Trabectedin in myxoid liposarcomas (MLS): a long-term analysis of a single-institution series

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Background: Trabectedin has been approved in Europe as second-line therapy for advanced soft tissue sarcomas. A previous analysis showed that myxoid liposarcomas (MLS) are particularly sensitive to the drug. We report on the long-term efficacy of trabectedin in a subgroup of that series.

Methods: Since September 2002, 32 advanced pretreated MLS patients received trabectedin at our center. Data were reviewed focusing on their long-term outcome.

Results: Trabectedin was given as a 24-h continuous infusion every 21 days. A total of 376 and a median of 12 courses per patient (range 2–26; interquartiles range (IQR) 8–15) were delivered. Response rate per RECIST was 50% [95% confidence interval (CI) 32% to 68%], median progression-free survival (PFS) was 17 months (95% CI 13.5–30.1) and median overall survival is still not reached. In 10 patients, therapy was stopped in the absence of any evident disease, mostly after complete surgery of residual lesions. In these 10 patients, at a median follow-up of 25 months, PFS was 28.1 months (95% CI 25.6–36.4) from treatment start.

Discussion: These data indicate that the high response rate of MLS to trabectedin translates into prolonged PFS. Surgery of residual metastatic disease is already used quite extensively in metastatic MLS. Trabectedin may give further significance to this kind of surgery.

Key words: liposarcoma, myxoid liposarcoma, round-cell liposarcoma, trabectedin

Introduction

In 2007, we reported the peculiar antitumor activity of trabectedin in advanced myxoid liposarcomas (MLS) as the result of a retrospective multi-institutional analysis of 51 patients. The response rate was in the 50% range, with a tumor control rate reaching 80% and progression-free survival (PFS) exceeding 1 year [1].

Trabectedin (Yondelis®, Pharma-Mar, Madrid, Spain) is now approved in the European Union as a second-line treatment for advanced soft tissue sarcomas (STS). STS are mesenchymal tumors representing 1% of adult malignancies and encompassing >50 different histological subtypes. Approximately 50%–60% of newly diagnosed patients die of metastatic disease [2, 3]. Chemosensitivity is poor: the probability of response to the most active drugs, anthracyclines and ifosfamide, ranges from 20% to 40% and the median survival is <1 year [4]. After failure of conventional chemotherapy, there is no standard of care and median survival is <1 year [3–7].

Trabectedin, though with response rate not exceeding 10%, was demonstrated to provide some disease control, with progression arrest rates exceeding 50% and PFS rates exceeding 20% at 6 months [8]. The main benefits have been documented in leiomyosarcoma and liposarcoma and possibly synovial sarcoma [9, 10]. A high sensitivity to trabectedin of MLS, a specific liposarcoma subtype, was also pointed out [11, 12]. MLS account for about 30%–35% of liposarcomas and carry characteristic chromosomal translocations, the t(12;16)(q13;p11), resulting in the DDIT3-TLS, and the rarer t(12;22)(q13;q12), resulting in DDIT3-EWS fusion protein. The clinical history is distinctive, with a peculiar pattern of metastatization including bones, abdominal cavity and serosal membranes even in the absence of lung metastases and with chances for prolonged survival even in the metastatic phase [13–16].

This study focuses on the long-term clinical impact of trabectedin in 31 of the originally reported MLS patients treated at our single institution plus one patient who at the time of the previous analysis was too early for any evaluation.
methods

This is a retrospective analysis including all the MLS patients treated at our institution within an expanded access program. Both Italian Ministry of Health’s authorization and PharmaMar approval, following an individual request by the treating physician, were needed for the single patient. The inclusion criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero to two, bilirubin/aspartate aminotransferase/alanine aminotransferase and alkaline phosphatase up to 2.5 times the upper normal limit, normal renal function, full recovery from toxicity of previous therapy, age >18 years, written informed consent to treatment and data collection for research purposes.

