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Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas ☆

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Abstract ***Aim:*** This randomised phase III trial evaluated first-line trabectedin versus doxorubicin-based chemotherapy (DXCT) in patients with advanced/metastatic translocation-related sarcomas (TRS).
Methods: Patients were randomly assigned (1:1) to receive trabectedin 1.5 mg/m^2 24-h intravenous (i.v.) infusion every 3 weeks (q3wk) (*Arm A*), or doxorubicin 75 mg/m^2 i.v. q3wk, or doxorubicin 60 mg/m^2 i.v. plus ifosfamide (range, 6–9 g/m^2) i.v. q3wk (*Arm B*). Progression-free survival (PFS) by independent review was the primary efficacy end-point.
Results: One hundred and twenty-one patients were randomised; 88 of them had TRS confirmed by central pathology review (efficacy population). Twenty-nine PFS events were

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assessed by independent review (16 with trabectedin; 13 with DXCT). PFS showed non-significant difference between arms (stratified log rank test, $p = 0.9573$; hazard ratio = 0.86, $p = 0.6992$). At the time of this analysis, 63.9% and 58.3% of patients were alive in trabectedin and DXCT arms, respectively. There was no statistically significant difference in survival curves. Response rate according to Response Evaluation Criteria in Solid Tumours (RECIST) v.1.0 was significantly higher in DXCT arm (27.0% versus 5.9%), but response according to Choi criteria showed fewer differences between treatment arms (45.9% versus 37.3%). Safety profile was as expected for both arms, with higher incidence of severe neutropenia, alopecia and mucositis in the DXCT arm.

Conclusion: Neither trabectedin nor doxorubicin-based chemotherapy showed significant superiority in the first-line treatment of patients with advanced translocation-related sarcoma.

1. Introduction

Trabectedin is a marine-derived antineoplastic agent active against advanced soft tissue sarcoma (STS) [1–4] which has shown relevant antitumor activity in prospective and retrospective series of patients with myxoid/round cell liposarcoma (MRCL) resistant or relapsed to conventional chemotherapy [5–7]. The genetic hallmark of MRCL is translocation t(12:16)(q13;p11) [8], which produces the chimeric fusion protein FUS-CHOP that binds to specific DNA promoters, leading to deregulated expression of downstream proteins which eventually cause neoplastic transformation [9]. *In vitro*, trabectedin interferes with the binding of this fusion protein to DNA promoters [10]. Based on structural and functional similarities of chimeric fusion proteins that generate new transcription factors, it was hypothesised that trabectedin could induce in other translocation-related sarcomas (TRS) effects similar to those described in MRCL. Indeed, trabectedin was efficacious in some patients with prevalent TRS: synovial sarcoma, alveolar soft part sarcoma and endometrial stromal sarcoma [7,11–13].

As preclinical and preliminary clinical data pointed to a potentially increased efficacy of trabectedin in MRCL and other TRS, this randomised trial compared trabectedin with standard first-line treatment (doxorubicin-based chemotherapy, DXCT) in patients with confirmed locally advanced unresectable or metastatic TRS. This is the first randomised trial performed in this subtype of STS.

2. Patients and methods

This study was conducted at 22 investigational sites from United States of America (USA) ($n = 8$), France ($n = 5$), United Kingdom (UK) ($n = 4$), Germany ($n = 2$), Italy ($n = 2$) and Spain ($n = 1$) according to the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations on clinical trials, and was approved by respective independent ethics committees. Signed informed consent was obtained from all patients. An Independent Data Monitoring Committee (IDMC) reviewed the study conduct.

Trial codes were Eudra CT: 2008-002326-11; ClinicalTrials.gov Identifier: NCT00796120.

2.1. Selection of patients

Eligibility criteria included patients $\geqslant 18$ year-olds with initial pathological diagnosis of TRS of following subtypes: alveolar soft part sarcoma, angiomatoid fibrous histiocytoma, clear cell sarcoma, desmoplastic small round cell tumour, low grade endometrial stromal sarcoma, low grade fibromyxoid sarcoma, myxoid chondrosarcoma, MRCL and synovial sarcoma. Ewing's sarcoma and dermatofibrosarcoma protuberans were excluded. Evidence of translocation by fluorescence *in situ* hybridisation was not required for patient enrolment into the trial, but only patients with confirmed translocation were included in the primary study analysis. Patients had to have unresectable locally advanced or metastatic progressive disease; measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST v.1.0); Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score 0–2; adequate cardiac function [left ventricular ejection function (LVEF) within normal limits], and adequate haematological (haemoglobin $\geqslant 9$ g/dl; absolute neutrophil count $\geqslant 1.5 \times 10^9$/l; platelets $\geqslant 100 \times 10^9$/l), renal (serum creatinine $\leqslant 1.5$ mg/dl) and hepatic function [bilirubin $\leqslant$ upper limit of normal (ULN); aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leqslant 2.5 \times$ ULN; alkaline phosphatase (AP)$\leqslant 2.5 \times$ ULN (if total AP $>2.5 \times$ ULN, AP liver fraction and/or gamma glutamyltransferase and/or 5′-nucleotidase had to be $\leqslant$ULN) and albumin >25 g/l].

Patients were excluded if they had received prior chemotherapy; prior lesion irradiation (if administered to a single target lesion); if they had any malignancy within the previous 5 years (except for basal cell carcinoma or treated cervical carcinoma *in situ*), or other relevant clinical conditions (active infection, active viral hepatitis or chronic liver disease, brain and/or leptomeningeal metastasis, congestive heart failure or angina pectoris,