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EORTC Soft Tissue and Bone Sarcoma Group (STBSG) experience with advanced/metastatic epithelioid sarcoma patients treated in prospective trials: clinical profile and response to systemic therapy

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Abstract

Background

Epithelioid sarcoma (ES) is a soft-tissue sarcoma associated with a high rate of local recurrence after wide resection and high incidence of distant metastasis. Little is known about the clinical course and response to systemic treatments in ES patients. We performed a retrospective analysis of clinical data from ES patients to provide a reference for the design of future ES-specific studies.

Patient and methods

Data from patients with ES entered in prospective multi-sarcoma phase II/III trials were pooled: EORTC trial 62012 (doxorubicin vs. doxorubicin/ifosfamide), 62043 (pazopanib), 62072 (pazopanib vs. placebo) and 62091 (doxorubicin vs. trabectedin). Patients had either a local or centrally confirmed diagnosis of ES, had inoperable/metastatic disease at study entry and were eligible for the according trial. Response was assessed according to RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were calculated from date of entry.

Results

Among 1099 patients with advanced sarcomas, 27 ES patients (2.5%) were eligible for the analysis (17 male, median age at diagnosis was 50 yrs, range 19-72). 18 (66.7%) received chemotherapy as 1st line treatment (5 doxorubicin, 8 doxorubicin/ifosfamide, 2 pazopanib, 3 trabectedin) and 9 (33.3%) received pazopanib as 2nd line or later. The primary tumor was located in the lower extremity (N=8; 29.6%), upper extremity (N=5; 18.5%), retro/intra-abdominal (N=4; 14.8%) and in other locations (N=10; 37.0%). At entry, metastases were mainly found in lung (N=17; 63%), lymph nodes (N=9; 33.3%), bone (N=8; 29.6%) and soft tissue (N=7; 25.9%). Best response for 1st line patients was 4 partial responses (PR, 22.2%), 10 stable disease (SD, 55.6%) and 4 progressive disease (PD, 22.2%). In subsequent lines, pazopanib achieved 1 PR (11.1%), 4 SD (44.4%) and 4 PD (44.4%). All patients but one progressed on treatment. Median PFS and median OS were 3.8 (95% CI: 2.2-4.8) and 10.8 months (95% CI: 8.1-21.3), respectively. 5 patients were still alive at time of the according trial analysis.

Conclusion

With all limitations of such a rare disease and small data set, objective response and survival outcomes are similar in ES than in non-selected sarcoma populations. The clinical testing of systemic treatment for ES remains an unmet medical need and a high priority.

Introduction

First reported by Laskowski in 1961 [1] and further described by Enzinger [2], epithelioid sarcoma (ES) is a very rare disease representing less than 1% of all sarcomas [3]. Due to its particular pathological aspect, this sarcoma was formerly difficult to diagnose because of confusion with a variety of tumors with similar morphology. ES are currently assessed by tissue biopsy and require examination by an experienced pathologist. . An important component of the diagnostic process of this disease is the demonstration of the loss of INI1 expression by immunohistochemistry [4, 5]

ES are classified by two recognized subtypes, the distal type and the less frequent proximal type. Both entities are predominant in young male adults. Distal-type ES has a high tendency to occur in the extremities, especially in the upper limb [6, 7, 8]. Conversely, proximal-type ES most commonly affect trunk or deep tissue sites and tend to have a more aggressive clinical course. Tumor grading of ES is based on the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system and is considered as a relevant prognostic factor [9, 10, 11]. ES has a high rate of loco-regional recurrence after wide resection as well as metastatic spread, with a specific high incidence of synchronous or metachronous distant metastasis [12, 13]. Metastases regularly involve lung and more particularly lymph nodes, representing one of the typical clinical special features of ES [6, 3]. With 5-year survival rates ranging from 55% to 70%, prognosis of ES patients is generally poor but relatively comparable to other soft tissue sarcomas (STS) [14, 15, 12]. Surgical resection with or without radiotherapy is the accepted standard treatment for localized disease [13, 16]. The role of systemic therapies in patients with advanced stage ES is unclear. Only a few retrospective analyses and case reports have assessed the value of systemic treatment [17, 18]. In these studies, the observed median progression-free survival (PFS) ranged from 3 to 9 months and the overall response rate (ORR) varied between 0 to 60% across the diverse drugs and lines. Prospective disease-specific trials with a focus on ES patients are not available.

