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Trabectedin in patients with advanced soft tissue sarcoma: A retrospective national analysis of the French Sarcoma Group

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Abstract ***Aim:*** The French Sarcoma Group performed this retrospective analysis of the 'RetrospectYon' database with data of patients with recurrent advanced soft tissue sarcoma (STS) treated with trabectedin 1.5 mg/m^2 as a 24-h infusion every three weeks.
Methods: Patients who achieved non-progressive disease after six initial cycles could receive long-term trabectedin treatment until disease progression.
Results: Overall, 885 patients from 25 French centres were included. Patients received a median of four trabectedin cycles (range: 1–28). The objective response rate was 17% (six complete/127 partial responses) and 50% ($n = 403$) of patients had stable disease for a disease control rate of 67%. After a median follow-up of 22.0 months, median progression-free survival (PFS) and overall survival (OS) were 4.4 and 12.2 months, respectively. After six cycles, 227/304 patients with non-progressive disease received trabectedin until disease progression and obtained a significantly superior median PFS (11.7 versus 7.6 months, $P < 0.003$) and OS (24.9 versus 16.9 months, $P < 0.001$) compared with those who stopped trabectedin treatment. Deaths and unscheduled hospitalisation attributed to drug-related events occurred in 0.5% and 9.4% of patients, respectively.
Conclusion: The results of this real-life study demonstrate that treatment with trabectedin of patients with STS yielded comparable or improved efficacy outcomes versus those observed in clinical trials. A long-term treatment with trabectedin given until disease progression is associated with significantly improved PFS and OS.

1. Introduction

Soft-tissue sarcomas (STS) are a group of rare, heterogeneous mesenchymal cancers that include around 50 histological types arising from extraskeletal connective tissues, which represent ~1% of all adult tumours and 4–8% of paediatric malignancies [1,2].

Trabectedin (Yondelis®), is a synthetic antineoplastic drug originally isolated from the Caribbean sea squirt *Ecteinascidia turbinata* [3]. Trabectedin binds covalently to the minor groove of the DNA double helix, stalling the replication fork and leading to double strand breaks, that trigger a cascade of events that ultimately lead to G2-M cell cycle arrest and apoptosis [4]. Recent data suggested that trabectedin has a pleiotropic mechanism of action, since at therapeutic concentrations trabectedin selectively targets macrophages and down-regulates the production of pro-inflammatory mediators, which induce changes in the tumour microenvironment contributing to its antitumour and antiangiogenic activity [4–7].

The efficacy of trabectedin as salvage chemotherapy in adults with advanced STS has been demonstrated in three phase II trials with unselected patients with recurrent disease [8–10], chemotherapy-naïve patients with unresectable advanced disease [11] as well as in compassionate use programmes [12–14]. The pivotal, open-label, randomised, phase II, registration study of trabectedin (ET-743-STS-201; ClinicalTrials.gov Identifier: NCT00060944) evaluated two trabectedin regimens in adult patients with unresectable advanced or metastatic liposarcoma or leiomyosarcoma (L-type sarcoma) [15]. The data from that study demonstrated that trabectedin 1.5 mg/m^2 given as a 24-h (h) intravenous (i.v.) infusion every three weeks (q3w) provided superior disease control versus weekly trabectedin 0.58 mg/m^2 in terms of longer time to progression (median TTP: 3.7 versus 2.3 months; $P = 0.0302$) and progression-free survival (median PFS: 3.3 versus 2.3 months; $P = 0.0418$) [15]. Based on these results, in 2007 trabectedin obtained marketing authorisation from the European Medical Agency and in many other countries worldwide for the treatment of patients with advanced STS following failure of anthracyclines and ifosfamide, or as front-line therapy for those patients who are unsuited to receive these agents.

The analysis presented here analysed the 'RetrospectYon' database with data from patients with recurrent advanced STS treated with trabectedin in France with the principal aim to provide a retrospective overview of the outcomes for patients in routine real-life clinical practice for the contributing medical centres in France. In addition, the response rates and time-to-event endpoints obtained in this analysis were compared to those reported in other clinical trials and compassionate use programmes.

2. Patients and methods

2.1. Study design

We have evaluated the RetrospectYon database with patients' data treated with trabectedin in accordance