available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Exatecan in pretreated adult patients with advanced soft tissue sarcoma: Results of a phase II – Study of the EORTC Soft Tissue and Bone Sarcoma Group

P. Reichardt[a,], O.S. Nielsen[b], S. Bauer[c], J.T. Hartmann[d], P. Schöffski[e], T.B. Christensen[b], D. Pink[a], S. Daugaard[f], S. Marreaud[g], M. Van Glabbeke[g], J.Y. Blay[h]*

[a]*Medizinische Klinik m. S. Hämatologie, Onkologie und Tumorimmunologie, Robert-Rössle-Klinik, HELIOS-Klinikum Berlin-Buch, Charité Campus Buch, Lindenberger Weg 80, 13125 Berlin, Germany*
[b]*Aarhus University Hospital, Aarhus, Denmark*
[c]*Essen University Hospital, Essen, Germany*
[d]*Tübingen University Hospital, Tübingen, Germany*
[e]*University Hospital Gasthuisberg, Leuven, Belgium*
[f]*Rigshospitalet, Copenhagen, Denmark*
[g]*EORTC Data Center, Brussels, Belgium*
[h]*Centre Leon Berard, Lyon, France*

ARTICLE INFO

Article history:
Received 4 January 2007
Accepted 15 January 2007
Available online 1 March 2007

Keywords:
Soft tissue sarcoma
Topoisomerase I-inhibitors
Exatecan

ABSTRACT

No standard treatment is established for patients with advanced soft tissue sarcoma after previous chemotherapy with anthracyclines and ifosfamide, given either in combination or sequentially. Exatecan (DX-8951f) is a totally synthetic analogue of the topoisomerase I-inhibitor camptothecin, which was synthesised to impart increased aqueous solubility, greater tumour efficacy, and less toxicity than camptothecin itself, topotecan or irinotecan. Since some activity against soft tissue sarcomas, especially leiomyosarcomas, has been reported for topoisomerase I-inhibitors, a study with a new and more potent agent seemed justified.

We report on a prospective multicentre phase II study of Exatecan in adult soft tissue sarcomas failing 1 or 2 lines of chemotherapy in advanced phase, performed within the STBSG of EORTC. Thirty-nine patients (16 leiomyosarcomas and 23 other histologies) were included in two independent strata and received a total of 141 cycles (median 2). Median age was 61 years, range 25–76. Exatecan was given as i.v. infusion over 30 min at a dose of 0.5 mg/m^2 every day for five consecutive days, repeated every 21 days. Seventy-four percentage of cycles could be given without dose or schedule modification. The main toxicity was haematotoxicity with grade 3/4 neutropenia in 49%, grade 3/4 thrombocytopenia in 23%, and grade 3/4 anaemia in 15% of patients, respectively. Non-haematological toxicity consisted mainly of grade 2/3 dyspnoea in 36% of patients and grade 2/3 fatigue in 28%. One treatment-related toxic death due to septic shock was reported. Best overall response was no change with 60% in the leiomyosarcoma group and 53% in the non-leiomysarcoma group, respectively. The 3 months progression-free survival estimates are 56% for leiomysarcomas and 26% for other histologies, respectively. Using a two-step statistical design, the trial was stopped after the first step in both strata, due to lack of activity.

* *Corresponding author:* Tel.: +49 30 9417 1203; fax: +49 30 9417 1053.
E-mail address: peter.reichardt@charite.de (P. Reichardt).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.01.014

In pretreated soft tissue sarcoma patients, Exatecan is well tolerated but does not achieve any objective responses. However, with respect to progression-free survival, Exatecan did show some activity in leiomyosarcomas.

1. Introduction

Soft tissue sarcomas are rare tumours. Their annual incidence is around 2–3/100.000. Overall, STS account for approximately 1% of all malignancies, while they give rise to 2% of the total cancer-related mortality. According to the EUROCARE data,[1] the 5-year survival in Europe of adult STS (excluding visceral ones) averages 60%, with substantial geographic variations. Thus further improvements in the treatment outcome of these rare tumours are needed.