As part of European Organisation for Research and Treatment of Cancer (EORTC) clinical trial activities, several drugs for treatment of advanced and metastatic sarcoma have been explored over the past decades. EORTC has created a large database compiling clinically relevant information from all trial participants. The aim of the current study was to investigate the outcome of patients with ES treated with systemic agents in historic prospective EORTC trials. These data provide an important reference for the design of future ES-specific clinical trials.

Material and methods

Patient population

This study combined clinical data of patients from the EORTC trials 62012 (NCT00061984), 62043 (NCT00297258), 62072 (NCT00753688) and 62091 (NCT01189253). These trials were performed by EORTC's Soft Tissue and Bone Sarcoma Group (STBSG). The phase II 62012 trial assessed whether results obtained with doxorubicin in advanced, inoperable STS can be improved by adding ifosfamide [19]. The phase II 62043 and phase III 62072 PALETTE trials investigated the activity of the tyrosine kinase inhibitor pazopanib in advanced/metastatic STS after failure of standard chemotherapy [20, 21]. The phase II 62091 TRUSTS trial evaluated whether the cytotoxic compound trabectedin given as first line chemotherapy for advanced/metastatic STS improves the outcome of patients as compared to doxorubicin [22]. We used these study populations as the basis for the current subgroup analysis focusing on patients with ES. Patients received either doxorubicin, doxorubicin/ifosfamide, trabectedin or pazopanib. Trial participants treated with placebo (EORTC 62072) were excluded from this analysis. The diagnosis of ES was based on local pathology or centrally reviewed by reference pathologists of STBSG when possible. The database does not differentiate between distal and proximal types of ES.

Endpoints

The best response was locally assessed per RECIST 1.1 [23]. The objective response rate was defined as the proportion of patients either achieving a PR or CR as best

response to treatment. The duration of objective response was determined from first documentation of CR/PR to RECIST progression.

PFS was calculated from the date of evaluation start to the first documentation of progression or death, whichever occurred first. The date of evaluation start was corresponding to the date of randomization for the 62012, 62072 and 62091 trials and the date of registration for the 62043 trial. Overall survival (OS) was calculated from the date of evaluation start to the date of death. Patients without an event were censored at the time of last follow-up.

Statistical analysis

Survival estimates and corresponding 95% confidence intervals (CI) for PFS and OS were generated using the Kaplan-Meier method. Survival curves were reported overall and according to the line of treatment for advanced disease (first line versus second+ line). All statistical analyses were performed using SAS software version 9.4 (SAS Institute).

Results

Patient and tumor characteristics

A total of 1099 patients with advanced STS were entered in the four prospective clinical trials. This included only 27 patients (2.5%) with ES who were found eligible for the current analysis (10 patients from 62012 trial, 4 from 62043, 7 from 62072 and 6 from 62091), illustrating the orphan character of this STS subtype. The diagnosis was based on local pathology in 9 cases and on central review in 18 cases. Baseline tumor and patient characteristics are summarized in Table 1.

Median age at diagnosis was 50 years (range 19-72 years) and male gender was predominant (63%). The clinical trials selected patients with good performance status; 11 patients (40.7%) had a performance status of 1 according to the World Health Organization (WHO) criteria.

The most common sites of primary tumor were the lower extremities (N=8, 29.6%), upper extremities (N=5, 18.5%) and retro/intra-abdominal locations (N=4, 14.8%). ES

were incidentally found in the chest (N=2, 7.4%), gynecological organs (N=2, 7.4%), breast (N=1, 3.7%), trunk (N=1, 3.7%), head and neck (N=1, 3.7%) or other locations (N=3, 11.1%).

The tumor grade was assessed for 21 patients and described as high for 10 patients (47.6% of known grade), intermediate for 10 (47.6%) and low for 1 (4.8%). Most patients had metastatic disease (N=24, 88.9%) and metastases were seen in lung (N=17, 63%), lymph nodes (N=9, 33.3%), bone (N=8, 29.6%) and soft tissue (N=7, 25.9%). The primary tumor was still *in situ* in 15 patients (55.6%), reflecting the early and aggressive metastatic spread of this disease.

