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A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas

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Abstract ***Aims:*** Approximately 20% of soft tissue sarcomas (STS) have subtype-specific chromosomal translocations; these generate chimeric oncoproteins which can act as abnormal transcription factors. Since trabectedin can bind to DNA and displace transcription factors, antitumour activity was explored in translocation-related sarcoma (TRS) subtypes.
Methods: The current retrospective pooled analysis includes data from 81 patients with TRS treated in 8 phase II trials.
Results: TRS subtypes were: synovial sarcoma (SS, $n = 45$), myxoid-round cell liposarcoma (MRC-L-sarcoma, $n = 27$), alveolar soft part sarcoma (ASPS, $n = 4$), endometrial stromal sarcoma (ESS, $n = 3$) and clear cell sarcoma (CCS, $n = 2$). All but one patient had received prior chemotherapy (median of 2 lines). Patients received a median of 4 trabectedin cycles (range, 1–48; median dose intensity = 0.40 mg/m^2/week). Partial responses according to Response Evaluation Criteria in Solid Tumours (RECIST) occurred in 8 patients

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(ORR = 10%; 95% CI, 4–19%): four in MRC-L-sarcoma; three in SS and one in ESS. Tumour control rate (ORR plus stable disease) was 59% (95% CI, 48–70%). Median PFS was 4.1 months (6-month PFS rate = 40%). Median overall survival was 17.4 months (survival rate at 12 months = 60%). Trabectedin had a manageable safety profile.

Conclusion: Trabectedin demonstrates encouraging disease control in TRS. Since these promising results were generally noted in patients following chemotherapy, a phase III randomised trial in first-line is ongoing to compare trabectedin with doxorubicin-based chemotherapy in patients with TRS.

1. Introduction

Chromosomal translocations are the most frequent molecular alterations in sarcomas, and occur in around 20% of cases.[1–4] Sarcoma translocations and the associated chimeric oncoproteins that they generate provide attractive targets for therapeutic intervention given that these fusion proteins are critical for disease pathogenesis and tumour cell survival, and no alternative pathways exist to avoid their blockade.[5–8]

Trabectedin is a marine-derived antineoplastic agent, initially isolated from the tunicate *Ecteinascidia turbinata* and currently produced synthetically, which has shown antitumour activity in advanced soft tissue sarcoma (STS),[9–11] as well as in other malignancies such as relapsed ovarian cancer,[12–16] metastatic hormone-refractory prostate cancer,[17] and advanced breast cancer.[18,19] Trabectedin is approved in Europe and many other countries for the treatment of patients with advanced STS after failure or unsuitability of anthracyclines and/or ifosfamide,[20] as well as in combination with pegylated liposomal doxorubicin for patients with relapsed, platinum-sensitive ovarian carcinoma.[15]

Trabectedin was noted early in clinical development to demonstrate very relevant antitumour activity against myxoid-round cell liposarcoma (MRC-L-sarcoma).[21,22] Pathogenesis of MRC-L-sarcoma is related to characteristic chromosomal translocations, such as t(12;16)(q13;p11) or less frequently t(12;22)(q13;q12), resulting in the expression of *FUS-DDIT3* and *EWS- DDIT3* fusion genes, respectively.[23] The high activity of trabectedin against MRC-L-sarcoma seems to be related to its ability to counteract the biological activity of the chimeric *FUS-DDIT3* oncoprotein, a hallmark of this disease.[24–26] *In vitro* studies showed that the expression of different variants of the *FUS-DDIT3* fusion transcripts correlated with the sensitivity to trabectedin.[27] The *FUS-DDIT3* oncoprotein acts as a deregulated transcription factor, and trabectedin may interfere with the binding of this fusion protein to specific DNA promoters, causing altered expression of genes encoding proteins such as PTX3 and IL-6.[25,28] Results with trabectedin from a retrospective series of patients with pretreated MRC-L-sarcoma treated in compassionate use programs[3,21] showed the t(12:16)(q13;p11) chromosomal translocation in a 33 of 51 patients. Type I, II, or IV *FUS-DDIT3* fusion transcripts were found in patients responding to trabectedin, while type III form, alone or together with type II, was found in non-responders. Furthermore, in a phase II exploratory clinical trial trabectedin administered as induction treatment in chemotherapy-naïve patients with a localised resectable MRC-L-sarcoma resulted in several pathological and molecular complete responses, i.e. complete disappearance of tumour tissue at histopathological evaluation as well as absence of cells with the *FUS-DDIT3* translocation in the post-treatment surgical specimen.[29] The maturation observed in the malignant liposarcoma cells, with transition of the residual spindle non-lipogenic cells into mature signet-ring vacuolated lipoblasts, was consistent with *in vitro* data showing that trabectedin can remove differentiation blockade mediated by the *FUS-DDIT3* chimera and induce adipocytic differentiation.[25]

Based on the hypothesis that STS subtypes harbouring fusion oncoproteins may have similar pathogenesis due to aberrant transcription induced by the chimera, the results observed in MRC-L-sarcoma could be extrapolated to other translocation-related sarcomas (TRS). To address this, we have conducted this retrospective pooled analysis to assess the efficacy of trabectedin in several subtypes of TRS.

2. Patients and methods

Trabectedin integrated database (PharmaMar, Colmenar Viejo, Madrid, Spain) was examined using pooled data from 81 adult patients with TRS who received single-agent trabectedin in 8 multicentre phase II clinical trials. Overall results from 7 of these 8 clinical trials were previously published[9–11,20,30–32]; the 81 patients evaluated here represent 10.5% of 771 STS patients treated in these clinical trials. All of them had histological confirmation of TRS and a life expectancy $\geqslant$ 3 months, a performance status 0–1, adequate renal, hepatic and bone marrow function according to laboratory standard parameters, and complete recovery from relevant toxicity derived from previous treatments. All trials were carried out in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice and local regulations, and were approved by the institutional review boards. In each clinical trial, informed written consent was obtained from all patients.