

Case Report

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# Trabectedin Cardiotoxicity in Soft Tissue Sarcoma: A Case Series and Clinical Insights

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## Keywords

Trabectedin · Heart failure · Arrhythmia · Cardiotoxicity

## Abstract

Trabectedin is a chemotherapeutic used to treat advanced soft tissue sarcoma and relapsed platinum-sensitive ovarian cancer. Although it is associated with a low incidence of cardiotoxicity, when this occurs it can be fatal or significantly compromise the quality of life in patients with advanced cancer. Here, we present a series of 4 cases where trabectedin-treated sarcoma patients developed cardiovascular complications. Similar to previous literature describing this association, all patients had prior treatment with anthracyclines and presented at different time points following treatment initiation. Each patient presented with exertional breathlessness and was found to have severely impaired left ventricular systolic function (ejection fraction  $\leq 35\%$ ), and 1 patient had concurrent atrial fibrillation with a fast ventricular rate. All of the patients were treated with neurohormonal blockade, and a multi-disciplinary decision was made to stop trabectedin in 3 patients and continue in 1 patient. Two of the 4 patients had an improvement in their left ventricular systolic function. It is unclear what effect preceding anthracycline or tyrosine kinase inhibitor treatment has in priming patients to develop cardiotoxicity in this setting. Our case series adds to the evidence surrounding this association and highlights that trabectedin-associated cardiotoxicity can present in an insidious fashion.

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## Introduction

Trabectedin is an anti-neoplastic drug [1] that originates from the marine Caribbean tunicate *Ecteinascidia turbinata*. It has a complex mechanism of action through interacting with key biological processes within the cell, altering the tumor micro-environment [2]. Trabectedin binds to the minor groove of deoxyribonucleic acid and alkylated guanine at the N2 position which bends the helix toward the major groove triggering several events: inhibition of trans-activated gene transcription and interaction with DNA repair proteins, modulation of the effect of tumor-associated macrophages by interfering with cytokine and chemokine signaling, displacing oncogenic transcription factors from their target promoters, and interfering with nucleotide excision repair and homologous recombination mechanisms promoting apoptosis [2].

Trabectedin gained its European authorization in 2015 with phase II, III, and IV trials demonstrating that it significantly increased progression-free survival in soft tissue sarcoma (STS) [1, 3, 4]. It is used to treat patients who have progressive STS despite ifosfamide and anthracycline chemotherapy, and patients with platinum-sensitive relapsed ovarian cancer in conjunction with PEGylated liposomal doxorubicin (PLD).

The most frequent adverse effects in early trials were hepatic toxicity, gastro-intestinal symptoms, and myelosuppression [1, 4]. Trabectedin was not initially reported to be cardiotoxic; however, this is an increasingly recognized phenomenon with its widespread use outside clinical trial settings [5–7]. Here, we present our institutional experience of trabectedin-related cardiac events to help physicians identify and treat this toxicity.

## Patients and Methods

We retrospectively identified patients at the Clatterbridge Cancer Centre (CCC) who were treated with trabectedin for STS and developed a subsequent adverse cardiac event. The CCC is the tertiary referral center for STS in Merseyside and North Cheshire and works in collaboration with the cardio-oncology service at the Liverpool Heart and Chest Hospital. We reviewed cases where trabectedin may have been an etiological factor in cardiotoxicity and present the results of cases where there was a likely causal relationship.

