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Original Article

European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Experience with Advanced/Metastatic Epithelioid Sarcoma Patients Treated in Prospective Trials: Clinical Profile and Response to Systemic Therapy

N. Touati^{*}, P. Schöffski[†], S. Litière^{*}, I. Judson[‡], S. Sleijfer[§], W.T. van der Graaf^{||}, A. Italiano[¶], N. Isambert^{**}, T. Gil^{††}, J.Y. Blay^{‡‡}, D. Stark^{§§}, T. Brodowicz^{||||}, S. Marréaud^{*}, A. Gronchi^{¶¶}

^{*}European Organisation for Research and Treatment of Cancer, Brussels, Belgium

[†]Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium

[‡]Royal Marsden Hospital, London, UK

[§]Erasmus MC – Cancer Institute, Rotterdam, the Netherlands

[¶]Institut Bergonié, Bordeaux, France

^{||}The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK

^{**}Centre Georges-François Leclerc, Dijon, France

^{††}Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium

^{‡‡}Centre Léon Bérard, Lyon, France

^{§§}Leeds Teaching Hospitals NHS Trust, St James University Hospital, Leeds, UK

^{¶¶}Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

^{||||}Medical University Vienna, General Hospital, Vienna, Austria

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Abstract

Aims: Epithelioid sarcoma 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 epithelioid sarcoma patients. We carried out a retrospective analysis of clinical data from epithelioid sarcoma patients to provide a reference for the design of future epithelioid sarcoma-specific studies.

Patients and methods: Data from patients with epithelioid sarcoma entered in prospective multi-sarcoma phase II/III trials were pooled: EORTC trial 62012 (doxorubicin versus doxorubicin/ifosfamide), 62043 (pazopanib), 62072 (pazopanib versus placebo) and 62091 (doxorubicin versus trabectedin). Patients had either a local or a centrally confirmed diagnosis of epithelioid sarcoma, 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 were calculated from date of entry.

Results: Among 976 patients with advanced sarcomas, 27 epithelioid sarcoma patients (2.8%) were eligible for the analysis (17 men, median age at diagnosis 50 years, range 19–72). Eighteen (66.7%) received chemotherapy as first-line treatment (five doxorubicin, eight doxorubicin/ifosfamide, two pazopanib, three trabectedin) and nine (33.3%) received pazopanib as second line or later. The primary tumour 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%). The best response for first-line patients was four partial responses (22.2%), 10 stable disease (55.6%) and four progressive disease (22.2%). In subsequent lines, pazopanib achieved one partial response (11.1%), four stable disease (44.4%) and four progressive disease (44.4%). All patients but one progressed on treatment. The median PFS and overall survival were 3.8 (95% confidence interval 2.2–4.8) and 10.8 months (95% confidence interval 8.1–21.3), respectively. Five patients were still alive at the time of the according trial analysis.

Author for correspondence: N. Touati, European Organisation for Research and Treatment of Cancer, Brussels, Belgium.

E-mail address: nathan.touati@eortc.be (N. Touati).

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Conclusion: With all limitations of such a rare disease and small data set, objective response and survival outcomes are similar in epithelioid sarcoma to non-selected sarcoma populations. The clinical testing of novel systemic treatments for epithelioid sarcoma remains an unmet medical need and a high priority. © 2018 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.

Key words: Epithelioid sarcoma; metastases; systemic therapy

Introduction

First reported by Laskowski in 1961 [1] and further described by Enzinger [2], epithelioid sarcoma 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 tumours with similar morphology. Epithelioid sarcomas 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].

Epithelioid sarcomas are classified by two recognised subtypes, the distal type and the less frequent proximal type. Both entities are predominant in young male adults. Distal-type epithelioid sarcoma has a high tendency to occur in the extremities, especially in the upper limb [6–8]. Conversely, proximal-type epithelioid sarcomas most commonly affect trunk or deep tissue sites and tend to have a more aggressive clinical course. Tumour grading of epithelioid sarcoma is based on the Fédération Nationale des Centres de Lutte Contre le Cancer system and is considered as a relevant prognostic factor [9–11]. Epithelioid sarcoma has a high rate of locoregional 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 epithelioid sarcoma [3,6]. With 5 year survival rates ranging from 55 to 70%, the prognosis of epithelioid sarcoma patients is generally poor but relatively comparable with other soft tissue sarcomas (STS) [12,14,15]. Surgical resection with or without radiotherapy is the accepted standard treatment for localised disease [13,16]. The role of systemic therapies in patients with advanced stage epithelioid sarcoma 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 and 60% across the diverse drugs and lines. Prospective disease-specific trials with a focus on epithelioid sarcoma patients are not available.

As part of the European Organisation for Research and Treatment of Cancer (EORTC) clinical trial activities, several drugs for the treatment of advanced and metastatic sarcoma have been explored over the past decades. The 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

epithelioid sarcoma treated with systemic agents in historic prospective EORTC trials. These data provide an important reference for the design of future epithelioid sarcoma-specific clinical trials.

Materials 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 the EORTC's Soft Tissue and Bone Sarcoma Group (STBSG). The phase III 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 with doxorubicin [22]. We used these study populations as the basis for the current subgroup analysis focusing on patients with epithelioid sarcoma. Patients received either doxorubicin, doxorubicin/ifosfamide, trabectedin or pazopanib. Trial participants treated with placebo (EORTC 62072) were excluded from this analysis. The diagnosis of epithelioid sarcoma 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 epithelioid sarcoma.

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 partial or complete response as best response to treatment. The duration of the objective response was determined from the first documentation of complete/partial response 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 corresponded to the date of randomisation for the 62012, 62072 and 62091 trials and the date of registration for the 62043 trial. Overall survival was calculated from the date of evaluation start to

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