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Trabectedin in the treatment of patients with soft tissue sarcoma

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Soft tissue sarcomas (STS) are rare malignant tumours derived from connective tissue. They constitute about 1% of malignancies occurring in adults. We distinguish over 60 subtypes of soft tissue sarcoma, each with a unique clinical course and a diversified response to systemic treatment. The prognosis for patients with locally advanced, unresectable or metastatic disease remains poor. For years, doxorubicin — used alone or in combination with ifosfamide — has been the basis of treatment for these patients. Trabectedin is a relatively new molecule registered in the treatment of patients diagnosed with STS. The drug was originally obtained from marine tunicates (*Ecteinascidia turbinata*), currently it is obtained semi-synthetically. So far, a number of potential mechanisms of trabectedin have been described, including DNA-binding, disruption of DNA repair mechanisms and cell cycle, as well as effects on transcription factors and the tumour microenvironment. The aim of the following review is to summarize the current knowledge on the efficacy and safety of trabectedin in the treatment of patients diagnosed with STS.

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Introduction

STS is a group of rare malignant neoplasms of mesenchymal origin. The standard treatment for locally advanced disease is radical resection of the tumour usually with pre- or post-operative radiotherapy. The place of perioperative chemotherapy is still not fully established. However, about 50% of patients diagnosed with high-grade tumours will develop metastatic disease. The prognosis remains bad, and the median overall survival (OS) is about 12 months. The basis of treatment in the case of diagnosis of metastatic disease is a systemic treatment. Unfortunately, the number of drugs with proven activity in this indication is still low. For many years, the most important drugs used in palliative treatment of STS have been doxorubicin and ifosfamide. There is also a number of new particles with proven efficacy, such as olaratumab, pazopanib, eribulin or trabecetidin, used for the longest time among this group [1].

Trabectedin is a synthetic alkylating agent, originally isolated from Caribbean tunicates *Ecteinascidia turbinata* [2]. The success of trabectedin in initial clinical trials among patients diagnosed with MTM has resulted in drug approval in many countries. Two years ago the results of a large, randomized phase III trial being the final trial approving the drug in the United States [3] were published. With limited systemic therapy options available to treat patients with STS, trabectedin is an important treatment line in this rare diagnosis.

Trabectedin — mechanism of action

A number of potential mechanisms of antitumor activity of trabectedin have been described, including cytotoxic and antiproliferative effects, inhibition of gene transcription and indirect immunological and anti-angiogenic effects. However, the effects of the drug are still not fully understood [4].

Molecular evidence suggests that the cytotoxic effect of trabectedin is due to its DNA-binding. In fact, trabectedin binds to a minor DNA groove, causing DNA double helix to be distorted with an interruption in the DNA itself. The interaction between trabectedin and the minor DNA groove determines structural changes in the molecule, resulting in

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a cascade of events that affects a number of transcription factors, DNA-binding proteins and DNA repair pathways, resulting in G2-M cell cycle arrest and eventually apoptosis [2]. It has been observed that cytotoxic mechanisms of trabectedin are affected by DNA repair mechanisms, such as nucleotide excision repair (NER) and homologous recombination repair (HRR), which recognize DNA damage and recruit various factors to repair the damaged place. Cell repair machinery, including both NER and HRR systems, is crucial for the interaction between trabectedin and DNA and appears to be the most important determinant of drug susceptibility [5]. Also the direct interaction between trabectedin and RNA polymerase II (pol II) has been described, causing the transcription process to stop, pol II degradation through the proteasome pathway and premature termination of the RNA transcript [2]. This type of antiproliferative mechanism appears to be particularly effective in MLPS (myxoid liposarcoma), which is the STS subtype most sensitive to trabectedin therapy. Furthermore, trabectedin has a stimulating effect on the differentiation of MLPS tumor cells. The tumor response to trabectedin in MLPS in vivo is characterized by tumor cell death and induction of mature adipocytes [6].

In addition to this cytotoxic activity, trabectedin modulates tumour microenvironment and it seems that this is the most important part of its therapeutic effect. The drug exerts a selected cytotoxic effect against tumour-associated monocytes and macrophages (TAM) present in tumour tissues. They are key promoters of inflammation associated with cancer. TAMs have a pro-cancer activity, including the production of growth factors that are necessary for proliferation, neoangiogenesis and the action of proteolytic enzymes. These elements degrade the extracellular matrix, determining the invasion of cancer cells and facilitating escape from the immune system [7]. It has been shown that trabectedin significantly reduces the expression of cytokines, chemokine, mediators of inflammation and angiogenesis, for example, interleukin-6, or vascular endothelial growth factor modifying the tumour microenvironment, thereby contributing to anti-angiogenic and antitumor effect of the drug [8].