## Description of Cases

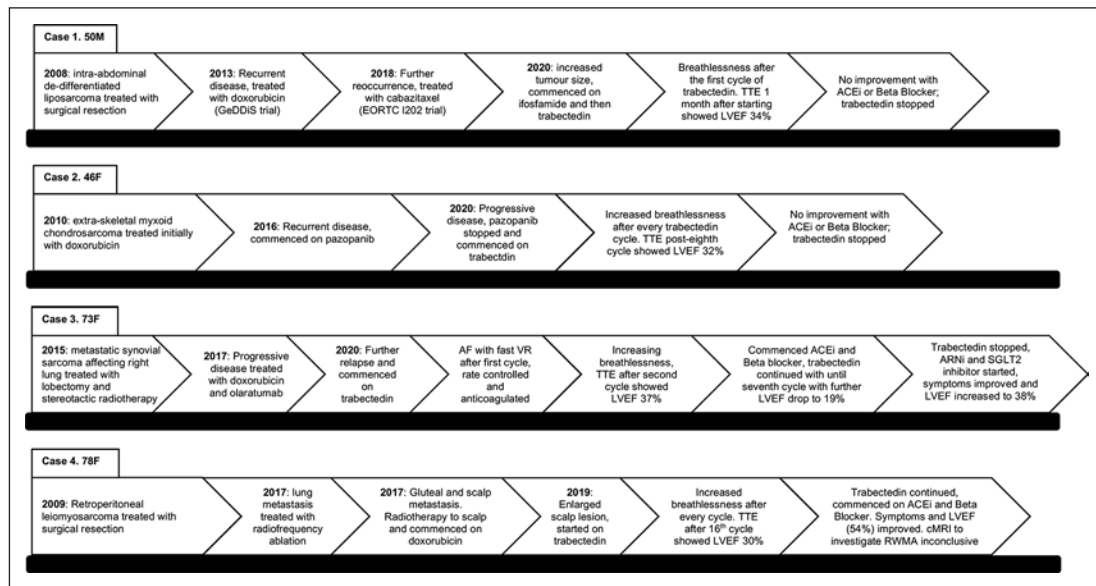
### Case 1

A 50-year-old man was diagnosed with intra-abdominal de-differentiated liposarcoma in 2008 and was initially treated with a surgical resection (Table 1; Fig. 1). He developed recurrent disease in 2013 and was treated with doxorubicin in the phase III gemcitabine and docetaxel versus doxorubicin (GeDDiS) trial [8]. In 2018, he developed progressive disease and was treated with cabazitaxel in the European Organization for Research and Treatment of Cancer (EORTC) phase II 1202 trial [9]. His disease had been stable until a computed tomography scan of his thorax, abdomen, and pelvis revealed an increase in the size of the intra-abdominal liposarcoma in August 2020. He commenced treatment with infusional ifosfamide (14 g/m<sup>2</sup> over 2 weeks), but the disease progressed and he was started on trabectedin (1.5 mg/m<sup>2</sup> every 3 weeks).

One week after starting trabectedin, he was admitted with neutropenic sepsis. No organism was identified, and he made a good recovery with empirical antibiotics. He had suffered with exertional breathlessness (New York Heart Association [NYHA] Class II) since

**Table 1.** Summary of patient characteristics

Case number	Sex	Age at presentation	Trabectedin indication	Cycle and day of presentation	Cardiac history and risk factors	History of anthracycline use	Clinical presentation	12-lead ECG	Cardiac imaging	Fatal event
1	M	50	Intra-abdominal de-differentiated liposarcoma	1 cycle August 2021; symptoms 1 week later	Treated high cholesterol	Yes	Exertional breathlessness, NYHA class III	Sinus tachycardia, normal axis	2D TTE: LVEF 34%, GLS -9%, normal LV cavity size, no valvular disease	No
2	F	46	Extra-skeletal myxoid chondrosarcoma	Completed 8 cycles starting in October 2020. Symptoms worsened progressively during treatment	Ex-smoker, type two diabetes	Yes	Exertional breathlessness, NYHA class III	Sinus tachycardia, normal axis, flat lateral T waves	2D TTE: LVEF 32%, GLS -11%, normal LV cavity size, no valvular disease	No
3	F	73	Metastatic synovial sarcoma	Commenced in October 2020. Symptoms developed 3 weeks after first cycle	Hypertension, AF	Yes	Exertional breathlessness, NYHA II, and AF with fast ventricular rate	AF, anterior Q waves	2D TTE: LVEF 37%, GLS -11%, severely dilated LV cavity, mild to moderate MR	No
4	F	78	Retroperitoneal leiomyosarcoma	Commenced in May 2020. Presented after the 16th cycle	No cardiac history or risk factors	Yes	Exertional breathlessness, NYHA class II	Sinus rhythm, normal axis	2D TTE: LVEF 30%, GLS not recorded, mild functional MR, dilated LV cavity	No



