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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

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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.

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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

patients presenting with an objective response, the duration of response was assessed.

The secondary objective was to characterise the safety of Exatecan in pretreated patients with advanced adult soft tissue sarcoma. Adverse drug reactions were graded according to the International 'Common Toxicity Criteria 2.0'.

2.3. *Treatment protocol*

Exatecan was given as an intravenous infusion over 30 min into a peripheral vein or through a central venous catheter, at a dose of 0.5 mg/m^2 every day for five consecutive days. The dose was based on body surface area calculation. Treatment was to be repeated every 21 days.

Treatment was administered until documented disease progression, unacceptable toxicity, or patient refusal. In case of clear-cut progression occurring before the first disease evaluation (6 weeks after treatment start), the treatment was discontinued and the response to treatment was assessed as 'early progression'.

In case of stabilisation of the disease, the patients were to be treated for a minimum of four cycles, and his/her disease status evaluated at the end of those 12 weeks. Thereafter, the decision to continue the treatment until disease progression was left to the responsible investigator. In case of objective response, the treatment was continued until documented disease progression. The disease status was regularly assessed every 8 weeks during this period to evaluate the duration of response.

2.4. *Dose modifications*

If recovery of all haematological and non-haematological toxicities had not occurred by day 22, the subsequent course of

Table 1 – Patient characteristics

	Leiomyosarcoma	Non-leiomyosarcoma
Total number of patients	16	23
Eligible for toxicity	16	21
Eligible for efficacy	15	19
Gender (%)		
Male	56	74
Female	44	26
Age (years)		
Median	63	60
Range	44–73	25–76
WHO performance status (%)		
0	38	39
1	62	61
Histological subtypes (local pathologist) (%)		
Synovial sarcoma		35
MFH		22
Other		43
Histological subtypes (panel review) (%)		
Synovial sarcoma		26
Undifferentiated		22
Other		26
Not reviewed		26
Disease origin (%)		
Retroperitoneum	25	0
Lower extremity	19	70
Upper extremity	6	13
GI visceral	19	9
GY visceral	19	0
Other	12	8
Site of lesions (%)		
Primary	44	48
Lung	75	78
Liver	44	22
Lymph nodes	38	22
Soft tissue	25	22
Prior treatment (%)		
Palliative chemotherapy	94	96
Adjuvant chemotherapy	6	4
Radiotherapy	31	57

Exatecan was delayed by 1 week. If recovery had still not occurred, Exatecan was delayed by a second week. If recovery did not occur by day 36, treatment was discontinued.

The dose of Exatecan was reduced based upon the maximum intensity of drug-related haematological and non-haematological toxicity that occurred in the preceding course.

For haematological toxicity, Exatecan was reduced by one dose level to 0.4 mg/m^2 per day for: ANC $< 0.5 \times 10^9$/L for $\geqslant 7$ days, WBC $< 1.0 \times 10^9$/L or neutropenic fever with ANC $< 1.0 \times 10^9$/L, WBC $< 1.5 \times 10^9$/L, platelet count $< 25 \times 10^9$/L, significant delays with ANC $< 1.5 \times 10^9$/L, WBC $< 2.5 \times 10^9$/L or platelets $< 75 \times 10^9$/L on day 22 or beyond.

For non-haematological toxicity, the dose of Exatecan was reduced by one dose level for significant treatment-related grade 3 events (or grade 2 neurotoxicity).

In case of subsequent toxicity, the dose was reduced to 0.3 mg/m^2 per day in the following cycle. If this dose could not be tolerated, the patient was taken off study and treated at the discretion of the individual investigator.

2.5. *Statistical analysis*

The trial was conducted as an open label, non-comparative phase II study. Two groups of patients were independently studied (leiomyosarcomas and non-leiomyosarcomas). A two-step Simon design was applied to each stratum ($\alpha = 0.1$, $\beta = 0.1$). In both strata, the following reference response rates were used for the hypothesis: P0 = 10%, and P1 = 30%. In each stratum, the total sample size was 25 patients, with 16 patients for step 1 and nine additional patients for step 2.

3. Results

3.1. *Patient characteristics*

A total of 39 patients from nine centres in four European countries including Germany, Denmark, Belgium and Slovakia were recruited in the trial. Details are shown in Table 1. Sixteen patients were entered in the leiomyosarcoma stratum and 23 in the non-leiomyosarcoma stratum, respectively. Four patients were ineligible due to wrong histology (GIST), unallowed prior treatment, treatment start before registration or failing laboratory requirements of inclusion. These patients are included in the safety analysis but excluded from efficacy analysis.

