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Efficacy and cardiac safety of aldoxorubicin in metastatic solitary fibrous tumour

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Abstract

Solitary fibrous tumours (SFT) are very rare mesenchymal neoplasms. While surgery remains a standard treatment for localised disease, effective and long term treatment options for metastatic disease are lacking, making the use of aldoxorubicin a novel and promising systemic treatment in SFTs. We present a 30-year-old male who underwent surgical resection for a solitary fibrous tumour of the right leg. Postoperative imaging revealed metastatic disease in the liver and left upper quadrant. He was initially treated with pazopanib but experienced disease progression after 24 weeks. The patient was then enrolled on a phase III trial evaluating aldoxorubicin for advanced soft tissue sarcomas and received 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously every 21 days, cumulative dose being 9100 mg/m^2. Treatment was well tolerated, with manageable toxicities including alopecia, leukopenia, mucositis, and grade 3 neutropenia requiring G-CSF support. Notably, serial echocardiograms showed no evidence of cardiotoxicity, with a preserved ejection fraction (56–65%). He completed 26 cycles with stable disease, followed by a 7-month treatment break before receiving compassionate-use aldoxorubicin. Disease stability persisted for 6 months until progression, which was treated with radiotherapy. Three months later, systemic progression led to treatment discontinuation. This case illustrates the favourable cardiac safety profile of aldoxorubicin and efficacy in solitary fibrous tumours.

Keywords

aldoxorubicin, anthracycline prodrug, soft tissue sarcomas, solitary fibrous tumours (SFT)

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Background

Solitary fibrous tumours (SFTs) are uncommon tumours of mesenchymal origin, capable of developing in various anatomical sites, with a higher prevalence in adults and with the incidence of one new case/million people/year.[1,2] These tumours display a distinctive histological pattern, characterized by fibroblast-like cells dispersed in a disorganized arrangement within a collagen-rich stroma, accompanied by staghorn-shaped, hyalinized blood vessels and characterised by the NAB2-STAT6 fusion.[3–5] The 2013 WHO classification categorizes SFTs as intermediate-grade neoplasms with a low risk of metastasis, though their clinical progression remains unpredictable.[1] While most cases exhibit a benign course, some cases have the potential to recur or spread, and histological malignancy does not always correlate with aggressive behaviour.[6,7] The G-score, a prognostic model incorporating mitotic count and patient age, has emerged as a highly significant predictor of both early and late recurrence, providing a more reliable tool for identifying patients at risk.[8] For local disease, complete surgical resection with negative margins remains the

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standard treatment approach.[9] In contrast, for metastatic or advanced solitary fibrous tumours, treatment options include radiotherapy and chemotherapy. Some studies suggest that radiotherapy may be effective not only in the metastatic setting but also as a primary treatment for localized disease.[10] However, chemotherapy is more commonly utilised for metastatic SFTs, with pazopanib demonstrating some therapeutic benefit, whereas anthracycline-based regimens have shown limited efficacy.[11,12] Anthracyclines however remain the most effective treatment for many soft tissue sarcomas,[13] despite their clinical utility being limited by dose-dependent cardiotoxicity, restricting the number of treatment cycles and potentially reducing therapeutic efficacy.[14] The limitations of current systemic treatment options for metastatic SFTs remain evident, and there is a clear need for an agent that could offer both long term efficacy and an improved toxicity profile. To overcome these limitations, novel drug delivery strategies, such as pegylation, liposomal formulations, and prodrugs, have been developed to enhance efficacy while minimizing systemic toxicity. Aldoxorubicin, a prodrug of doxorubicin, binds to serum albumin and selectively releases the active drug in the acidic tumour microenvironment, reducing systemic exposure and cardiotoxicity.[15,16] This targeted delivery allows for higher cumulative dosing compared to conventional doxorubicin.[17,18] Extending anthracycline therapy while reducing cardiotoxicity could make these agents a viable treatment option for SFTs.

