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ONCOLOGY: BRIEF REPORT

Epithelioid hemangioendothelioma in children: The European Pediatric Soft Tissue Sarcoma Study Group experience

Daniel Orbach[1] | Max M. Van Noesel[2,3] | Bernadette Brennan[4] | Nadège Corradini[5] | Rita Alaggio[6] | Myriam Ben Arush[7] | Reineke A. Schoot[2,3] | Pablo Berlanga[8] | Ilaria Zanetti[9] | Lisa Lyngsie Hjalgrim[10] | Federica Di Corti[11] | Gema Ramirez[12] | Michela Casanova[13] | Andrea Ferrari[13]

[1]SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, PSL University, Paris, France

[2]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[3]Division Cancer and Imaging, University Medical Center Utrecht, Utrecht, The Netherlands

[4]Paediatric Oncology, Royal Manchester Children's Hospital, Manchester, UK

[5]Department of Pediatric Hematology and Oncology-IHOPe, Léon Bérard center, Lyon, France

[6]Pathology Department, Ospedale Pediatrico Bambino Gesù IRCCS, Roma, Italy

[7]Ruth Rappaport Children's Hospital, Haifa, Israel

[8]Department of Pediatric and Adolescent Oncology, Gustave-Roussy, Cancer Campus, Université Paris-Saclay, Villejuif, France

[9]Haematology Oncology Division, Department of Women's and Children's Health, Padova University Hospital, Padova, Italy

[10]Department of Pediatrics and Adolescent Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[11]Pediatric Surgery, Women and Children's Health Department, University Hospital of Padua, Padua, Italy

[12]Pediatric Oncology and Hematology, Pediatric Hospital Virgen del Rocío, Sevilla, Spain

[13]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

Correspondence
Daniel Orbach, SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, Paris, France.
Email: Daniel.orbach@curie.fr

Abstract

The European pediatric Soft tissue sarcoma Study Group analyzed all children with epithelioid hemangioendothelioma prospectively registered in the NRSTS-05 (EUDRACT 2005-001139-31) and in MTS-2008 (NCT00379457) studies: 10 patients with localized and one with metastatic disease. Median age was 14.3 years (range, 9.0–18.8). Local therapy was initial primary surgery in seven cases, and five patients received systemic therapy. No patients received radiotherapy. After a median follow-up of 50 months (range, 6–176) for living patients, nine patients remain alive off therapy and two died. Five-year progression free and overall survivals are, respectively, 77.1% (95% confidence interval [CI]: 34.5–93.9) and 74.1% (95% CI: 28.1–93.0).

KEYWORDS
children, hemangioendothelioma, soft tissue sarcoma, surgery

Abbreviations: CI, confidential interval; EHE, epithelioid hemangioendothelioma; EpSSG, European Pediatric Soft Tissue Sarcoma Study Group; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, p rogression-free survival.

1 | INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a malignant vascular sarcoma (ICD-O-3.2: 9133/3) composed of epithelioid endothelial cells within a distinctive myxo-hyaline stroma. Most cases are characterized by the presence of a *WWTR1::CAMTA1* gene fusion in tumor cells.[1] A small subset of tumors, characterized by a *YAP1::TFE3* gene fusion, show a distinctive morphology with nests of cells with prominent eosinophilic cytoplasm and tendency to form vascular spaces and are more frequent in younger patients.[2,3] The clinical behavior of EHE in adults is variable with more often indolent behavior and propensity for metastases, the most common sites being the liver, lungs, and bone.[3,4] This tumor is considered as "ultra-rare" with an in incidence of 0.038/100,000/year. The peak of incidence is in the fourth to fifth decade with exceptional cases during childhood.[3,4] Due to this rarity, little is known about EHE in children. Therefore, the aim of this study is to analyze tumor behavior in young patients with EHE prospectively registered in European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) protocols.