**Fig. 1.** Timeline showing the clinical course of patients within the case series. GeDDis, gemcitabine and docetaxel versus doxorubicin phase III trial; EORTC I202, European Organization for Research and Treatment of Cancer phase II I202 trial; TTE, trans-thoracic echocardiography; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; VR, ventricular rate; ARNi, angiotensin receptor/neprilysin inhibitor; SGLT2 inhibitor, sodium-glucose co-transporter-2 inhibitors; cMRI, cardiac magnetic resonance imaging; RWMA, regional wall motion abnormality.

the first cycle of trabectedin and was referred to the cardio-oncology clinic 1 month later. A trans-thoracic echocardiogram (TTE) at the time of the clinic showed a severely impaired left ventricular ejection fraction (LVEF) of 34% by Simpson’s biplane assessment and a global longitudinal strain (GLS) of  $-9\%$ . There was no echocardiogram available for comparison, and there was no history of cardiac disease. The 12-lead electrocardiogram (ECG) showed a resting sinus tachycardia with a normal cardiac axis. He was commenced on 1.25 mg ramipril and 1.25 mg bisoprolol once daily, and trabectedin was stopped.

A TTE 4 weeks later showed persistent moderate to severe left ventricular (LV) systolic impairment, and the breathlessness continued. There was a mild increase in his N-terminal pro-brain natriuretic peptide (NT pro-BNP) from 407 ng/L to 566 ng/L, and he remained in sinus rhythm. He was hypervolemic on examination, and 40 mg once daily furosemide was prescribed which precipitated an acute kidney injury and hyponatremia. After an admission for rehydration and renal monitoring, he was discharged on 20 mg once daily furosemide. He remains on furosemide with slowly progressive disease.

### Case 2

A 46-year-old woman was diagnosed with extra-skeletal myxoid chondrosarcoma complicated by lung, peritoneal, and pelvic lymph node metastasis in 2010 (Table 1; Fig. 1). She had a course of doxorubicin at the time of diagnosis and received pazopanib in 2016 which she responded to. She continued pazopanib until 2020, at which point there was evidence of progressive disease and trabectedin was started. She received eight cycles of trabectedin (1.5 mg/m<sup>2</sup> every 3 weeks) and noticed progressive breathlessness since starting treatment.

She was reviewed in the cardio-oncology clinic in May 2021. At this point, she had symptomatic breathlessness with minimal activity (NYHA class III) and a TTE showed severely impaired LV systolic function with a LVEF of 32% by Simpson’s biplane assessment and GLS

of –11% without any structural abnormalities. A previous TTE in 2017 showed mildly impaired LV systolic function. Her 12-lead ECG showed a resting sinus tachycardia with a normal cardiac axis and flattened lateral T waves. The NT pro-BNP was 647 ng/L.

Due to the reduced LVEF, she was commenced on once daily 1.25 mg ramipril, 1.25 mg nebivolol, and 40 mg furosemide. The furosemide was given to clear small bilateral pleural effusions. She was re-reviewed in clinic 3 months later where her symptoms had improved; she was now only breathless when she exerted herself. Despite this, a TTE showed a LVEF of 29% and GLS of –7%. Her NT pro-BNP had increased to 873 ng/L. She was not offered any further courses of trabectedin and remains under review with progressive disease.

### Case 3

A 73-year-old woman was diagnosed with metastatic synovial sarcoma affecting her right lung in 2015 (Table 1; Fig. 1). She had a right upper lobectomy and 60 grays of stereotactic ablative radiotherapy. Two years later, she had progressive disease and received a course of doxorubicin and olaratumab. She had a further relapse in 2020 and started treatment with trabectedin (1.5 mg/m<sup>2</sup> every 3 weeks).

