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Safety and efficacy of pazopanib as a second-line treatment and beyond for soft tissue sarcomas: A real-life tertiary-center experience in the MENA region

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ABSTRACT

Introduction: Sarcomas are uncommon malignancies. No advances have been recently achieved despite multiple efforts. Pazopanib is a safe and effective tyrosine kinase inhibitor used in managing soft tissue sarcomas (STS) after chemotherapy failure. However, its use is limited in developing countries and no efficacy data exist from our region. We aimed to study the efficacy of pazopanib in our population, characterized by response rates of patients with chemotherapy-refractory advanced STS receiving pazopanib. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and toxicity profile.

Materials and Methods: 15 patients (age ≥ 18 year) diagnosed with advanced STS, refractory to first-line chemotherapy, receiving pazopanib as ≥ second-line therapy in one tertiary center in Lebanon were included between January 1st, 2014 and October 31st, 2018. Patient and disease characteristics, disease evaluation, as well as tolerance to treatment, were extracted from charts retrospectively. Statistical analysis was done using SPSS version 24.

Results: The mean age was 48.6 [19–66] years. Eleven patients (73.3%) received pazopanib in second-line, whereas four patients (26.7%) received it in third-line. Thirteen patients (86.7%) progressed, and two patients (13.3%) had stable disease. The median PFS was three months [1–19] and the mean OS was 25.4 months [17.2–33.6]. Five patients required dose-reductions due to poor tolerance.

Conclusion: Conclusions cannot be drawn due to small patient numbers. However, given the 3-month PFS, 13% of patients maintaining stable disease, and tolerable safety profile, it is reasonable to incorporate pazopanib in STS treatment. More focused studies with larger patient populations need to be done in Lebanon.

Introduction

Sarcomas are a group of rare mesenchymal tumors that arise at ubiquitous sites of connective tissue throughout the body. They are virtually dichotomized into two large groups: soft tissue sarcomas (STS) and bone sarcomas. Although STS account for only 0.7–1% of all adult malignant tumors, the World Health Organization (WHO) has described

more than 100 histological STS subtypes with distinct clinical, prognostic and therapeutic features. STS subtypes include fibrosarcomas, gastrointestinal stromal tumors (GIST), leiomyosarcomas, liposarcomas, rhabdomyosarcomas and others [1,2]. This heterogeneity poses significant diagnostic and therapeutic challenges, which render it very difficult to establish efficient national data-based registries as well as effective unified treatment strategies in countries around the globe,

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especially in small countries with restricted financial capacities such as Lebanon.

STS subtypes can vary significantly from slow-growing to more aggressive metastatic forms of disease depending on histopathology, size, and grade of the tumor [3]. Gender does not seem to impact incidence in all age groups; but age plays a role with incidence of STS peaking between 45 and 90 years [4]. This wide heterogeneity and difference in clinical course of variants have emphasized the importance of multidisciplinary approach in the diagnosis and management of STS. Typically, local tumors are treated with surgical resection, with chemotherapy and radiotherapy addition being dependent on risk stratification and the possibility of local and distant recurrence [3]. In patients with metastatic or advanced STS, cytotoxic chemotherapy remains the first line of treatment [3]. Despite optimal available treatment, the overall survival of patients with advanced STS remains low at 12 months [5-7]. Unfortunately, further lines of systemic therapy for advanced STS are scarce, and little progress has been made.

Researchers have strived to find alternative treatment options, investigating the pathophysiology of disease at the molecular and cellular levels. Next generation sequencing has become trending in attempts to improve diagnosis accuracy [8], and find targetable mutations [9]. With the exception of rare driver genetic alterations whose antagonists have shown to amount a response in different tumor types such as NTRK, there is no solid evidence to support the use of these genetically-targeted investigational therapeutic options [10,11]. Some enthusiasm was achieved with Olaratumab, which is a human antiplatelet-derived growth factor receptor α monoclonal antibody that achieved a highly significant improvement of 11.8 months in median OS in combination with doxorubicin in a phase II JGDG trial [12]; however, the final phase III ANNOUNCE trial were disappointing [13]. On the other hand, when targeting dysfunctional angiogenesis, which is a common feature of sarcomas, it has proven to show some promising results [14,15]. High expression of vascular endothelial growth factor (VEGF) as well as platelet-derived growth factor (PDGF) has been shown to be involved in amplified angiogenesis and to be correlated with higher tumor grade as well as worsened survival outcomes in sarcomas [16,17]. Anti-angiogenic drugs from monoclonal antibodies such as bevacizumab used in monotherapy and/or in combination with other systemic treatments, and multiple tyrosine kinase inhibitors such as sunitinib, cediranib, sorafenib, regorafenib and pazopanib, were studied as possible treatment options in STS [15].