The efficacy of trabectedin in clinical trials

Phase II clinical trials

The year 2004 saw the publication of the results of two phase II clinical trials that demonstrated the efficacy of trabectedin in the treatment of MTM. The first of these studies was conducted on a group of 54 previously treated patients. There was a low rate of objective response to treatment — 4%, but a high rate of disease control after six months of therapy — 24%. Trabectedin was administered at a dose of 1.5 mg/m^2, for 24 hours every three weeks [9]. The second study noted again a low response rate of 8% and one year OS amounting to 53% in 36 previously treated patients with STS. The same dosing regimen of trabectedin was also used in this study (1.5 mg/m^2, over 24 hours every three weeks) [10].

Promising results of the Phase II studies led EORTC (European Organization for the Research and Treatment of Cancer) to conduct a phase II trabectedin trial in 104 patients in the second and third line of treatment. Again, a low rate of objective responses of 8% was noted. The six-month PFS was 29% and the median overall survival was 9.2 months [11]. A further phase II trial was carried out in 36 patients to evaluate the activity of trabectedin in the first line of treatment. The treatment response rate was 17%, and the annual PFS and OS rates were 21% and 72% respectively [12].

Then a phase II randomized study was conducted, including 270 patients diagnosed with leiomyosarcomas (LMS) and liposarcoma (LPS). Patients were randomized to one of two arms — in the first the drug was given at a dose of 1.5 mg/m^2 for 24 hours every three weeks, in the other arm at a dose of 0.58 mg/m^2 for 3 hours once a week for three weeks out of four. Prior to enrolment, patients had to document the disease progression while receiving doxorubicin and ifosfamide. The 24-hour infusion regimen showed a much longer mean time to progression (TTP) (3.7 vs 2.3 months) and progression-free survival (PFS) 3.3 vs 2.3 months compared to the 3-hour infusion schedule. There was no significant difference in the overall survival between the two arms of the study, but there was a strong trend favouring the 24-hour infusion schedule (13.9 months vs 11.8 months) [13]. The results of this study led to the registration of trabectedin in the European Union in 2007.

Trabectedin is an expensive drug and has some side effects, which is why it was very important to ask whether the treatment should be continued until it is effective or it is possible to stop it after achieving control of the disease. The second phase II trial involved 53 patients with at least stabilization after 6 cycles of trabectedin. They were divided into one of the two arms of the study at random. In the first arm the treatment was continued until the disease progressed, in the second one it was discontinued. The percentage of PFS at 6 months after randomization was 51.9% in the group where trabectedin was not discontinued compared to 23.1% in the group where trabectedin was discontinued after 6 cycles. Toxicity did not increase significantly with continuation of therapy. This study confirms that treatment with trabectedin should not be discontinued after the disease has been controlled and therapy should be continued as maintenance treatment [14].

Phase III clinical trials

Trabectedin has a higher efficacy in the treatment of patients diagnosed with so-called sarcomas associated with translocation (such as, for example, MLPS or synovial sarco-

ma). Therefore, this group of patients was selected for the study in which the drug was compared with doxorubicin, which is the current standard of first-line treatment. In the phase III study, 121 patients with translocation sarcomas were randomly assigned to the arm in which they received trabectedin or doxorubicin in the first line of treatment. There was no significant difference in PFS between the two arms, which was the primary endpoint of the study. At the time of analysis, 63.9% and 58.3% of patients were still alive in the arms with trabectedin and doxorubicin (without a statistically significant difference in overall survival) respectively. The objective response rate according to RECIST criteria was significantly higher in the doxorubicin group (27%) compared to trabectedin (5.9%). However, when the response was assessed according to Choi's criteria, differences between doxorubicin (45.9%) and trabectedin (37.3%) were smaller [15]. Thus, doxorubicin (or doxorubicin based regimens) remains the standard first line treatment.

The pivotal phase III trial compared the use of trabectedin to dacarbazine in patients with locally advanced/metastatic LMS and LPS. Patients were randomized in a 2:1 ratio to the arm with trabectedin or dacarbazine. A total of 518 patients took part in the study, 345 of whom were randomly assigned to the trabectedin arm and 173 patients to the dacarbazine arm. In the final PFS analysis, the use of trabectedin was associated with a reduction in the risk of disease progression or death compared to dacarbazine by 45% (the median PFS for trabectedin was 4.2 vs 1.5 months for dacarbazine, hazard ratio 0.55; $p < 0.001$). Benefits were observed in all pre-planned subgroup analyses. An interim OS analysis (64% censored) showed a 13% reduction in the risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin was 12.4 to 12.9 months for dacarbazine, hazard ratio, 0.87; p = 0, 37). Based on a significant improvement in PFS for the arm with trabectedin, this drug was registered in the United States in October 2015 for the treatment of patients diagnosed with advanced LPS and LMS [3, 16].