Shortly after the first cycle, she was admitted to hospital with atrial fibrillation (AF) with fast ventricular rate manifesting as palpitations. She was rate controlled and started on apixaban. She had increasing breathlessness and was seen in the cardio-oncology clinic after her second cycle. A TTE showed impaired LV systolic function with a LVEF of 37%, a GLS of –8%, severe LV dilation, severe left atrial dilation, and mild to moderate mitral regurgitation (MR). There was no previous TTE for comparison. Her 12-lead ECG showed sinus rhythm, and her NT pro-BNP was 5,195 ng/L. A multi-disciplinary team (MDT) decision was made to continue trabectedin, and she was started on once daily bisoprolol 5 mg, ramipril 2.5 mg, and furosemide 40 mg with a plan to commence spironolactone after the initial therapy had been established.

She was reviewed after the seventh cycle of trabectedin; the breathlessness persisted (NYHA class III symptoms), and a repeat TTE showed that the LVEF had decreased to 29% with a GLS of –8%. She remained in sinus rhythm. The NT pro-BNP had increased to 9,755 ng/L, and a MDT decision was made to stop trabectedin. One month later, her symptoms had improved but she still had a severely dilated LV with a LVEF of 19% and GLS of –10% on repeat TTE. The NT pro-BNP started to decline to 3,859 ng/L, and sacubitril/valsartan and dapagliflozin were commenced with cessation of the ramipril. Her symptoms and exercise tolerance continued to improve, and a TTE 2 months later showed a LVEF of 38% and GLS of –13%. This mirrored a continued decline in the NT pro-BNP to 1,015 ng/L. She remains well with a stable LVEF.

### Case 4

A 78-year-old woman was diagnosed with retroperitoneal leiomyosarcoma in 2009 (Table 1; Fig. 1). She had a surgical resection and remained disease free until 2017 when she re-presented with bilateral lung metastasis. Her lung lesions were treated with radiofrequency ablation, but a new lung metastasis presented 2 months later followed by gluteal and scalp metastasis. She started six cycles of palliative chemotherapy with doxorubicin and had radiotherapy to her scalp lesions which stabilized her disease. Her leiomyosarcoma was slow growing, and 2 years later, the scalp lesion had enlarged with pain that was interfering with her quality of life. Due to the previous good response to chemotherapy, she was assessed for trabectedin (1.5 mg/m<sup>2</sup> every 4 weeks due to relative neutropenia) to help control her symptoms.

Her first presentation to the cardio-oncology clinic was after the 16th cycle of trabectedin. On review, she had exertional breathlessness for 2 weeks after each trabectedin infusion. An initial TTE showed an LVEF of 30%, severely dilated LV cavity, and moderate functional MR. The technical quality was not good enough for GLS assessment. A TTE 3 years earlier showed

a preserved LV systolic function with normal LV cavity size. Her 12-lead ECG showed sinus rhythm with a normal cardiac axis, and her NT pro-BNP was 4,516 ng/L. She was started on once daily bisoprolol 2.5 mg and ramipril 2.5 mg, and a MDT decision was made to continue the trabectedin alongside heart failure therapy.

Three months later, she reported that her symptoms had improved. A repeat TTE showed a LVEF of 54%, but the LV cavity was still severely dilated with inferior regional wall motion abnormalities (RWMAs) and the moderate functional MR persisted. Due to the RWMAs, she had a cardiac magnetic resonance imaging scan 1 month later which showed widespread subtle patchy fibrosis but nothing to explain the TTE findings. Her NT pro-BNP continued to remain elevated 6 months after the initial presentation (4,528 ng/L) although her symptoms remained under control. Her heart failure therapy was optimized with the introduction of once daily spironolactone and an increased dose of bisoprolol and ramipril. She was able to continue the trabectedin, and her disease remained stable.

## Discussion

Adverse cardiac events were rare during trabectedin development with an incidence between 0.2% and 3.3% across a range of STS subtypes (Table 2) [5]. The incidence continued to remain low from 2010 to 2020 at 3.4% [6]. Most of the earlier cases were arrhythmias with a recent increase in the number of heart failure presentations [1, 4]. Post-marketing surveillance using the World Health Organization VigiBase revealed that there were significantly more events than expected up to August 2020 (Table 2) [6]. Case reports and series have shown wide variation in the clinical presentation from myocardial infarcts to exacerbations of heart failure with preserved ejection fraction (Table 2) [6, 7].