There are multiple histological subtypes of STS. At present all these subtypes are usually grouped under the heading of STS for the purpose of treatment, although an increasing number of new treatment options are expected to be directed more specifically at individual histological subtypes.[2]

STS metastasise primarily to the lungs but also to bone, liver and other organs depending on the subtype. The median survival with metastatic disease is generally <12 months, though long term survival may follow optimal response to chemotherapy in a limited number of patients.[3] Chemotherapy is widely used in the treatment of advanced disease, basically with a palliative intent. Doxorubicin and ifosfamide appear to be the most active drugs in the treatment of STS with reproducible response rates in the range of 10–30%. No standard treatment option has been identified so far for patients with STS failing pre-treatment with anthracyclines and ifosfamide. Therefore, the identification of new active drugs is of greatest importance. In previous EORTC-STBSG trials, it has been shown that drugs with interesting activity for first-line therapy can be identified by sufficient activity in second-line treatment.

Exatecan (DX-8951f) is a totally synthetic analogue of camptothecin, a natural product isolated from the Chinese tree, *Camptotheca acuminata*. The mode of action of camptothecin and its analogues involves inhibition of the nuclear enzyme, topoisomerase I, which plays a key role in DNA replication and transcription. Topoisomerase I binds covalently to double-stranded DNA and forms a break in one strand; this intermediate is known as the cleavable complex. The intact strand of DNA is passed through the gap in the broken strand, which is then resealed, and the enzyme dissociates from the helix. Camptothecins bind to the topoisomerase I-DNA cleavable complex and prevent resealing of the DNA. Evidence shows that double-stranded breaks in DNA occur when the topoisomerase I-inhibited cell attempts to replicate the DNA, probably as a result of collisions between the stabilised, cleavable complex and the replication fork. This drug-induced DNA damage is not efficiently repaired and cell death results. Thus, camptothecin analogues convert topoisomerase I into an S-phase-specific cellular poison.

Several topoisomerase I-inhibitors including irinotecan and topotecan have been tested against soft tissue sarcomas so far and occasional responses, mainly in leiomyosarcoma, were observed.[4–6] Exatecan has been studied in multiple phase I trials and has shown activity in a number of solid tumour types, including sarcoma. Based on activity and tolerability, a fractionated daily times 5 every 3 weeks dosing scheme was selected for phase II trials.[7]

Given these results, the EORTC Soft Tissue and Bone Sarcoma Group launched and conducted a non-comparative phase II trial with Exatecan in previously treated adult patients with progressive soft tissue sarcoma.

2. Patients and methods

2.1. *Eligibility*

The patients had to have histological evidence of soft tissue sarcoma of any type with at least one measurable lesion and evidence of progression within 6 weeks prior to treatment. Pretreatment consisted of one line of previous combination chemotherapy or two single agent regimens containing anthracyclines and ifosfamide. Patients were between 15 and 75 years of age and had a performance status of <2. Pretreatment laboratory workup was required to show WBC $\geqslant 4 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, serum creatinine $\leqslant 120$ μmol/L, bilirubin $\leqslant 30$ μmol/L, and albumin $\geqslant 25$ g/L. No other severe medical illnesses, including psychosis and previous history of cardiovascular disease or symptomatic or known CNS metastases, were allowed.

Women of child-bearing potential agreed to take adequate contraceptive measures and male patients of reproductive potential agreed to employ an effective barrier method of birth control throughout the study and for up to 6 months following discontinuation of study drug. All pathological material had to be available for central review. Before patient registration/randomisation, informed consent had to be given according to ICH/EU GCP, and national/local regulations.

Exclusion criteria were the histological diagnosis of GIST, chondrosarcoma, malignant mesothelioma, neuroblastoma, osteosarcoma, Ewing's sarcoma or embryonal rhabdomyosarcoma. Patients were also excluded if they were unable to comply with regular visits or follow-up. Concomittant chemotherapy, immunotherapy or investigational therapy of any type was not allowed.

2.2. *End-points*

The principal objective of the trial was to assess the therapeutic activity of Exatecan in patients with advanced adult soft tissue sarcoma after prior exposure to chemotherapy for advanced disease. The principal end-point was the objective response to treatment, as defined by the 'RECIST' criteria.[8] For