant 100 \times 10^9$/L), hepatic (bilirubin $\leqslant$ ULN, alanine aminotransferase (SGPT/ALT) and aspartate aminotransferase (SGOT/AST) $\leqslant 2.5 \times$ ULN) and renal (serum creatinine $\leqslant 1.5 \times$ ULN) functions, normal left ventricular ejection fraction (LVEF) assessed by echocardiography or multiple gated acquisition scan (MUGA), alkaline phosphatase $\leqslant 2.5 \times$ ULN and albumin $\geqslant 25$ g/L.

No patient had received any anti-cancer therapy including other systemic therapy, radiotherapy and surgery, within 28 days prior to treatment start. Main