Our series differs from previously published cases due to the insidious onset of breathlessness with repeated cycles of trabectedin, combined with a reduced LVEF. Only one other case had documented symptomatic improvement after stopping trabectedin [6], and here, we report an improvement in LVEF in 1 patient who stopped trabectedin and another who continued. Like previous reports, we found that the clinical picture is heterogeneous but the reason for this is unclear. In case 3, there was no obvious AF trigger; however, these patients are predisposed due to systemic disease, underlying inflammation, and increased risk of electrolyte abnormalities. In the case series by Doherty et al. [7], the 2 patients who developed AF had a clear arrhythmogenic trigger with masses abutting the pericardium.

In practice, most patients receiving trabectedin have had anthracyclines which may increase susceptibility to cardiotoxicity. A pooled analysis of phase I trials comparing trabectedin given alongside doxorubicin or PLD showed that a decrease in LVEF only occurred in the doxorubicin group and LVEF recovery occurred when doxorubicin, not trabectedin, was stopped [5]. A separate phase III trial comparing trabectedin and PLD to PLD alone showed a significantly higher incidence of heart failure in the combined trabectedin-PLD arm [10]. Both studies hint toward a synergistic cardiotoxic adverse effect of trabectedin and doxorubicin combined. In addition to doxorubicin, case 2 was treated with the tyrosine kinase inhibitor pazopanib for 4 years prior to trabectedin. Pazopanib has been independently associated with cardiotoxicity, in particular LV systolic dysfunction [11]. It is unclear how much of an effect anthracyclines, with or without tyrosine kinase inhibitors, have in “priming” a susceptible individual to develop cardiotoxicity prior to trabectedin use.

STS encompasses over 70 histological subtypes with heterogenous mutational profiles. Chemotherapy is used for locally advanced or metastatic disease, but it can be difficult to predict treatment response with some sarcomas lacking a strong evidence base for certain treatments. This is exemplified by uterine leiomyosarcoma where there is no clear benefit of

**Table 2.** Summary of the clinical evidence for adverse cardiovascular outcomes with trabectedin use

Level of evidence	Trabectedin cardiovascular complications
Case reports and case series	<ul style="list-style-type: none"> <li>• Doherty et al. [7]               <ul style="list-style-type: none"> <li>○ AF and fast ventricular rates in 2 patients who also had masses abutting the pericardium</li> <li>○ Myocardial infarction in 2 patients with one suffering an out of hospital cardiac arrest</li> <li>○ Acute pulmonary edema in 2 patients with impaired left ventricular systolic function</li> </ul> </li> <li>• Catherine et al. [6]               <ul style="list-style-type: none"> <li>○ Acute pulmonary edema with a preserved LVEF</li> </ul> </li> </ul>
Phase I to III preclinical trials	<ul style="list-style-type: none"> <li>• Cardiac safety review to 2011 [5]               <ul style="list-style-type: none"> <li>○ Cardiac adverse event incidence rate of 0.2–3.3% although several patients in the study arms developed dyspnea of unknown cause</li> </ul> </li> <li>• Cardiac safety review outcomes from 2010 to 2020 [6]               <ul style="list-style-type: none"> <li>○ Cardiac adverse event incidence rate remained low at 3.4%</li> <li>○ Five cases of QT interval prolongation</li> <li>○ Eleven cases of heart failure (although seven of these did not have their LVEF published)</li> <li>○ Eleven cases of arrhythmias (only one case deemed significant based on CTCAE)</li> <li>○ Five cases of corrected QT prolongation</li> <li>○ One case of myocardial infarction</li> </ul> </li> </ul>
Post-marketing surveillance	<ul style="list-style-type: none"> <li>• World Health Organization VigiBase system [6]               <ul style="list-style-type: none"> <li>○ 38 adverse cardiac events up to August 2020 which was 32 more than predicted over the same time period</li> </ul> </li> </ul>
CTCAE, common terminology criteria for adverse events.	

adjuvant chemotherapy on outcomes including distant recurrence rates and overall survival despite its widespread use in this setting [12].