Systemic treatment

As first line of treatment, 5 patients (18.5%) received doxorubicin alone, 8 (29.6%) doxorubicin and ifosfamide, 2 (7.4%) pazopanib and 3 (11.1%) trabectedin. Nine (33.3%) were treated with pazopanib as second or later line (2nd line: 4 patients; 3rd line: 4 patients; 4th line: 1 patient). Five patients (18.5%) had received previous systemic adjuvant therapy and nine (33.3%) had previous systemic therapy for palliation of advanced disease.

The median duration of the administered treatment in the EORTC trials was 13.3 weeks and more specifically 14.3 weeks for doxorubicin alone, 12.4 weeks for doxorubicin and ifosfamide, 17.3 weeks for pazopanib and 10.7 weeks for trabectedin. The median follow-up was 45.3 months, regardless of the study and one patient was still on trabectedin at the time of the corresponding trial's final analysis.

Response to treatment and survival

As shown in Table 2, the best response for first line treatment patients was 4 PR (22.2%), 10 stable disease (SD, 55.6%) and 4 progressive disease (PD, 22.2%). There were one PR (11.1%), 4 SD (44.4%) and 4 PD (44.4%) among patients treated in second line or later. Overall, 5 patients (18.5%) experienced an objective response. For responders, the median duration of response and time to onset of response from treatment/evaluation start were 56 and 86 days, respectively. The partial responder in 2nd line treatment had the shortest response duration which lasted 28 days.

All patients but one progressed. No patient died without having experienced PD. Overall median PFS was 3.8 months (95% CI: 2.2-4.8). Median PFS was 4 months (95% CI; 2.7-7.5) and 2.7 months (95% CI; 0.8-4.5) for 1st line treatment and 2nd line or later, respectively (Table 3).

Overall median OS was 10.8 months (95% CI: 8.1-2.3). Five patients were still alive or without reported death at the time of the analyses cut-offs. A total of 13 patients died because of PD. The Kaplan-Meier curves overall and stratified by the line of treatment are shown in Figure 1 and Figure 2.

Discussion

Aiming to document the outcome and response of advanced/metastatic ES patients to systemic therapy, this retrospective study has the advantage of combining high-quality data from various prospective clinical trials, providing a detailed and continued follow-up of the patients. ES is a very rare disease which represents only 2.5% of the 976 eligible patients entered and treated with systemic therapy into prospective multi-sarcoma sarcoma trials performed by EORTC between 2003 and 2012. Although restricted by the small sample size, our results can provide guidance for the development of future ES-specific trials.

The response rate to chemotherapy in ES appears to be similar to pooled populations of multiple STS subtypes, ranging from 5% to 25% in the different trials. However, median PFS and OS for ES patients were lower than for STS patients in all trials, which would indicate that even with equivalent response to treatment, ES patients have a worse prognosis than other STS. It can also be noted that a relatively low response rate (1/13, ORR=8%) was observed in patients with doxorubicin-based regimen compared to those with other 1st line regimens (3/5, ORR=60%).

Although not considered into this analysis, 5 ES patients were randomized to the placebo arm of the 62072 trial (pazopanib versus placebo) and median PFS was 0.9 months (CI 95%: 0.62-1.84) while median OS was 11.5 months (CI 95%: 0.69-N).

No data from prospective trials have been specifically published yet on the role of systemic therapy in ES patients but a Phase II trial investigating tazemetostat, an EZH2