Case presentation

We report a 30-year-old male who initially presented with a small, painless mass in his right leg, which progressively increased in size over 6 months, prompting medical evaluation. MRI revealed a dumbbell-shaped tumour, and biopsy confirmed the diagnosis of a solitary fibrous tumour. The patient subsequently underwent surgical excision of the lesion. Histopathological analysis of the excised tumour demonstrated a spindle-cell neoplasm with areas of variable cellularity, focal hemangiopericytic features, and necrosis. The mitotic index was up to five mitoses per 10 high-power fields, with mild focal atypia. Immunohistochemistry was positive for STAT6, CD34, and CD99, confirming the diagnosis.

Postoperative staging CT revealed metastatic disease in the liver and left upper quadrant of the abdomen, and biopsy of a hepatic lesion confirmed metastatic solitary fibrous tumour. The patient was subsequently enrolled in the EMPRASS trial evaluating pazopanib in advanced soft tissue sarcomas, including solitary fibrous tumours.[19] However, disease progression was observed after 24 weeks, leading to trial discontinuation.

The patient was subsequently enrolled in a phase III multicentre, randomized, open-label study assessing the efficacy and safety of aldoxorubicin compared to investigator choice of therapy in patients with metastatic, locally advanced, or unresectable soft tissue sarcomas refractory to prior systemic treatment. He was randomized to the aldoxorubicin arm and received treatment at a dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) administered intravenously on day 1 of each 21-days cycle (Figure 1). In total the patient received 26 cycles of aldoxorubicin with a cumulative dose of 9100 mg/ m^2. During treatment, the patient experienced toxicities including alopecia, grade 1 infusion site extravasation, leukopenia, mucositis, and grade 3 neutropenia, the latter resulting in treatment delays and necessitating granulocyte colony-stimulating factor (G-CSF) support. Importantly, no evidence of cardiotoxicity was observed, with serial echocardiograms performed every 2 months demonstrating a preserved left ventricular ejection fraction (56–65%).

The patient received a total of 26 cycles of aldoxorubicin, maintaining stable disease throughout the treatment period as assessed by Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1) (Figure 2). Following a 7-month treatment break, he was granted compassionate access to aldoxorubicin. During this treatment break, the patient underwent radiotherapy, receiving a total dose of 36 Gy to the pelvic region for the management of oligo-progression. After 6 months of resumed aldoxorubicin therapy, imaging revealed solitary progression of hepatic lesion, which was subsequently treated with chemoembolisation. However, 3 months later, further systemic disease progression was identified on CT imaging, leading to the discontinuation of aldoxorubicin treatment (Table 1).

Discussion

The standard treatment for advanced soft tissue sarcoma (STS) has remained largely unchanged for decades, with anthracyclines as the first-line therapy across various subtypes.[20] However, their clinical utility is restricted by cumulative dose-limiting cardiotoxicity, which limits prolonged use and rechallenge strategies in advanced or metastatic disease.[14] In response to these challenges, novel approaches such as aldoxorubicin have emerged, demonstrating potential in overcoming the dose limitations associated with conventional doxorubicin.[21–23]

Aldoxorubicin is designed to deliver doxorubicin selectively to tumour tissue through its albumin-binding mechanism, allowing for higher cumulative dosing while minimizing systemic toxicity, particularly cardiac toxicity and in that way potentially increasing efficacy. Clinical studies have reported that aldoxorubicin can be safely administered at cumulative doses exceeding 2 g/m^2 without evidence of clinically significant cardiotoxicity.[24] This extended dosing potential allows for continued treatment as long as there is clinical benefit in terms of tumour response and disease stabilisation.