Recent work analyzing the molecular profile of samples from sarcoma primary tumors and metastasis has highlighted pathogenic mutations in several genes which may act as predictive genetic biomarkers, thus allowing specific treatments to be tailored to different mutations [13, 14]. For example, we may be reluctant to use trabectedin in a patient with mutations in DNA damage repair genes [13]. Pre-treatment molecular profiling may facilitate more judicious selection of patients for certain treatments, thus minimizing the likelihood of exposing them to potentially cardiotoxic agents like trabectedin and pazopanib if there was no expected benefit. This is important for treatment-refractory STS patients due to their poor prognosis and need to focus on optimizing their quality of life.

There is no clear role for troponin or NT-pro-BNP measurements either before or during trabectedin. Most work looking at biomarkers in cancer treatment has focused on anthracyclines where both an early troponin I release post-treatment and persistent elevation after 1 month were associated with an increased incidence of major adverse cardiac events [15]. NT-pro-BNP measurements provide a better representation of chronic changes in cardiac wall stress, and in our series, this seemed to be a more sensitive marker of cardiotoxicity with an improvement in NT-pro-BNP mirroring an improvement in symptoms and LVEF.

The European Medicine Agency (EMA) recommends that a formal assessment of LVEF should be made prior to treatment and trabectedin should be withheld if there is either a decline in LVEF  $\geq 15\%$  or if the decline is  $\geq 5\%$  in the presence of pre-existing impaired LV systolic function [16]. It is not clear how often this recommendation is followed in practice and it was not done in our cases. The EMA does not state a time interval for repeat scanning; this would be difficult to recommend given the variation in the timing of clinical presentation. We do not currently have any way of predicting which patients will develop cardiotoxicity, and it is not clear if a normal pre-treatment TTE has any prognostic relevance.

There are no specific treatments for trabectedin cardiotoxicity. In our series, we gave all patients beta-blockers and renin-angiotensin-aldosterone system blockers and withdrew trabectedin in 3 cases. It is not clear which of these actions had the biggest effect on outcomes. Studies in anthracycline cardiotoxicity have shown that enalapril and carvedilol both help preserve [17] LVEF and restore [18] function if it has declined, although it is difficult to directly stratify this effect to trabectedin as the cardiotoxic mechanisms are likely to be different [16].

All of the patients included in this case series were discussed at the regional cardio-oncology MDT. This was paramount to the decision-making in a field where there is limited guiding evidence. The decision to stop trabectedin was made on a case-by-case basis in conjunction with the patient. Although all patients had a severely impaired LVEF, the balance of cardiac- or sarcoma-related symptoms was the most significant factor supporting a decision to either stop or continue trabectedin.

## Conclusions

Trabectedin cardiotoxicity is a rare, life-threatening complication that has a heterogeneous presentation. Our case series contributes to the previous literature describing this association and calls on clinicians to think about this as a cause of clinical deterioration in this patient cohort. All patients should have a pre-treatment 12-lead ECG and TTE to provide a baseline. Given both the low numbers treated and low incidence, it is difficult to design prospective trials focused on screening for cardiotoxicity, pre-treatment of patients at risk, and treatment of those suffering cardiac side effects. Future work should focus on the underlying mechanism of cardiotoxicity, the utility of treatment stratification based on STS



mutational profile, and the role of other agents (in particular anthracyclines and pazopanib) in priming a patient to be susceptible to trabectedin complications.

## Statement of Ethics

This is a case series, and the retrospective review of patient data did not require ethical approval in accordance with local guidelines. Written informed consent was obtained from cases 2, 3, and 4 for the publication of details of their medical cases and any accompanying images. Written informed consent was obtained from the next of kin for case number 1 for publication of details of their medical case and any accompanying images on their behalf, because case 1 had died at the time of writing the case series. The completed consent forms are available to the editor if requested.

## Conflict of Interest Statement

David G. Gent, Nasim Ali, Anna Olsson-Brown, and Rebecca Dobson have no conflicts of interest to declare. Professor Gregory Y.H. Lip has received consultancy and speaker fees from Bayer, Bayer/Janssen, Bristol Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo outside the submitted work. Professor David J. Wright has received consultancy and speaker fees from Boston Scientific and Medtronic outside the submitted work. All other authors have no relationships relevant to the content of this paper to disclose.