Trabectedin was supplied by PharmaMar as a lyophilized powder in glass vials containing 0.25 or 1 mg and was given at different dose levels (1100–1650 µg/m²) using two different schedules either a 3-h infusion or a 24-h continuous infusion via a central venous line. The starting dose was selected according to baseline liver tests, PS and previous treatments. All patients received a hepatoprotective steroid premedication consisting in dexamethasone 4 mg orally twice a day the day before therapy [17]. Routine antiemetic premedication included dexamethasone 8–20 mg i.v. and a 5HT3 antagonist. Each cycle was administered on day 21 provided complete recovery of any hematological and hepatic toxicity was achieved. Recovery of any non-hematological toxicity to at least grade 1 was required. If these criteria were not met on day 21, the next cycle was postponed by 1 week. A delay of 3 weeks was allowed, and if a persistent lack of recovery was documented, the treatment was stopped, unless a clinical benefit was evident. Treatment was continued until achievement of complete remission, surgical removal of residual disease, disease progression, unacceptable toxicity or patient refusal.

Surgery or radiotherapy of residual disease if response or prolonged tumor control has been obtained was resorted to whenever the tumors could be completely treated.

All patients were evaluated by full medical history, physical examination, full blood count and serum biochemistry and a staging computed tomography (CT) or magnetic resonance imaging (MRI) scan. Tumor assessment was carried out every two to three cycles. The RECIST criteria were used to assess response [18]. Any radiologically dimensional reduction in the sum of the longest diameter of target lesions not reaching criteria for an objective partial response (PR) was defined as minor response (MR).

Patient medical records were examined collecting in a database the details of interest and tumor assessments were reviewed by a radiologist. Since the analysis did not focus on toxic effects, only serious adverse or unexpected events were sought.

To explore patterns of tumor response, any change in tumor density on CT and/or consistent changes on MRI (consistent signal alterations and/or decrease in contrast enhancement) were documented.

The diagnosis of MLS was confirmed in all cases by a pathologist. Whenever feasible, the presence of t(12;16) or t(12;22) was confirmed by FISH analysis using two BAC clones directly labeled by Spectrum Orange and Spectrum Green by nick translation. The former, RP11-196G-11, contains a region upstream TLS gene; the latter, RP11-181L23, spans the entire DDIT3 gene. When frozen tissue was available, RT-PCR was carried out for sequencing and characterizing the fusion transcript [19].

In tumor specimens of patients operated on after trabectedin, the pathologically documented response (pathological response) was assessed and defined according to the percentage of cell component and vascular network loss (cells and vessels score system) comparing pre- and post-treatment tumor specimens. Both parameters were scored as 0 when the loss was <10%; 1 when the loss was 10 up to <50%; 2 when the loss was 50 up to <90% and 3 when the loss was >90%; the presence of a mature component and coagulative necrosis was recorded.

results

patient characteristics

This retrospective analysis included 32 patients (nine females, 28% and 21 males, 78%) treated from September 2002 to May 2007. The median age was 51 years (range 32–73). ECOG/World Health Organization PS was zero in 17 patients (54%) and one in 15 patients (46%). Histological diagnosis was pure MLS in six patients (19%), and MLS with cellular component representing 5%–90% of the total tumor in the other 26 patients (81%). FISH analysis was carried out in 27 patients (84%), all of whose tumors harbored the t(12;16); in 13 of them (50% of the entire series), the TLS-DDIT3 fusion product was determined by RT-PCR: type II fusion transcript was found in 10 patients; type I in two; types I and IV in one; type III in one and types II and III in one.

The most common primary site was the thigh (60%). Six patients (19%) presented with metastatic disease at diagnosis. Fifteen patients had received adjuvant radiotherapy and six adjuvant chemotherapy. All but three patients had been previously treated with chemotherapy. Twenty-eight patients (87%) had received anthracyclines and ifosfamide in combination as their first-line chemotherapy. The median number of previous chemotherapy regimens was 2 (range 1–3). The median time from initial diagnosis and from first relapse to commencing trabectedin were 47 months (IQR 33–122) and 23.7 months (IQR 14.1–45.8), respectively. Three patients (9%) had locally advanced disease when starting trabectedin, and 29 (91%) had metastatic disease, with a median of two sites involved (range 1–7). Lung and pleura were the most common sites of metastasis (53%), followed by abdominal cavity and soft parts (50%). The other sites were pericardium and heart, 38%; mediastinum, 31%; bone, 25% and liver, 3%. Patients’ characteristics are summarized in Table 1.