At this year's ASCO 2018 meeting (American Society of Clinical Oncology) the results of the next phase III trial were presented. The study compared the efficacy and safety of trabectedin to the best supportive care (BSC) in patients diagnosed with STS after failure of at least one line of systemic treatment (no more than previous 3 lines of chemotherapy). In the case of confirmation of further disease progression, patients in the BSC arm were able to go to the arm with trabectedin (cross-over option).

The primary endpoint of the study was PFS. The study included both patients with so-called L-sarcomas (LPS and LMS) as well as other MTM subtypes. In the group receiving trabectedin, the objective response rate (ORR) was 11.8%, all responses were observed in the L-sarcoma group (ORR in this group 18.8%). 23% of patients in the trabectedin arm received more than 9 courses of treatment. The median PFS was 1.5 months in the BSC arm and 3.1 months in the trabectedin arm (HR: 0.39, $p < 0.0001$). In the L-sarcoma cohort, the median PFS was 1.4 months in the BSC arm and 5.1 months in the drug arm (HR: 0.29, $p < 0.0001$), while in the group without L-sarcomas it was 1.5 m and 1.8 m respectively ($p = 0.16$). Cross-over was performed in 92% of patients included in the BSC arm. After a median follow-up of 25.7 months, the differences between the two arms in terms of OS were not statistically significant and were 13.6 months for the drug arm vs 10.8 months for the BSC arm ($p = 0.86$) [17]. Again, these results confirm the higher efficacy of the drug in patients with the diagnosis of the so-called L-sarcomas when compared to other MTM subtypes.

Also in the published results of the extended drug access program, which included 1895 patients diagnosed with STS treated with trabectedin, the results achieved in the group of patients diagnosed with L-sarcomas are significantly better. ORR in the group of L-sarcomas was 6.9% compared to 4% in the group of other histological subtypes. OS was also significantly better in the group of L-sarcomas and amounted to 16.2 vs 8.4 months [18].

In Poland, the drug is available as part of the National Health Fund drug program only for patients diagnosed with L-sarcomas. In 2015, we published the results of trabectedin treatment of 50 patients with LPS and LMS at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. The median number of given treatment cycles was 5 (range 2–40); 18 patients (36%) received ≥ 10 cycles. Four patients (8%) had a partial response, in 23 (46%) a disease stabilization was noted (for a minimum of 3 months), and in 23 (46%) — disease progression. After six months of treatment, 47% of patients were progression-free, more in the group with LPS — 66% compared with 27% in the LMS group ($p = 0.023$). PFS was significantly longer in patients receiving trabectedin in the 2nd or 3rd line of treatment (median 7 months) than > 3rd line of treatment (median 2 months) $p = 0.038$. The median overall survival (OS) was 13 months [19]. Table I summarizes the results of clinical trials on efficacy of trabactedin in STS.

Trabectedin in the treatment of myxoid liposarcomas (MLPS)

It has been found that trabectedin is particularly effective in sarcomas associated with translocation, such as MLPS, exerting anti-tumour activity, *inter alia*, by inactivation of an oncogene FUS-CHOP, which is believed to alter expression of a protein encoding gene and induce adipocyte differentiation [6].

Results of two retrospective studies were published on the efficacy of trabectedin only among patients with this diagnosis. In the first one including a group of 32 patients the drug was used after failure of previous therapies. The objective response rate was 50%, 2 patients had a complete

remission (CR), 14 had partial response (PR) to treatment. The stabilization of the disease (SD) was noted in another 14 patients. 90% of patients achieved disease control (CR + PR + SD). The median PFS for the whole group was 17 months. Six months after the start of treatment, 90% of subjects were free of disease progression. Some patients after the use of this treatment were qualified for resection of residual lesions, which was not possible before starting the therapy. The median duration of treatment was 10 months and 24 subjects (75%) received more than 8 courses of treatment [20]. In another study conducted in a group of 51 patients from several centres, the results were quite similar: 2 CR, 24 PR were found, in total 51% of patients had an objective response to treatment. The median PFS was 14 months and the proportion of patients free of progression after six months after starting treatment — 88%. Interestingly, 17 of 23 responders were found to have changes in the density of neoplastic lesions assessed in the CT scan or reduced contrast uptake in the magnetic resonance imaging study, which preceded the finding of tumour size reduction [21].