Pazopanib is a multi-kinase inhibitor that acts as an oral angiogenesis inhibitor targeting VEGF, PDGF, and c-kit receptors among others. It works by binding to these receptors, then crossing the cell membrane to interact with the intracellular domain of the tyrosine kinase receptor and later on to compete with adenosine triphosphate (ATP), where it inhibits downstream signaling pathways involved in tumor angiogenesis, growth and metastasis [18]. The FDA approved Pazopanib in 2012 for use in soft tissue sarcomas (STS). A few international studies such as SPIRE [19], EORTC Study 62,043 [20] and PALLETE [21] have demonstrated the efficacy of Pazopanib administered as second-line following chemotherapy failure in STS; yet, no data exist concerning its effectiveness in developing countries such as Lebanon. In the SPIRE study [19], 211 patients received pazopanib as second-line and beyond therapy, with a median duration of treatment reaching 3.1 months. The median PFS was 3 months and the median OS was 11.1 months. The clinical benefit rate was 46%, and it was seen across most histological subtypes. By the end of the study, 40% of patients were alive, 18% of whom remained on pazopanib. 13% of patients discontinued pazopanib due to adverse events (AEs). On the other hand, in the PALLETTE trial, 246 patients were assigned to receive pazopanib and 123 patients were allocated placebo. The median PFS was 4.6 months (95% CI 3.7–4.8) for the pazopanib group compared with 1.6 months (0.9–1.8) for placebo (hazard ratio [HR] 0.31, 95% CI 0.24–0.40; $p < 0.0001$). The median OS was 12.5 months (10.6–14.8) with pazopanib versus 10.7 months (8.7–12.8) with placebo (HR 0.86, 0.67–1.11; $p = 0.25$). Furthermore,

the most common AE experienced was fatigue (65%), and no major dose reductions were performed [21].

In light of the proven clinical benefit of pazopanib as well as the clear lack of studies to assess its role in our region, we decided to retrospectively assess the outcomes of patients with advanced or metastatic STS receiving pazopanib as second-line or beyond therapy in Lebanon. Our primary endpoint included the efficacy of pazopanib, represented by the clinical response rate of our patients, whereas our secondary endpoints included the progression-free survival (PFS), overall survival (OS) and safety profile of pazopanib in our patient population.

Materials and methods

This is an institutional retrospective chart review analysis. Inclusion criteria included: age of 18 years or older, a diagnosis of advanced soft tissue sarcoma with central review of pathology, imaging re-read by sarcoma specialists at our tertiary center, documented failure of prior chemotherapy, and treatment with pazopanib as a second- or further-line therapy within guideline indications. Chemotherapy failure was identified as disease progression on imaging after at least one line of chemotherapy. Progression-free survival was defined as the time interval from the start of pazopanib till progression or death. Overall survival was defined as the time interval from the start of pazopanib till death or loss of follow-up. Data was collected from the American University of Beirut Medical Center both electronic and paper-based clinic charts. Ethical approval of the Institutional Review Board (IRB) of the American University of Beirut in-line with the Common Rule, was obtained according to local and national regulations. Descriptive summary statistics of patient, tumor and treatment characteristics, as well as overall response to treatment were noted. Overall response as well as disease progression were determined clinically and radiologically as per the RECIST 1.1 criteria. Responsive patients included those with clinical or radiologic improvement, or stable disease. Survival curves for PFS and OS were generated using the Kaplan-Meier method. Estimates of means and medians, as well as the corresponding 95% confidence intervals (CI), were reported. All statistics was performed using SPSS, version 24.