The median age was 61 years (range 25–76) with 67% of male and 33% of female patients. WHO performance status was reported 1 in 61% of patients. Disease origin was the lower extremity in 49%, GI-tract/visceral in 13%, upper extremity in 10%, retroperitoneal in 10% and other localisations in 18% of cases. Time since initial diagnosis was less than 6 months in 10%, 6–12 months in 28%, 1–2 years in 21% and beyond 2 years in 41%. Ninety-five percentage of patients had received prior chemotherapy for metastatic disease and 5% as adjuvant treatment, respectively. Forty-six percentage of patients had received prior radiotherapy. Progressive or recurrent primary tumour was present at study inclusion in 46% of patients. Metastatic sites were lungs in 77%, liver in 31%, lymph nodes in 28% and soft tissue in 23%.

Predominant histological subtypes of the non-leiomyosarcomas as per local pathologists were synovial sarcomas in 35% and MFH in 22%. By panel review in 17 of the 23 cases, predominant histological subtypes were synovial sarcomas in 26% and undifferentiated sarcomas in 22%.

3.2. *Treatment and toxicity*

Two patients did not receive any protocol therapy and were excluded from toxicity analysis. A total of 144 cycles were applied with a median number of 2. However, 18 patients received 4–9 cycles. Fifty-nine percentage of patients did not require any dose reduction or treatment delay. Treatment delay occurred in 19% of patients, dose reduction in 5% and a combination of both in 16% of patients, respectively. All but one delays were either non-treatment related (46%) or due to haematological toxicity (46%). All dose reductions were due to haematological toxicity. The median relative dose intensity was 97%.

Haematological toxicity was the predominant side effect of study treatment with 65% of patients showing grade 3 or 4 leukopenia and 51% grade 3 or 4 granulocytopenia. Thrombocytopenia and anaemia grade 3 or 4 occurred in 24% and 17% of patients, respectively. Non-haematological toxicity was generally mild. Asymptomatic grade 3 or 4 elevation of alkaline phosphatase was seen in 17% of patients, elevation of ASAT in 14% and ALAT in 11%, respectively. However, baseline levels were already elevated in the majority of patients. One treatment related death (septic shock) and 5 life-threatening events in 3 patients (febrile neutropenia: 3, pneumonia: 2) occurred. Reasons for stopping treatment were progression in 82% of patients, toxicity in 5% (one toxic death, one neutropenic fever) and other in 13%, respectively.

3.3. *Efficacy*

Thirty-four patients were eligible for evaluation of efficacy. No objective responses were observed. However, disease stabilisation was documented in 60% of patients with leiomyosarcomas and 53% of patients with non-leiomyosarcomas, respectively. The 3 months progression-free survival estimates are 56% for leiomysarcomas and 26% for other histologies, respectively (Fig. 1a). The 12 months overall survival estimates are 47% for leiomyosarcomas and 28% for non-leiomyosarcomas, respectively (Fig. 1b). At the time of the analysis, 9 patients were still alive. The cause of death in the other patients was disease progression in 20, septic shock in 1 and unknown in 4 patients, respectively.

4. Discussion

The prognosis of adult patients with advanced soft tissue sarcoma remains poor with no standard therapy available for patients pretreated with anthracyclines and ifosfamide. Among many other new agents including gemcitabine, the taxanes and ET-743, several topoisomerase I-inhibitors have been tested so far in chemo-naive and pretreated soft tissue sarcomas. In a trial of the NCI Canada, Topotecan yielded a response rate of 10% plus 41% of disease stabilisation in 29 unpretreated patients.[4] A 21 days continuous infusion regimen of topotecan was tested by the SWOG in 21 evaluable patients who had received no prior chemotherapy. No objective

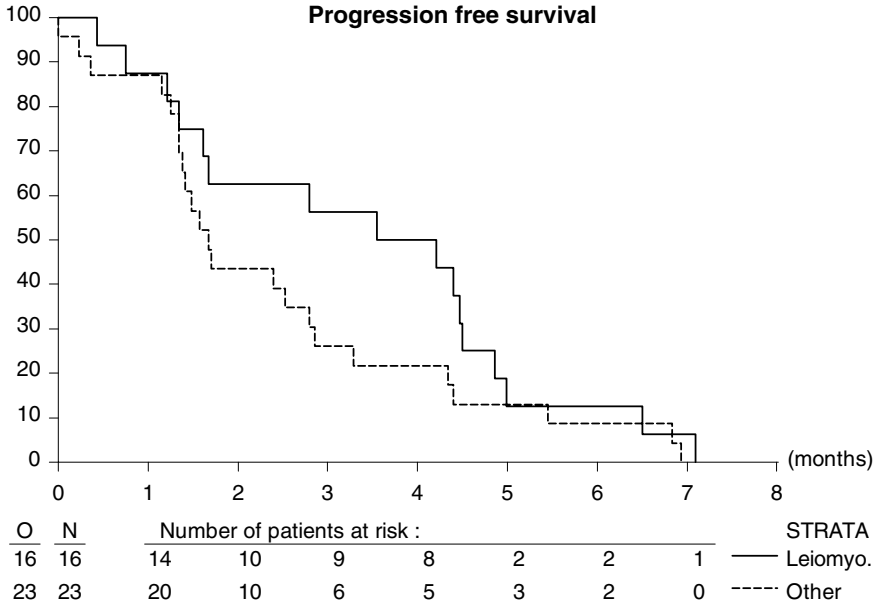

Fig. 1a – Progression-free survival (Kaplan–Meyer plot).