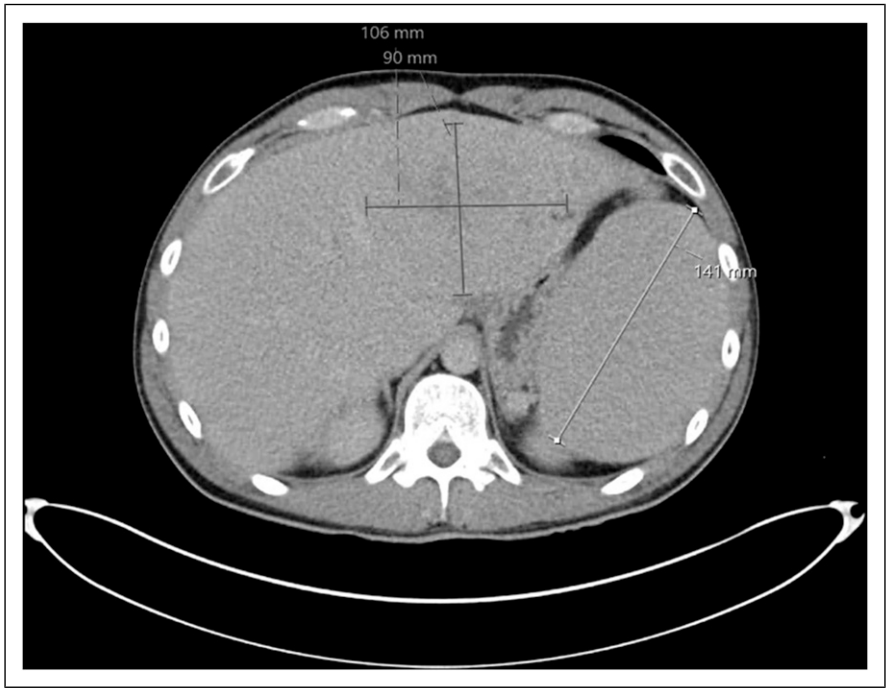

Figure 1. Contrast-enhanced computed tomography (CT) scan demonstrating the extent of disease involvement in the liver and upper abdomen prior to initiation of treatment with aldoxorubicin, October 2015.

Previous phase I-II trials have demonstrated the efficacy of aldoxorubicin in both first-line and later-line treatment across various malignancies, including advanced soft tissue sarcomas, with the most frequently reported adverse events including myelosuppression, nausea, fatigue, alopecia, stomatitis, and vomiting.[21,23,25] These trials not only demonstrated the efficacy of aldoxorubicin but also emphasised its favourable tolerability profile. A phase III trial

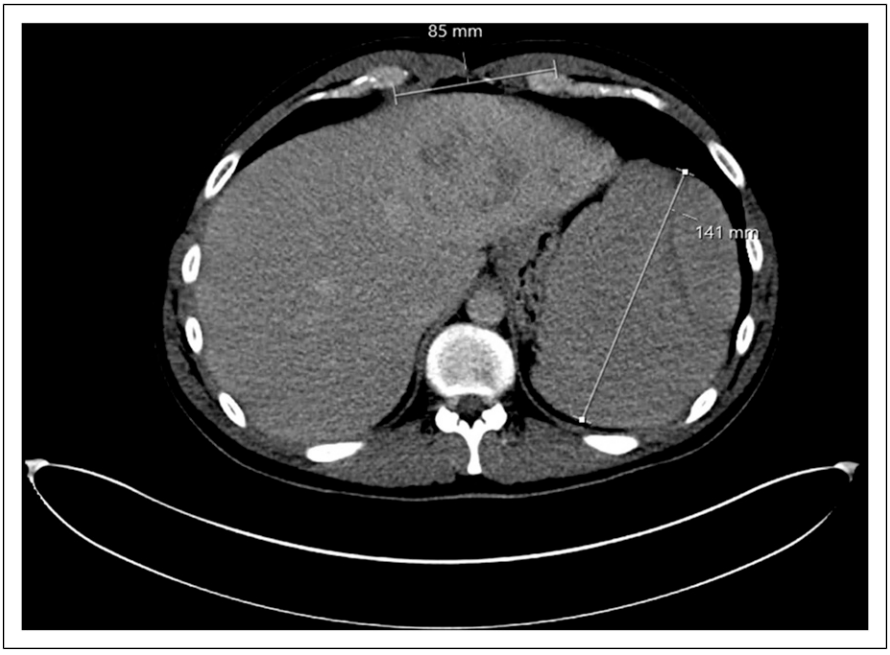

Figure 2. Contrast-enhanced computed tomography (CT) scan illustrating the best observed response to treatment in the liver and upper abdomen, obtained 14 months after initiation of aldoxorubicin therapy, February 2017.