Seven hundred patients with STS were identified from January 1st 2014 till October 31st 2018. Out of these 700 patients, 20 were recognized to have received pazopanib as a 2nd- or beyond treatment. Five patients were excluded for use of pazopanib out of indication (3 with liposarcoma [not approved by FDA]; 2 with bone sarcoma). All patients had high-grade tumors, and all received prior chemotherapy in the first-line setting. Chemotherapy protocols used included: gemcitabine/docetaxel, doxorubicin/olaratumab, adriamycin/ifosfamide, doxorubicin/etoposide, gemcitabine single agent, vincristine/doxorubicin/cyclophosphamide, and cyclophosphamide/doxorubicin/cisplatin.

Results

The median duration of follow-up was seven months (95% IC 3–33). The mean age was 48.6 [19–66] years. 53.3% of the patients were males (Table 1). Most patients were of ECOG performance status 0–1. One patient had an ECOG status of 2, and three patients had an ECOG status of 3. The most common primary tumor site was the retro-peritoneum ($n = 9$), followed by the thigh, buttock, and groin regions ($n = 4$), upper extremities ($n = 1$) and torso ($n = 1$). Three patients received radiation therapy in earlier stage settings; 1 with spindle cell sarcoma, and 2 with phyllodes tumors. The most common metastatic site was the lungs ($n = 11$, 73.3%), followed by the abdomen/pelvis ($n = 7$, 46.7%), lymph nodes ($n = 5$, 33.3%) and bones ($n = 3$, 20%). In eleven patients (73.3%), pazopanib was given in second-line, and four patients (26.7%) received it as third-line therapy. Thirteen patients (86.7%) progressed on pazopanib, whereas two patients (13.3%) had stable disease and were considered to have a response to pazopanib (Table 1).

Of the 2 patients with stable disease, one had an undifferentiated/unclassified STS and the other had synovial sarcoma. Different

Table 1
Patient and tumor characteristics.

Characteristics	Patients
Age (years), Mean (Range)	48.6 (19–66)
Sex, n(%)	
Male	8 (53.3)
Female	7 (46.7)
Sarcoma Recurrence, n(%)	
No	12 (80.0)
Yes	3 (20.0)
Tumor Size (cm), n(%)	
1–4.2	1 (6.7)
4.2–10	10 (66.7)
10–20	2 (13.3)
20 or more	2 (13.3)
Tumor Location, n (%)	
Thigh, Buttock, and Groin	4 (26.7)
Upper Extremity	1 (6.7)
Torso	1 (6.7)
Retroperitoneum	9 (60.0)
Surgery, n (%)	
No	4 (26.7)
Yes	11 (73.3)
Radiotherapy	
No	12 (80.0)
Yes	3 (20.0)
2nd or 3rd line indication of Pazopanib, n (%)	
2nd	11 (73.3)
3rd	4 (26.7)
Disease Status on Last Follow-Up, n (%)	
Progression	13 (86.7)
Stable Disease	2 (13.3)

histologic subtypes are described in Fig. 1.

The median PFS was three months [1–19], and the mean OS was 25.4 months [17.2–33.6] (Figs. 2 and 3). Median OS could not be reached. The median duration of pazopanib use was three months [1–13]. Five patients required dose-reductions of pazopanib, with the main toxicities being poor tolerance and a general feeling of malaise and fatigue, followed by decreased appetite (Table 2). Neither hepatic toxicities nor cardiac toxicities were noted. No thrombotic events were described. Four (26.7%) deaths were reported on the last follow-up date (31.12.2018). Two deaths were reported, with the primary cause being respiratory distress, two others were due to cardiac arrest and all were attributed to disease progression by investigators.

Discussion

Soft tissue sarcomas constitute a large family of rare and very heterogeneous tumors. Almost 50% of patients develop metastases. With appropriate treatment, the median survival in advanced cases of STS ranges from 12 to 20 months [3,6,7]. The development of new life-prolonging systemic therapies for STS has evolved slowly in the past

few decades [22]. The treatment of advanced STS should be tailored to each patient. The first-line treatment to be used usually consists of systemic cytotoxic chemotherapy, mainly an anthracycline and an alkylating agent [23,24]. Different subtypes respond differently to treatment. For example, it was shown that patients with rhabdomyosarcoma, myxofibrosarcoma, myxoid/round cell liposarcoma, synovial sarcoma, angiosarcoma and leiomyosarcoma respond better to chemotherapy, while alveolar soft part sarcoma (ASPS), clear cell sarcoma and GIST are more resistant to standard chemotherapy [4,6]. However, due to the scarcity of the disease, clinical studies usually group the STS and recruit patients with different histological subtypes. In these patients, several lines of treatment are typically exhausted early on. The main drawback to using multiple lines of chemotherapy, particularly with dose-intense combination regimens sometimes needed for a rapid response [25], is their toxicity in patients already fatigued with treatment burden. Despite several therapeutic advances, the prognosis of patients with advanced STS remains poor. Therefore, there is notably a high unmet need for more effective treatment options in STS.