Particularly good results among patients with the diagnosis of metastatic MLPS encouraged the assessment of the usefulness of the drug used as pre-operative therapy. In a study conducted by the Italian sarcoma group, 23 patients received the drug pre-operatively for 3–6 cycles of treatment. Then, the response to treatment was evaluated — in 3 patients CR was noted, confirmed in later histopathological examination, in 12 patients showed a significant response to the treatment which also manifested in the histopathological material as decreased tumour cellularity, decreased number of blood vessels, as well as greater maturity of tumour-forming lipoblasts. In 7 people, PR was diagnosed. None of the patients had progression of disease [22].

Side effects

Phase II and III trials showed that trabectedin is a fairly well-tolerated treatment, with no cumulative toxicity. The most common side effects of the drug are nausea, tiredness, vomiting, constipation and oedema. Adverse drug reactions of grade III and IV occur only in about 10% of treated cases.

Table I. The results of clinical trials on the efficacy of trabectedin in STS

Trial	Number of patients treated with trabectedin	Treatment line	Histological subtypes	Results	
Yovine et al. [9] II Phase	54	≥ 2	LMS 22 (41%) LPS 6 (11%) GIST 4 (7%) *Synovial sarcoma* 3 (6%) MFH 3 (6%) *Fibrosarcoma* 4 (7%) Other 12 (22%)	PR 2 (3.7%) SD ≥ 6 months 9 (16.7%) SD ≥ 2 ≤ 6 months 9 (16.7%) PD 28 (51.9%)	6-months PFS 24.1% Median OS 12.8 months
Le Cesne et al. [11] II Phase	99	≥ 2	LMS 43 (41%) LPS 10 (9.6%) *Sarcoma synoviale* 18 (17.3%) MFH 6 (5.7%) *Fibrosarcoma* 1 Other 26	PR 8 (8.1%) SD 45 (45.5%) PD 35 (35.4%)	6-months PFS 29% Median OS 9.2 months
Garcia-Carbonero et al. [10] II Phase	36	≥ 2	LMS 13 (36%) LPS 10 (28%) MPNST 2 (6%) *Synovial sarcoma* 6 (17%) Other 5 (13%)	CR 1 (3%) PR 2(6%)	Median OS 12.1 months OS after 1 year 53.1% Median PFS 1.7 months
Blay et al. [15] (vs Doxorubicin) III Phase	60	1	MLPS 23 (37.7%) Other translocation related subtypes 28 (45.9%) Other STS subtypes 10 (16.4%)	PR 3 (5.9%) SD 39 (76.5%) PD 6 (11.8 %)	No statistically significant difference between the study arms in PFS and OS
Demetri et al. (Dacarbazine) [3] III Phase	345	≥ 2	LMS 252 (73%) LPS 93 (27%)	ORR 34 (9.9%) SD 177 (51%)	Median PFS 4.2 months (vs 1.5 months for dacarbazine $p < 0.001$)
Le Cesne et al. [17] (vs best supportive care — BSC) III Phase	52	≥ 2	LMS 31.1% LPS 29.1% *Pleomorphic sarcoma* 10.7% *Myxofibrosarcoma* 7.8% *Synovial sarcoma* 4.9% Other 16.5%	PR 7 (13.7%) SD 34 (66.7%) PD 10 (19.6 %)	Median PFS 3.12 months (vs 1.5 months for BSC $p < 0.0001$)

The most common grade III and IV adverse reactions are: reversible elevation of aminotransferases and myelotoxicity, in particular neutropenia and anaemia [4, 23].

Transient increase of transaminases typically occurs several days after administration of trabectedin and it usually resolves spontaneously after about 15 days. If the level of transaminase does not normalize after 21 days, it is necessary to postpone treatment or reduce the dose. Intravenous premedication with corticosteroids, such as dexamethasone, is strongly recommended as an antiemetic and prophylactic for hepatic toxicity. Some clinical trials have shown that concomitant steroid treatment induces hepatic activity of the cytochrome P450 variant 3A4, reducing exposure to trabectedin in the liver and consequently correlated hepatotoxicity [24].

Rarely occurring, potentially dangerous side effects of trabectedin include neutropenic fever, rhabdomyolysis, cardiotoxicity or extravasation of the drug (the drug must be administered through a catheter inserted into the central vein due to the strong local irritant action of the drug on the vessel wall) [25].

Summary

Patients diagnosed with unresectable/metastatic soft tissue sarcoma are still a group of patients with poor prognosis. There are still not many systemic treatment options available. Research in recent years has, however, resulted in a number of new drug registrations in this indication. One of them is trabectedin — a drug with proven efficacy, especially in patients diagnosed with so-called L-sarcomas. The unique anti-tumour activity of trabectedin is not only its cytotoxic activity, but also its ability to modulate the tumour microenvironment. Trabectedin in subsequent studies shows a constant activity in patients after failure of treatment with doxorubicin, allowing to obtain long-term control of the disease.

Conflict of interest: none declared

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