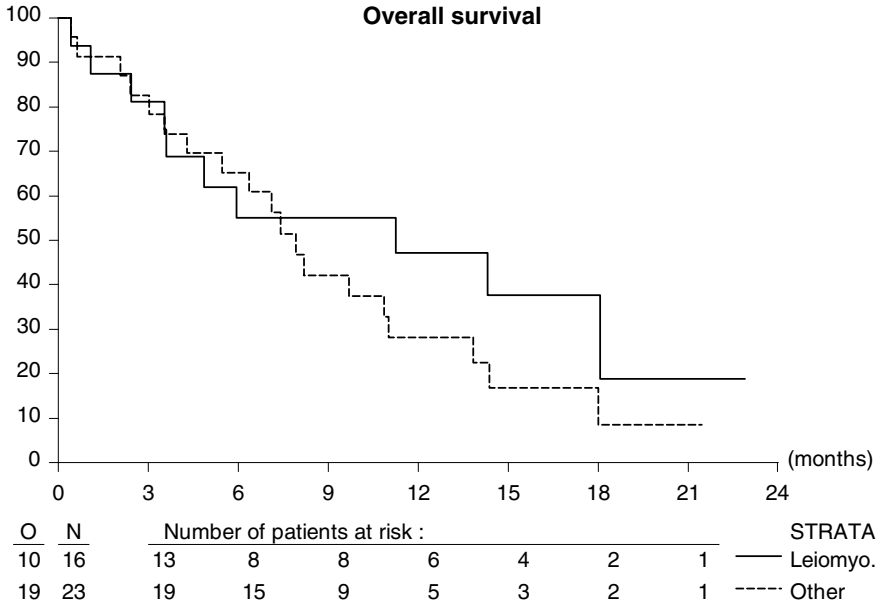

Fig. 1b – Overall survival (Kaplan–Meyer plot).

responses were observed.[9] Topotecan was also tested in chemo-naïve patients with uterine leiomyosarcomas only. One complete and three partial responses as well as 11 cases of stable disease were seen among 36 enrolled patients resulting in a response rate of 11%.[6] Reichardt et al. reported no responses for topotecan in 16 previously treated patients with advanced soft tissue sarcomas.[10] A high response rate of 10 out of 15 paediatric patients with refractory rhabdomyosarcoma was achieved with the combination of cyclophosphamide and topotecan. Also, 6 of 17 patients with Ewings's tumours responded, thus suggesting a role for topotecan in a subset of sarcomas.[11] This is further supported by an Italian trial using a protracted infusion schedule with irinotecan in children with refractory or recurrent soft tissue sarcoma. The overall response rate was 23% with a higher activity of 38% in the subgroup of patients with PNET.[12] 9-Nitrocamptothecin, an oral topoisomerase I-inhibitor, was tested in a trial entering a total of 56 previously treated patients with gastrointestinal leiomyosarcomas or other histologies. With one short lasting minor response in the first and 8% partial responses in the latter group, the drug did show only minimal activity.[13]

Progression-free survival rather than response rate has been suggested as principal end-point for phase II trials in

soft tissue sarcomas by the EORTC Soft Tissue and Bone Sarcoma Group.[14] Based on the analysis of 380 patients from several trials on second-line treatment, a 3 months progression-free survival estimate of more than 40% would suggest a drug activity, and less than 20% would suggest inactivity. Given the absence of any objective responses according to RECIST criteria in the current trial, Exatecan was considered inactive in pretreated adult soft tissue sarcomas according to the primary end-point. However, the 3 months progression-free survival estimates of 56% for leiomyosarcomas, irrespective of the site of origin, and 26% for non-leiomyosarcomas would suggest some activity at least for leiomyosarcomas.

In conclusion, all topoisomerase I-inhibitors tested so far including Exatecan did not show meaningful response rates in pretreated soft tissue sarcomas with the obvious exception of rhabdomyosarcoma and PNET. However, with respect to progression-free survival, Exatecan did show some activity in leiomyosarcomas.

Conflict of interest statement

None declared.

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