Before receiving trabectedin, 15 patients had chemotherapy for relapsed/metastatic disease, seven patients underwent surgery, one had radiotherapy and nine patients had surgery combined with radiotherapy or chemotherapy or both. The PFS on the prior treatment was 7.8 months [95% confidence interval (CI) 4–14.2].

drug delivery and toxicity

A total of 376 cycles were administered, with a median of 12 cycles per patient (range 1–26, IQR 8–15) and a median duration of treatment of 10.3 months (range 2.7–20.3, IQR 5.7–14.2). At the time of this analysis, one patient is still on treatment.

The starting dose was 1.5 mg/m² in four patients (13%), 1.3 mg/m² in 27 patients (84%) and 1.2 mg/m² in the remaining patients (3%); 31 patients were treated with the 24-h continuous i.v. schedule and one with the 3-h schedule, both recycled every 21 days. The mean received dose intensity was 0.390 mg/week (IQR 0.344–0.374). No treatment interruption due to toxicity and no unexpected or severe adverse events were documented.

activity and efficacy

All patients were assessed for response. Overall, two complete responses (CRs) and 14 PRs were achieved and the objective response rate was 50% (95% CI 32% to 68%) per RECIST.
Fourteen patients had stable disease (SD) (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions) (44%), five of them showing minor tumor shrinkage (16%). Overall, tumor control (CR + PR + SD) was achieved in 90% of the patients. Two patients (6%) had progressive disease on the first assessment.

Four of the 16 patients (25%) with a confirmed CR or PR had achieved it on the first response assessment; seven (44%) had an MR and five (31%) had SD on first assessment; in all these 12 patients, tissue changes consisting in a decrease of tumor density were seen on radiology. The same signs were seen in 79% of patients (11 of 14) who achieved SD as best response.

Responses according to the fusion transcript were CR in a patient with type II, PR in five patients with type II and one with types I and IV, MR in two patients with type I, SD in four patients with type II, PD in one patient with type III and one patient with types II and III.

After a median follow-up of 24 months (IQR 13–31), the PFS of the entire patient group was 17 months (95% CI 13.5–30.1). The rates of PFS at 3 and 6 months were 96% and 90%, respectively. Figure 1 shows the PFS Kaplan–Meier curve. The median overall survival has still to be reached.

The PFS of patients who had PR/CR anticipated by radiological decrease in tissue density was 21 months (95% CI 16–36.4). A subgroup of 10 patients (31%) of this series stopped treatment after a median duration of therapy of 10.4 months (IQR 6–11.4) in the absence of evident disease [no evidence of disease (NED)]. Seven underwent surgery of residual disease; one received radiotherapy on residual disease; two patients stopped trabectedin as a shared decision with the threatening clinician having reached a CR. The characteristics of the subgroup of patients who stopped treatment NED are detailed in Table 2. The median PFS is 28.1 months (95% CI 25.6–36.4) and 18 months (95% CI 14–19) calculated, respectively, from the first course and from the last course of trabectedin.

Of the seven patients who underwent surgery, two had a multifocal locoregional relapse and five metastatic disease at the time of starting trabectedin.

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<th>Table 1. Patients’ characteristics</th>
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PS, performance status; ECOG, Eastern Cooperative Oncology Group.

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Of the seven patients who underwent surgery, two had a multifocal locoregional relapse and five metastatic disease at the time of starting trabectedin. The pathological response assessment according to the cellular and vascular regression...
score system and the correspondent radiological response were as follows: 1 + 1 in one patient who had PR, 2 + 3 in one patient having an SD, 2 + 2 in three patients of whom one had a PR and two had an SD and 3 + 3 in two patients having an SD. Mature featuring lipoblasts were present in both patients with the highest regression score and in one patient with regression score 2 + 2. The fusion gene and the fusion protein could be detected in all post-treatment pathological samples.

At a median observation period of 24.8 months from trabectedin onset and of 15.1 months from the last course, 5 of the 10 patients who stopped NED relapsed. All of them have been rechallenged with Trabectedin and four of them who already had tumor assessed showed an MR.

**Discussion**

In this series of 32 advanced MLS patients, trabectedin displayed an objective RECIST response rate of 50%. With a median follow-up of 24 months, the median PFS was 17 months, with 90% of patients free of progression at 6 months. Substantial radiological changes in tumor density anticipated tumor shrinkage in 75% of responding patients and were visible in almost 80% of patients having obtained disease stabilization. As many as one-third of patients stopped therapy in absence of evident disease, most of them after complete surgery of residual disease. PFS of patients who were NED after stopping therapy was 15 months longer than the others.