Overexpression of vascular endothelial growth factor receptors (VEGFRs) has been widely observed in STS. Angiogenic growth factor up-regulation in tumors plays a significant role in disease pathogenesis [26]. Increased expression of tumor VEGFR, PDGFR, and other downstream components in sarcomas has frequently been associated with worse clinical outcomes, increased metastatic potential, resistance to chemotherapy, and higher histologic grade. It was found that the plasma levels of VEGF and basic FGF were 10–13 fold higher in sarcoma patients compared with controls [27].

Apart from GIST, several subtypes of sarcomas have demonstrated promising responses to antiangiogenic therapies [28] such as bevacizumab, cediranib, sorafenib [29, 30], sunitinib [31, 32], and regorafenib [33], though specific targets and mechanisms remain to be elucidated.

Pazopanib, an anti-angiogenic multi-targeted small-molecule tyrosine kinase inhibitor [34], was approved in 2012 for the treatment of patients with advanced STS who failed previous chemotherapy regimens, based on improved PFS when compared to placebo [21]. It has demonstrated efficacy across a wide range of STS tumor subtypes following chemotherapy failure. However, no OS benefit was noted. Multiple questions arise regarding pazopanib prescription: the most appropriate setting to use it, best timing, subtypes, patient population and adverse events with effect on quality of life. Evidence has shown that pazopanib is not only effective as a third-line agent, but also has good results in the second-line setting in certain STS histologic subtypes and in patients who are intolerant of chemotherapy. Some patients can have a modest benefit, while others can experience long term benefits [35].

Although the use of pazopanib in the first-line setting is not recommended, it is being studied in the elderly [36], along with its possible use as adjuvant or neoadjuvant therapy for resectable advanced STS, or its use in combination with other systemic therapies or complementary agents such as PI3K/mTOR agents that might enhance its modest activity [37–39]. Enthusiasm for combination therapy with doxorubicin, on the other hand, has been tempered by the adverse events seen with the bevacizumab/doxorubicin combination [40]. In one Phase I study, pazopanib was given in combination with gemcitabine and docetaxel, but major toxicity was reported [41]. Furthermore, pazopanib monotherapy is not devoid of adverse events, which may include fatigue, nausea, anorexia, weight loss, and dysgeusia. Venous thromboembolic events, pneumothorax, hepatotoxicity and cardiotoxicity have also been observed with pazopanib use [21,42]. Pazopanib offers a targeted therapy option that has demonstrated clinical benefit in most types of advanced STS, with a relatively favorable safety profile. We have tried to assess the use of pazopanib in advanced STS in our population. The Middle East and North Africa region is known to have high incidence of consanguinity and in-breeding [43], which may increase the possibility of emergence of homogeneous forms of disease with specific genetic

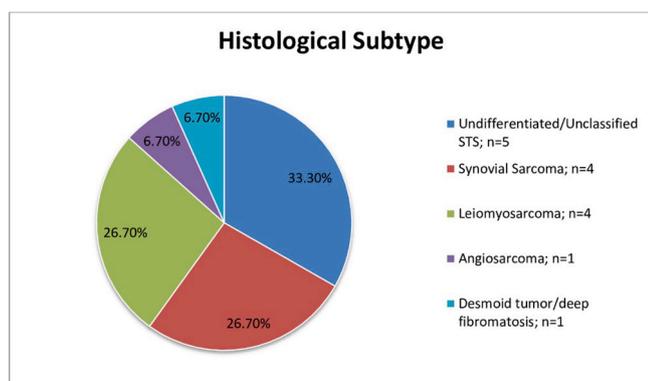


Fig. 1. The Histological Subtypes observed in the study.