inhibitor, is currently ongoing [24]. This is a single arm trial where enrolled subjects were allocated according to their tumor type to one of five different cohorts, including a specific ES subset. Only a few retrospective case series on ES are available. Jones et al. [17] documented 21 ES patients treated with anthracycline (A, 2nd+ line) alone, in combination with ifosfamide (A/I, 1st line) as well as trabectedin alone as palliative chemotherapy and observed 3 PR, 12 SD, 5 PD for 1st line treatment (ORR=15%) and 4 SD, 5 PD for second/third line (ORR=0%). No clear distinction of the observed response according to first and other lines of treatment was provided by Pink et al. [18], but patients who received A or A/I experienced 6 SD, 7 PD (ORR=0%) and those who had gemcitabine/docetaxel had 1 CR, 6 PR, 3 SD and 2 PD (ORR=58%). The surprisingly high response rate to the latter combination deserves yet to be confirmed by prospective trials. Tumor responses among ES patients from EORTC trials were similar to those on A and A/I in both first (ORR=22%) and second or further lines of treatment (ORR=11%), but survival endpoints were shorter. Indeed, median PFS and OS were 7.3 (95% CI; 5.3-8.1) and 11.8 months (95% CI; 6.7-16.8) in Jones et al. and 8 and 21 months in Pink et al., irrespective of the treatment line. Only specific subgroups treated with A alone or diverse other regimens – such as high-dose ifosfamide, trofosfamide, gemcitabine/cisplatin, cisplatin/dacarbazine or doxorubicin/dacarbazine - had a median PFS of 3 months [18].

As a limitation of our study we could not sub-classify the ES cases in this project but we believe that our series included a high proportion of proximal-type ES (older patients, few primary tumors in the upper limb and relatively poor prognosis). We performed additional exploratory survival analyses by differentiating tumors initially situated in extremities (N=13) versus other locations (N=14), expecting a better prognosis for extremity locations as potentially associated with distal-type. However, PFS and OS were nearly equivalent in these ES populations.

The current standard of care for advanced, inoperable ES remains yet to be defined. There is a strong need for specific, prospective clinical trials in ES, ideally involving drugs with a good biological rationale in this disease, and ideally such trials should be randomized. Stratification between first and later lines of treatment, and possibly for proximal versus distal type ES may be required.

To conclude, this analysis reinforces the existing knowledge on systemic therapy in this rare type of sarcoma, notably with previously unstudied drugs such as pazopanib. The low number of patients of this study and its retrospective nature remains a limit in formulating definitive clinical conclusions. This is why systemic treatment of ES remains an unmet medical need and basic and translational research as well as clinical testing of agents for this disease in ES-specific trials stands as a high priority for the sarcoma research community.

Tables

Table 1: Patient and tumor characteristics

	Total (N=27) N (%)
Diagnosis of ES	
Local diagnosis only (no central review)	9 (33.3)
Central diagnosis	18 (66.6)
Study	
62012 (doxorubicin, doxorubicin + ifosfamide)	10 (37.0)
62043 (pazopanib)	4 (14.8)
62072 (pazopanib)	7 (25.9)
62091 (doxorubicin, trabectedin)	6 (22.2)
Gender	
Male	17 (63.0)
Female	10 (37.0)
Age at diagnosis	
≤40	10 (37.0)
40-50	4 (14.8)
50-70	12 (44.4)
>70	1 (3.7)
Performance status (WHO criteria)	
0	16 (59.3)
1	11 (40.7)
Site of primary tumor	
Lower extremity	8 (29.6)
Upper extremity	5 (18.5)
Retro-intra abdominal	4 (14.8)
Thoracic	2 (7.4)
Gynecological	2 (7.4)
Head and neck	1 (3.7)
Trunk	1 (3.7)
Breast	1 (3.7)
Other	3 (11.1)
Tumor grade at study entry (FNCLCC criteria)	
Low	1 (3.7)
Intermediate	10 (37.0)
High	10 (37.0)
Missing	6 (22.2)
Extension of disease at entry*	
Primary	15 (55.6)
Metastatic	24 (88.9)
<i>Lung</i>	17 (63.0)
<i>Lymph nodes</i>	9 (33.3)
<i>Bone</i>	8 (29.6)
<i>Soft tissue</i>	7 (25.9)
<i>Skin</i>	4 (14.8)

	Total (N=27) N (%)
<i>Pleural effusion</i>	4 (14.8)
<i>Liver</i>	2 (7.4)
<i>Ascites</i>	0 (0.0)
<i>Other site</i>	4 (14.8)
Administered treatment	
Doxorubicin	5 (18.5)
Doxorubicin + ifosfamide	8 (29.6)
Pazopanib	11 (40.7)
Trabectedin	3 (11.1)
Treatment line	
First line chemotherapy	18 (66.7)
Second and later lines of chemotherapy	9 (33.3)