2 | MATERIAL AND METHODS

The analysis was based on all patients registered within the EpSSG NRSTS05 trial (from August 2005 to December 2016; European Union Drug Regulating Authorities Clinical Trials (EUDRACT) No. 2005-001139-31[5]) and the EpSSG MTS2008 study (open from June 2010 to December 2016). The EpSSG MTS2008 protocol (NCT00379457) was a prospective, observational, single-arm study dedicated to pediatric and young adults with metastatic sarcomas.[6]

Patients' inclusion in the protocol was based on the local pathologist's diagnosis and/or the central review, when available. Histological review by the EpSSG pathology panel was recommended, but not considered mandatory for the protocol enrolment. IRS-I/R0 resection was defined as clear margins, IRS-II/R1 as gross complete resection with tumor cells present at the inked surgical margin and IRS-III/R2 with macroscopic residual disease.[7]

For localized tumors, immediate surgical approach was advised with potential requirement of vascular resection and reconstruction techniques in case of abutting major vessels. No adjuvant therapy was required for patients with localized totally resected EHE. For unresectable tumors, an upfront wait-and-see period might be suggested to identify those cases with an indolent course and those with a more aggressive disease. For patients with advanced metastatic and progressive disease, systemic therapy options were proposed: interferon-alpha and mammalian target of rapamycin (mTOR) inhibitors.[4]

For statistical analysis, survival probabilities were estimated using the Kaplan–Meier method. The primary outcome, progression-free survival (PFS), was defined as the time from diagnosis to the first event (tumor progression, relapse, or death due to any cause) or to the latest follow-up. Overall survival (OS) was measured as the time from diagnosis to death due to any cause, or to the latest follow-up.

3 | RESULTS

Among the 1356 patients registered in both studies, 11 patients had EHE (0.8%). Histologic diagnosis was obtained after biopsy of primary or metastatic site, in three cases and one case, respectively, or upfront surgery, in seven cases. Overall, four patients had national or international histological review and three of these had somatic *WWTR1::CAMTA1* gene fusion. The histologic description in local pathology reports highlighted the characteristic epithelioid cytology ($n = 9$) with eosinophilic cytoplasm and blistering ($n = 4$) and a distinctive myxo-hyaline stroma ($n = 4$). Immuno-staining revealed CD31 (9/9), CD34 (8/8) and ERG positivity (5/5).

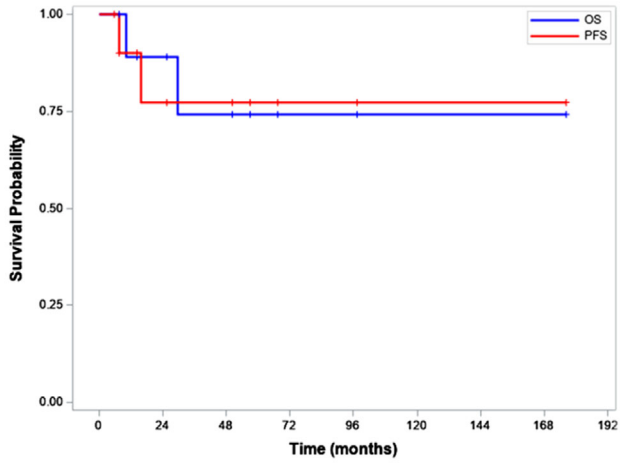
Clinical characteristics at diagnosis are summarized in Table 1. Sex ratio was 6/5 (male/female ratio), and median age was 14.3 years (range, 9.0–18.8). Primary site was mainly limbs (six cases), than trunk (four cases) and one patient had a metastatic disease with bone, lung, liver and meningeal involvement. Tumors were smaller than 5 cm in all cases with available information and confined in the organ of origin in 64% of patients (T1 status). No patient had regional nodal involvement.

For the 10 localized tumors, local therapy was initial primary tumor resection (seven cases) followed by an immediate primary re-resection (four cases). Overall, IRS groups were group-I six cases, II one case and III three cases (biopsy). In addition, two patients had delayed surgery after medical therapy (R0, R2). No focal radiotherapy was delivered

TABLE 1 Clinical characteristics of the pediatric patients with epithelioid hemangioendothelioma

	Total number	%
Age (years)	–	–
Gender (male/female)	6/5	–
Primary site		
Extremities	6	57
Trunk	4	36
Unknown (metastatic)	1	8
TNM status		
T1	6	60
T2	4	40
Tx	1	–
Tumor primary size		
≤5 cm	8	100
Not available	3	–
Loco-regional lymph node involvement		
N0	11	100
IRS group		
IRS I	6	57
IRS II	1	8
IRS III	3	27
IRS IV	1	8

Abbreviation: TNM, tumor node metastasis.