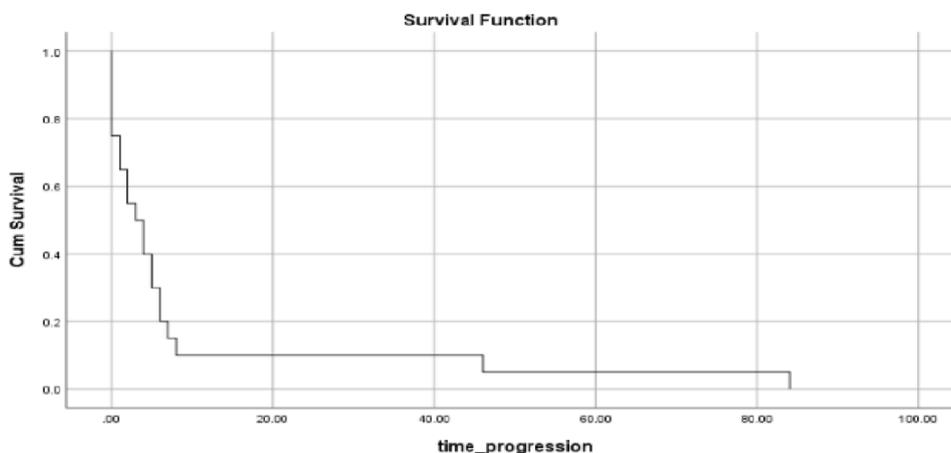


Fig. 2. Kaplan-Meier curve of Progression Free Survival.

patterns that may have similar responses to certain drugs [44]. Furthermore, the region is known for its prevalent low-middle income status as well as relative deficiency in infra-structure. If we are able to shift more patients on oral medications while delaying disease progression and providing acceptable quality of life, we may be able to spare some patients, patient families as well as health-care systems from excessive costs of lengthy hospitalizations related to chemotherapy, chemotherapy complications, as well as palliative care needs. Unfortunately, we noted a limited use of pazopanib in our population, as out of 700 patients recognized with advanced STS, we were only able to recruit 15 patients who have received pazopanib after chemotherapy failure, from the American University of Beirut Medical center, which is considered to be one of the largest referral tertiary care centers in Lebanon and the region. It is probably indicative of the lack of exposure and/or knowledge of Lebanese physicians to this relatively safe therapeutic option. When comparing the characteristics of our patients with those in international studies, our patients were rather younger, with the oldest being 66 years of age, while usually 40% of the STS population is comprised of elderly patients more than or equal 65 years of age [45]. No special risk criteria were identified in our patient population, and no significant family histories were noted. Furthermore, sarcoma subtypes in our study were relatively similar to the SPIRE and PALETTE trials with the majority having LMS (33% in our trial versus 40% in SPIRE versus 44% in PALETTE), followed by synovial sarcomas (27.6%, 11%, and 10% respectively), and undifferentiated subtypes. Thirteen out of fifteen patients (87%) were metastatic in our study, almost in line with SPIRE and PALETTE trials where all patients were metastatic. Most common metastatic site was the lung (seen in 9 patients equivalent to 60% of cases), followed by the abdomen (46%), with no specific

involvement of the liver that has been found in 30% of the PALETTE population and linked with poor prognosis. Moreover, 73% of our population received pazopanib in 2nd line in comparison to only 28% in SPIRE trial and 45% in the PALETTE trial, which could have been responsible for some response advantage that had not really been seen in our population.

Although the number of patients in our trial was small, our median PFS reached 3 months, a number comparable to that in the SPIRE Trial [19], as well as the PALETTE trial [21] where median PFS was 3 months and 4.6 months respectively. The median OS in our study was not reached as only 4 out of 15 patients passed away. The mean OS was 25.4 months, which is a number relatively higher than in previous studies. This could be explained by a selection bias, as patients may have had less aggressive and probably more slowly progressing or more treatment responsive tumors, especially given the absence of high-risk criteria, absence of liver metastases, and less heavily pre-treated status of patients. Treatment responsive patients merely had stable disease. Given that most of our patients were younger than 65 and most were receiving pazopanib in 2nd line setting, it was difficult to compare outcomes, considering that a post-hoc sub-group analysis of PALETTE has shown better survival in patients receiving pazopanib as second-line rather than beyond therapy. However, there was no difference between different age groups [46].