**Percentages are not cumulative*

Abbreviations: ES, epithelioid sarcoma;

Table 2: Best response and objective response rate according to RECIST 1.1

	Patients (N)	Tumor Response			Objective Response rate
		Partial Response	Stable disease	Progressive disease	
1st line treatment	18	4 (22.2)	10 (55.6)	4 (22.2)	4/18 = 22.2%
<i>Doxorubicin</i>	5	0	3	2	0/5
<i>Doxorubicin + ifosfamide</i>	8	1	6	1	1/8
<i>Pazopanib</i>	2	2	0	0	2/2
<i>Trabectedin</i>	3	1	1	1	1/3
2nd + line treatment (only pazopanib)	9	1 (11.1)	4 (44.4)	4 (44.4)	1/9 = 11.1%
All patients	27	5 (18.5)	14 (51.9)	8 (29.6)	5/27 = 18.5%

Table 3: Progression-free survival and overall survival according to the line of treatment and overall

	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 6 months (95% CI)	% at 9 months (95% CI)	% at 12 months (95% CI)
PFS duration from evaluation start						
1st line treatment	18	17	4.04 (2.73, 7.52)	38.9 (17.5, 60.0)	22.2 (6.9, 42.9)	16.7 (4.1, 36.5)
2nd + line treatment	9	9	2.73 (0.76, 4.47)	11.1 (0.6, 38.8)	11.1 (0.6, 38.8)	11.1 (0.6, 38.8)
All patients	27	26	3.75 (2.20, 4.80)	29.6 (14.1, 47.0)	18.5 (6.8, 34.8)	14.8 (4.7, 30.5)
OS duration from evaluation start						
1st line treatment	18	16	10.83 (8.44, 21.29)	77.8 (51.1, 91.0)	61.1 (35.3, 79.2)	44.4 (21.6, 65.1)
2nd + line treatment	9	6	9.79 (4.63, 24.71)	87.5 (38.7, 98.1)	50.0 (15.2, 77.5)	33.3 (5.6, 65.8)
All patients	27	22	10.83 (8.11, 21.29)	80.8 (59.8, 91.5)	57.7 (36.8, 73.9)	42.0 (23.1, 59.8)

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Figures

Figure 1: Progression-free survival (left) and overall survival (right)