Table 1. Timetable reflecting key events.

Timeline	Event (diagnostics/imaging/treatment)	Outcome	Complications/ toxicities
March 2014	First noticed a small lump in the right upper leg		
September 2014	Lump increasing in size	Patient sought medical advice for the first time	
28 October 2014	MRI shows a dumbbell shaped tumour in the right leg	Biopsy confirms solitary fibrous tumour	
November 2014	Surgical excision of tumour	Tumour size 190 × 110 × 65 mm, adequacy of margins - marginal	Post-operative CT reveals multiple liver lesions and a left upper quadrant lesion
January 2015	Biopsy of one of the liver lesions	Consistent with metastatic solitary fibrous tumour	
February 2015 - September 2015	Pazopanib on the EMPRASS trial	CT confirms progressing disease as per RECIST 1.1 in August 2015	Toxicities related to treatment: Diarrhoea, fatigue, hypoglycaemia episodes requiring hospital admission
November 2015 – April 2017	Commenced treatment in the phase III aldoxorubicin trial - in total received 26 cycles of aldoxorubicin with cumulative dose being 9100 mg/ m^2	Disease remained stable throughout as per RECIST 1.1	Toxicities related to treatment: alopecia, grade 1 infusion site extravasation, leukopenia, mucositis, and grade 3 neutropenia
September 2017	Completed 36 Gy in 12 fractions to left pelvic oligometastatic disease		Toxicities: mild diarrhoea
November 2017 – October 2018	Aldoxorubicin under compassionate use in the USA	CT in August 2018 confirms disease progression	June 2018 – chemoembolization for oligoprogressive liver lesion

comparing aldoxorubicin to the investigator choice of treatment for relapsed or refractory STS found that aldoxorubicin was an active and well-tolerated therapeutic option. Notably, it demonstrated superior efficacy over standard treatments in patients with L-sarcomas, including liposarcomas and leiomyosarcomas.[26] However, the all-comer design of the phase III trial included a heterogeneous population of STS subtypes, potentially diluting treatment effects. Additionally, the use of an investigator's choice control arm, which permitted a range of standard therapies with varying mechanisms of action and efficacy, introduces significant variability that complicates direct comparisons with aldoxorubicin. Furthermore, differences in patient populations between this phase III trial and prior phase II trials further confound efficacy assessment. Unlike the phase II trial, which primarily enrolled treatment-naïve patients, the phase III trial included individuals who had relapsed or had treatment-refractory disease, potentially altering the therapeutic impact of the drug.[21,22]

This case highlights the potential role of aldoxorubicin as a long-term treatment option for metastatic SFT, achieving sustained disease stability over an extended period. Importantly, aldoxorubicin demonstrated a favourable safety profile from a cardiac perspective, with no evidence of cardiotoxicity despite prolonged exposure, and its adverse effects remained manageable with supportive care. These findings suggest that aldoxorubicin may offer a viable therapeutic alternative for SFTs, particularly in cases where prolonged treatment duration is necessary to maintain disease control.

Although aldoxorubicin has demonstrated efficacy in metastatic soft tissue sarcomas, its role in the treatment of solitary fibrous tumours remains largely unexplored.[21,22,26] Given the rarity of SFT and the limited availability of clinical data, further investigation is warranted to establish the efficacy and safety of aldoxorubicin in this subset of patients.

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