This single-institution series of patients was included in the original report of a multi-institutional compassionate use series of MLS patients treated with trabectedin [1]. At that time, we reported that MLS are much more sensitive to trabectedin than other histological types of STS. Although it was a compassionate series, clinical observations were felt to be so striking as to be meaningful. In the meantime, trabectedin has been approved in the European Union as a second-line therapy for advanced STS.

In the present series, median duration of therapy was 10 months, and 24 patients (75%) received more than eight courses of therapy. Indeed, the lack of cumulative toxic effects makes it possible to carry on therapy with trabectedin for long intervals. The safety profile is in fact favorable, acute reversible elevation of transaminases being the most prevalent adverse effect [20]. All patients in this series received steroid premedication and no severe or unexpected adverse event was reported. Incidentally, this confirms that dexamethasone given the day before therapy can ameliorate the drug toxicity profile [17]. The clinician is thus left with the open issue of how long therapy should be continued in responding patients. In this regard, standard cytotoxic chemotherapy is generally stopped after a number of cycles. On the contrary, the new 'molecularly targeted' therapies are currently continued as long as tumor response is in place. Clinical studies are clearly needed on how long trabectedin should be continued or not. Rationally, the more the mechanism of action is close to a molecularly targeted one, the more one would be induced to continue indefinitely. Some patients in this series have remained progression free after stopping therapy for relatively long intervals, although most of them have then progressed.

The persistence of the fusion gene transcript after trabectedin, even in patients who achieved a pathological CR,
indicates that treatment does not eradicate the disease completely. This prompted us to use surgery in some of our patients. On one side, again, this parallels what is done, say, in advanced gastrointestinal stromal cancer (GIST) patients responding to imatinib [21]. On the other side, MLS have always been treated with surgery of metastatic disease, even when extrapulmonary (as is the rule with this subgroup), given their slow course of disease even in the metastatic stage. Clearly, no formal conclusion can be drawn on the inherent efficacy of surgery in these selected patients. This is another important issue to be addressed by future studies.

In the seven patients whose disease was removed after trabectedin, different degrees of cellular and vessel regression were seen. The pathologic response score used in this series has only a descriptive intention and requires to be validated in prospective studies. Intriguingly, the highest scores of regression were seen in two patients with dimensionally stable tumors and marked decrease in tissue density (in both patients also an increase of mature featuring lipoblasts was observed). This finding provides the proof of principle that the radiological changes in tissue density induced by trabectedin definitely represent a biological and clinical tumor response. This further strengthens the value of ‘tissue response’, which is now becoming an accepted criterion of response at least in GIST and other tumors responding to molecularly targeted therapies [22–24]. Of main clinical interest in this long-term analysis, patients who had tumor shrinkage anticipated by radiological changes in tissue density had longer progression-free intervals.

Currently, a confirmatory phase II study in pretreated advanced MLS patients is ongoing in Italy on behalf of the Italian Sarcoma Group, and an international study is ongoing for patients with localized operable disease who might benefit from cytoreduction. Meanwhile, the assumption that trabectedin could act in MLS through a mechanism that overcomes the transcription deregulation caused by the pathogenetic fusion transcript and the clinical activity noted in other translocation-related sarcomas such as synovial sarcoma, Ewing sarcoma and endometrial stromal sarcoma provided the rationale for testing the efficacy of the drug as a first-line therapy in metastatic MLS and other translocation-related sarcomas within an international phase III study [25–27].

These studies will help clarify how to optimize the use of trabectedin in MLS. For the moment, this series confirms on a long follow-up of the peculiar impact of the drug in this histological type. The peculiar patterns of tumor response are somewhat suggestive of a targeted mechanism of action, which seems preliminarily confirmed by experimental observations [28]. In addition, the duration of response is also consistent with this, although in the setting of a peculiar disease, with a spontaneously long natural history even in the metastatic setting. This is the reason why surgery even of extrapulmonary lesions has been always resorted to in the metastatic phase of MLS. Trabectedin may give further significance to this kind of surgery.

acknowledgements

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references


original article