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## Author Contributions

David G. Gent collected the information, consented the patients and wrote the manuscript. Nasim Ali, Anna Olsson-Brown and Rebecca Dobson identified the patients. Nasim Ali, Anna Olsson-Brown, Gregory Y. H. Lip, David J. Wright and Rebecca Dobson reviewed and edited the manuscript before subscription.

## Data Availability Statement

All relevant data pertaining to individual cases are included within the case series. Further inquiries can be directed to the corresponding author.

## References

- 1 Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. 2009 Sep;27(25):4188–96.

- 2 Larsen AK, Galmarini CM, D’Incalci M. Unique features of trabectedin mechanism of action. *Cancer Chemother Pharmacol*. 2016 Apr;77(4):663–71.
- 3 Buonadonna A, Benson C, Casanova J, Kasper B, López Pousa A, Mazzeo F, et al. A noninterventional, multi-center, prospective phase IV study of trabectedin in patients with advanced soft tissue sarcoma. *Anticancer Drugs*. 2017 Nov;28(10):1157–65.
- 4 Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016 Mar;34(8):786–93.
- 5 Lebedinsky C, Gómez J, Park YC, Nieto A, Soto-Matos A, Parekh T, et al. Trabectedin has a low cardiac risk profile: a comprehensive cardiac safety analysis. *Cancer Chemother Pharmacol*. 2011 Nov;68(5):1223–31.
- 6 Catherine J, Jungels C, Durieux V, Deliens C, Grigoriu B. Trabectedin-related heart failure: case report and a systematic review of the literature. *Front Oncol*. 2021 Nov;11:694620.
- 7 Doherty GJ, Davidson D, Wong HH, Hatcher HM. Cardiotoxicity with trabectedin in the treatment of advanced soft tissue sarcoma. *Anticancer Drugs*. 2019 Jan;30(1):110–5.
- 8 Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol*. 2017 Oct;18(10):1397–410.
- 9 Sanfilippo R, Hayward RL, Musoro J, Benson C, Leahy MG, Brunello A, et al. Updated results of European Organization for Research and Treatment of Cancer (EORTC) phase 2 trial 1202 cabazitaxel in patients with metastatic or inoperable locally advanced dedifferentiated liposarcoma. *J Clin Oncol*. 2021 May;39(15 suppl):11518.
- 10 Poveda A, Vergote I, Tjulandin S, Kong B, Roy M, Chan S, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6–12 months) subpopulation of OVA-301 phase III randomized trial. *Ann Oncol*. 2011 Jan;22(1):39–48.
- 11 Justice CN, Derbala MH, Baich TM, Kempton AN, Guo AS, Ho TH, et al. The impact of pazopanib on the cardiovascular system. *J Cardiovasc Pharmacol Ther*. 2018 Sep;23(5):387–98.
- 12 Rizzo A, Nannini M, Astolfi A, Indio V, de Iaco P, Perrone AM, et al. Impact of chemotherapy in the adjuvant setting of early stage uterine leiomyosarcoma: a systematic review and updated meta-analysis. *Cancers*. 2020 Jul;12(7):1899.
- 13 Moura DS, Peña-Chilet M, Cordero Varela JA, Alvarez-Alegret R, Agra-Pujol C, Izquierdo F, et al. A DNA damage repair gene-associated signature predicts responses of patients with advanced soft-tissue sarcoma to treatment with trabectedin. *Mol Oncol*. 2021 Dec;15(12):3691–705.
- 14 Astolfi A, Nannini M, Indio V, Schipani A, Rizzo A, Perrone AM, et al. Genomic database analysis of uterine leiomyosarcoma mutational profile. *Cancers*. 2020 Aug;12(8):2126.
- 15 Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004 Jun;109(22):2749–54.
- 16 European Medicines Agency. Yondelis: EPAR – product information. 2021.
- 17 Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left ventricular dysfunction with enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of malignant hEmopathies). *J Am Coll Cardiol*. 2013 Jun;61(23):2355–62.
- 18 Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015 Jun;131(22):1981–8.