	N	Events	5-yr PFS (95%CI)	Deaths	5-yr OS (95%CI)
All patients	11	2	77.1 (34.5-93.9)	2	74.1 (28.9-93.0)

FIGURE 1 Outcome of patients with hemangioendothelioma. Abbreviations: OS, overall survival; PFS, progression-free survival; CI, confidential intervals

(Table 1). Systemic therapy for localized tumors after incomplete surgery (IRS-II one case, IRS-III three cases) consisted of interferon (two cases), temsirolimus and paclitaxel (one case each). The adolescent with metastatic (IRS-IV) tumors with no obvious primary had a past medical history of a Fallot tetralogy. She received paclitaxel during 15 months after a liver biopsy of a metastatic site. After tumor progression, second-line therapy consisted of regorafenib for 2 months leading to stabilization of the disease. Doxorubicin was then delivered for five cycles (350 mg/m^2 cumulative doses) but stopped due to severe cardiac failure resulting in death of the patient 29 months after diagnosis. Among the four patients with measurable disease, response to medical therapy showed only one partial response after paclitaxel (case no. 9). Other had minor partial response, stable disease or progressive disease (respectively, cases no. 9, 10 and 11).

The median follow-up for alive patients was 50 months (range, 6–176). Nine patients are alive off therapy: eight in complete remission and one with a stable residual disease 5 years after diagnosis. One patient with a localized thoracic tumor developed bone metastasis and died 10.3 months after initial diagnosis. Five-year PFS and OS are, respectively, 77.1% (95% confidence interval [CI]: 34.5–93.9) and 74.1% (95% CI: 28.1–93.0; Figure 1).

4 | DISCUSSION

EHE is rare (<0.9% of all EpSSG registered cases) and develop without any documented genetic background. Due to its rarity, a pathology review with systematic molecular analyses is recommended to confirm the diagnosis. The detection of *WWTR1::CAMTA1* or *YAP1::TFE3* gene fusion is a helpful diagnostic tool.[4] Notably, two patients in this study with a tumor event had an EHE with *WWTR1-CAMTA1* fusion transcript.

The European pediatric *Cooperative Weichteilsarkom Studiengruppe* (CWS) has studied 16 cases of EHE (0–21 year) over a period of 28 years. Median age was 9.7 years (0.2–16.8) and patients had localized tumors in 62% of cases.[8] At the end of follow-up, eight patients are alive in complete remission, three alive in partial remission, one with progressive disease and four died. Another bicentric American experience analyzed 24 young cases (mean age, 13.8 years; range, 2.5–25.6).[9] In this latter publication, multiorgan disease was present in 79% of patients and mostly involved lungs (79%), liver (46%) and bone (42%). Despite frequent tumor progression (63% of patients), at a mean time of 18.4 months (range, 0–72), overall survival was 73% at 5 years for evaluable patients. In our series, these tumors mainly occurred in the adolescent population, in limbs and were mostly localized. Therefore, tumor resection remains the cornerstone therapy in unifocal EHE and most patients have been cured with exclusive surgery, possibly with immediate re-excision.[4,8,10] Interestingly, the overall outcome seems favorable without any use of radiotherapy, even after incomplete tumor resection. Therefore, these data do not support the use of adjuvant radiotherapy in EHE in children. It is reported that conventional sarcoma chemotherapy had very limited activity. Some other drugs may lead to a prolonged tumor control: interferon, thalidomide, multityrosine kinase inhibitors, and mTOR inhibitors.[4,11–14] The best first line of therapy is not defined. Specific efficient targeted therapies against these tumors harboring a specific fusion transcript are still lacking. Therefore, the first recommended strategy, in case of unresectable lesion, even metastatic, is to propose an initial observation and to consider these drugs only in case of progression.[4,8,9,11] In our experience, only one out of four tumors with macroscopic disease showed a partial response.

In conclusion, this pediatric experience on these exceptional entities confirms the overall favorable course of these tumors with exclusive surgery for localized diseases. In the case of diffuse progressive disease, patients should be included in trials to validate the value of new drugs. Even considering the limited number of pediatric patients, the precise role of these treatments needs further exploration in larger international cohorts of pediatric and adult patients in collaboration with medical oncologists.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Daniel Orbach https://orcid.org/0000-0002-2520-139X
Max M. Van Noesel https://orcid.org/0000-0003-0503-5838
Bernadette Brennan https://orcid.org/0000-0003-1614-0289
Myriam Ben Arush https://orcid.org/0000-0003-3931-7243
Gema Ramirez https://orcid.org/0000-0001-9986-5861
Andrea Ferrari https://orcid.org/0000-0002-4724-0517

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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