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Original article

What makes real world outcomes in soft tissue sarcomas? A mono-institutional trabectedin experience

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Keywords
Soft tissue sarcoma
Relapse
Trabectedin
Efficacy
Tolerance

Summary

Introduction > Trabectedin proved its efficacy in relapsed advanced soft tissue sarcomas (STS) in 3 multicenter phase II studies with selected patients. The aim of the present study is to investigate trabectedin efficacy and tolerance in a cohort of "real-life" unselected patients with sarcoma.
Methods > A single-center analysis was carried out on all consecutive patients with histologically proven unresectable advanced or metastatic STS, who received at least one cycle of trabectedin. Data on efficacy and tolerance were retrospectively reported.
Results > From 2004 to 2014, data of 59 patients were reviewed. Median age was 62 years (from 23 to 87). A total of 317 cycles of trabectedin were administered. Twenty-five patients (42%) suffered grade 3–4 hematological toxicity, mainly with neutropenia (22 patients, 37%). Disease control rate was 24%, mainly with stable disease, and 45 patients (76%) experienced disease progression. Median overall survival was 6.6 months (95%CI [4.9–12.6]).
Conclusion > Trabectedin might be an option for patients without any other validated alternative, but phase III study evaluating trabectedin + best supportive care (BSC) versus BSC is necessary.

Mots clés
Sarcome des tissus mous
Récidive
Trabectedine
Efficacité
Toxicité

Résumé

Évaluation de la trabectedine dans les sarcomes des tissus mous « de la vraie vie ». Un essai mono-institutionnel

Introduction > Trois essais multicentriques de phase II ont montré une efficacité de la trabectedine dans le traitement des récidives des sarcomes des tissus mous, au stade avancé (STM), chez des patients sélectionnés. L'objectif principal est de rapporter l'efficacité et la tolérance de la trabectedine dans une cohorte de patients non sélectionnés atteints de STM.

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Méthodes > *Les données d'efficacité et de toxicité de tous les patients traités par trabectedine à l'encontre d'un STM histologiquement prouvé, en récidive localement avancé inopérable ou métastatique, ont été recueillies rétrospectivement dans cette étude monocentrique.*

Résultats > *Entre 2004 et 2014, 59 patients ont été inclus. L'âge médian était de 62 ans (23–87 ans). Au total, 317 cycles de trabectedine ont été administrés. Vingt-cinq patients (42 %) ont présenté une toxicité hématologique de grade 3–4, principalement des neutropénies (22 patients, 37 %). Le contrôle de la maladie était obtenu dans 24 % des cas, avec une stabilisation des lésions dans la plupart des cas. Quarante-cinq patients (76 %) ont progressé sous trabectedine. La médiane de survie globale était de 6,6 mois (IC 95 % [4,9–12,6]).*

Conclusion > *La trabectedine a probablement un intérêt chez des patients non sélectionnés atteints de STM avancé en récidive, sans autre alternative validée. Une étude de phase III comparant la trabectedine couplée aux soins de support versus les soins de support seuls semble néanmoins nécessaire.*

Introduction

In the last decade, more than 30 new anti-cancer drugs obtained a European agreement and were marketed in France. It costs French public health insurance a billion euro, in 2010 [1]. Between 2010 and 2013, French health authority removed some treatments, such as trabectedin (ET743; Yondelis®, Pharma Mar, Madrid, Spain), from the list of reimbursed medicines. Soft tissue sarcomas (STS) are a heterogeneous group of malignancies, induced by the transformation of cells of mesenchymal origin. If STS are rare, long-term prognosis is poor with a median overall survival (OS) for patients with unresectable STS of approximately 1 year [2–4]. Doxorubicin and ifosfamide were used in STS for more than 30 years. They proved single-agent activity, with response rates of 10 to 25% [5–7]. Doxorubicin is indicated in first-line treatment for patients with STS but prescription is limited by cumulative dose-dependent and irreversible cardio-toxicity [8]. Ifosfamide is indicated in first-line combination treatment with anthracycline or as a single-agent in second-line therapy, after doxorubicin failure [9,10]. Chemotherapy combination showed best response rates, but similar overall survival in comparison with single-agent anthracycline regimen (given at optimal doses) [11]. Trabectedin showed efficacy in three multicenter phase II studies with selected patients and was granted marketing authorization in Europe for relapsed (after anthracycline or ifosfamide or for patients contraindicated to these treatments) or resistant advanced STS [12–14]. With the temporary loss of trabectedin eligibility for reimbursement, questions about the real-life efficacy of trabectedin were raised.

The objective of the present study was to retrospectively assess trabectedin efficacy and tolerance in a single-center cohort of "real-life" patients with STS. Results were then compared to reference phase II trials.

Methods

A retrospective study was conducted at Lucien Neuwirth comprehensive cancer care center (France). The institutional review board approved the study, which was conducted in compliance with the Helsinki declaration.

Patient population

Medical records of consecutive patients receiving at least one cycle of trabectedin, between 2004 and 2013, for histologically proven STS, were retrospectively reviewed. Histology was systematically reviewed by sarcoma expert center (French Sarcoma Group, Netsarc). All patients received prior cytotoxic regimens and experienced metastatic relapse or disease progression. Clinical data were collected in medical records and in local chemotherapy database, using electronic case report forms. Patients' characteristic, prior treatment history, number of cycles administered, doses reductions, reasons of treatment discontinuation, disease control rate, time to disease progression, and overall survival were studied. Toxicities and chemotherapy side effects were also investigated. Patients were clinically and radiologically assessed for efficacy every 4 cycles, with Response Evaluation Criteria in Solid Tumors (RECIST) [15]. Toxicities were graded using the National Cancer Institute – Common Terminology Criteria for Adverse Events version 3.0 [16].

Trabectedin administration

Trabectedin was administered during a 24-hour continuous intravenous infusion at a dose of 1.5 mg/m^2, every 3 weeks. In case of poor clinical condition (age, comorbidities) and/or hepatic failure at baseline, initial dose was restricted from 80 to 66%, depending on oncologist. In case of related-to-trabectedin toxicity (grade 3 or 4 hepatic dysfunction, hematologic toxicity, cardiac dysfunction, asthenia), optimal dose was reduced to 80%. Dose could be reduced to 75, 66 and 50% in case of toxicity persistence. Antiemetic prophylaxis was routinely administered. If needed, antiemetic therapy included ondansetron, corticosteroids, and metoclopramide. Aprepitant was not prescribed because of hepatic cytochrome interactions. After each chemotherapy cycle, neutropenia prophylaxis was prescribed, with granulocyte colony stimulating factor (G-CSF).