Pazopanib was relatively well tolerated, though it is noteworthy that 26.7% of our population had a poor performance status of 2–3. The duration of treatment was 3 months, similarly to that of the PALETTE trial with a reported number of 16.4 weeks. Only 33% of patients were subject to dose reduction, and there were no reported instances of drug discontinuation. No grade 3–4 adverse events took place. Although the

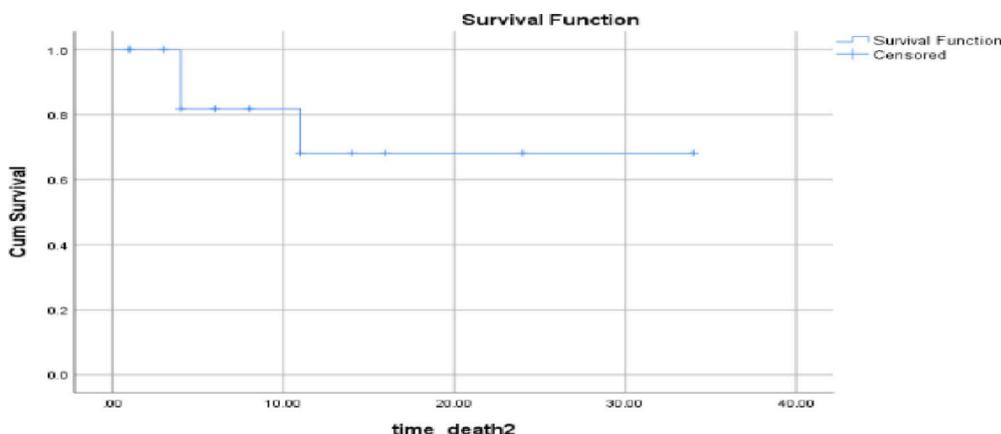


Fig. 3. Kaplan-Meier Curve of Overall Survival.

Table 2
Adverse events encountered by patients.

Adverse Event Encountered	Number of patients
Malaise and fatigue	4
Deceased Appetite	2

documentation of AE was relatively poor, AEs included generalized malaise and fatigue. This was also seen in PALETTE trial where fatigue was manifested in 65% of cases, and decreased appetite was frequently reported, both of which were considered as intolerance to therapy. Unfortunately, the numbers were too small, rendering it very difficult to compare whether or not dose reduction had any impact on response or time to progression.

Given the role of angiogenesis in the pathogenesis of STS, and the proven but modest effect that the anti-angiogenic pazopanib has on STS, this drug seems like a reasonable therapeutic option, especially in an over-treated population with failure of chemotherapy. Whether the potential benefits of pazopanib outweigh the financial costs to either health systems or societies is yet to be determined, and can only be addressed through considering ethics, resources and competing societal needs in a more extensive prospective study in our region.

Limitations

Our study had multiple limitations, including its retrospective chart-review nature, the extremely small number of patients with very heterogeneous tumors, and the absence of a comparator arm.

Conclusion

Sarcomas being rare and heterogeneous, have limited treatment options in the metastatic setting. Pazopanib, an approved multi-targeted tyrosine kinase inhibitor, has generated excitement with a significant impact on PFS for soft tissue sarcoma patients. It has been shown to improve PFS but not OS, with a broad spectrum of action. Nevertheless, it is not devoid of adverse events. Our small retrospective study attempted to evaluate the clinical benefit pazopanib plays in our Middle Eastern population of patients with advanced STS after chemotherapy failure. Despite the small sample size, we had a relatively similar PFS as prior international studies, with 13% of patients maintaining stable disease at data analysis cut-off, and a very tolerable safety profile. This may be indicative of the fact that pazopanib can be offered as an alternative option in later lines of treatment of STS, and needs to be more incorporated in treatment protocols after chemotherapy failure in the region. We are still waiting for further prospective studies using pazopanib in STS. More focused studies within a larger population of patients using pazopanib alone or in combination, need to be done, especially in our region which suffers from exhausted health-care systems, and can benefit from deferring hospital admissions for further chemotherapy and chemotherapy complications, by prescribing effective oral medications that may improve outcomes as well as quality of life from a palliative point of view. More work is required to adequately address the major unmet need faced by patients with advanced STS.

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Ethical approval

All the procedures performed in this study involving human

participants were in accordance with the ethical standards of the institutional research board (IRB) at the American University of Beirut Medical Center, in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Competing Interest

The authors declare that the funder was not involved in the study design, collection, analysis. There is no conflict of interest to declare.

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