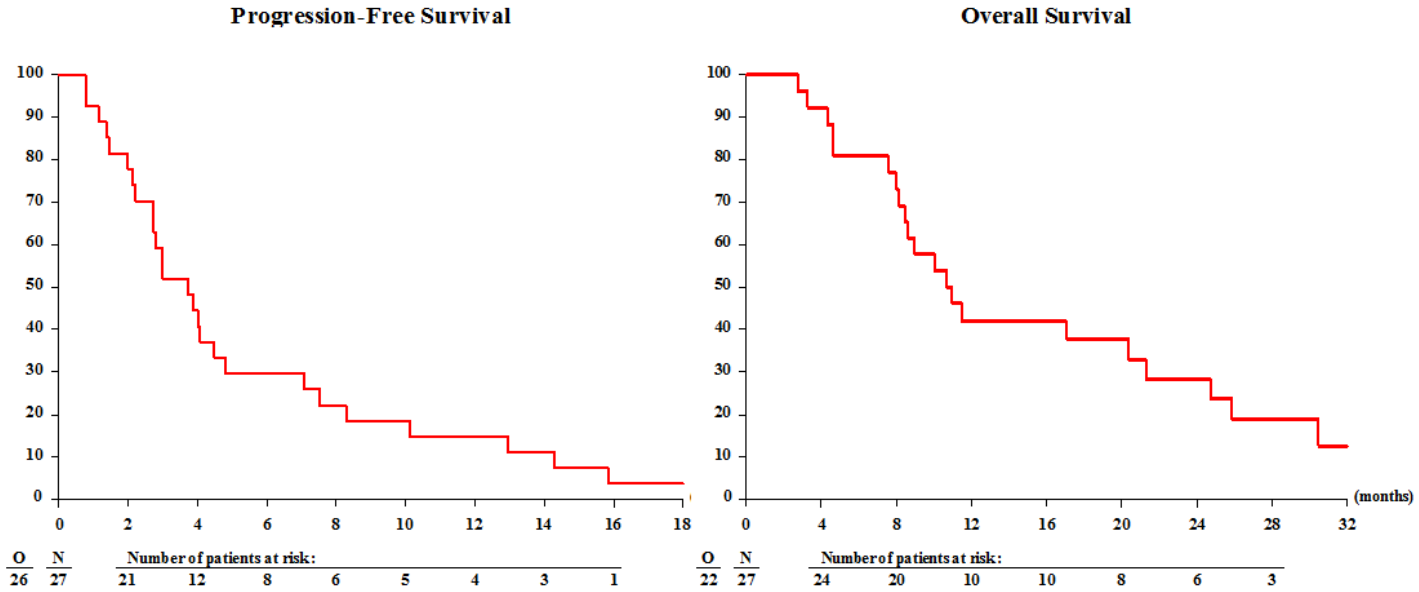
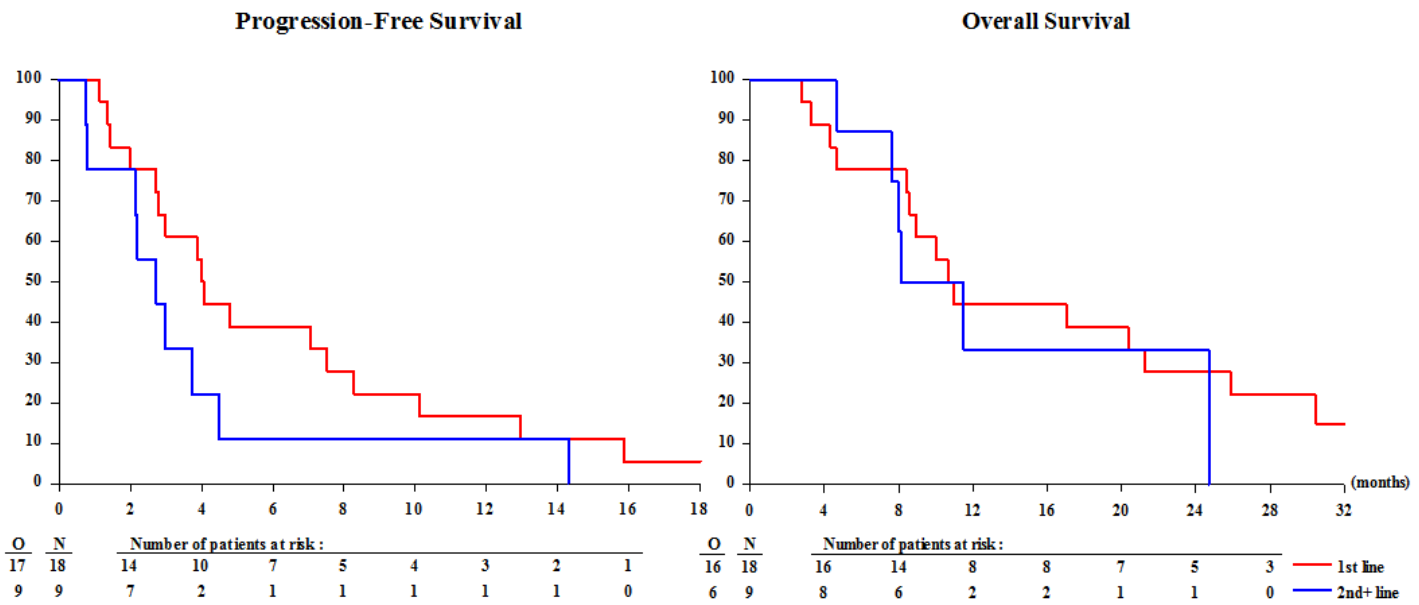


Figure 2: Progression-free survival (left) and overall survival (right) by line of treatment; 1st line of treatment in red and 2nd line or later in blue



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