Epithelioid sarcoma.

An observational study

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AMENDAMENT AND MODIFICATION

Amendment EPISOb

Date	Type of amendment	Protocol Version	Summary of changes	Pages
18 Aug 2017	Substantial	2.0	A retrospective cohort has been introduced in 3 selected sites. Collection of data of localised, primary, resected epithelioid sarcoma is aimed to better understanding of the natural history of the disease and to improve the current knowledge on the clinical behaviour of the two morphological variants ("classic or "distal" versus "proximal").	6, 9, 10
04 Dec 2019	Not substantial	2.1	1) Increase in duration of > 10 % of the overall time of the trial, confirming that: • By the study design there is no any exposure to treatment • the definition of the end of the trial is unchanged, and • monitoring arrangements are unchanged 2) New affiliation of Prof. Angelo Paolo Dei Tos of central Pathology laboratory	5 6

Epithelioid sarcoma: background.

1.1 Histopathology and clinical features

Epithelioid sarcoma (ES) is a rare malignant mesenchymal neoplasm, accounting for less than 1% of all sarcomas[1]. It is regarded as a high-grade soft-tissue sarcoma by definition and it is characterized by epithelioid cytomorphology.

The 2013 WHO classification of Tumours of Soft Tissue and Bone identifies two different subtypes of ES, with distinct clinical and pathological features: the conventional or classic ("distal") form and the proximal-type ("large-cell") variant[1]. The classic-type ES is morphologically characterized by nodules of epithelioid and spindle cells, with a granulomatous appearance. Necrosis can be prominent and cellular atypia is relatively mild, although usually more pronounced in recurrent lesions. The proximal-type variant is composed by a multinodular and sheet-like growth of large polygonal cells with moderate pleomorphic appearance[2]. Rhabdoid morphology is common[3]. Rarely, ES can demonstrate mixed histological features of both conventional and proximal-type.

Primary ES usually presents as firm, painless nodules, often ulcerated arising predominantly in the extremities, but no anatomical site is exempt. The high local relapse rate (26% to 77% in different series) and the tendency toward multifocality (both at presentation and at the time of the recurrence) are characteristic. Spreading to regional lymph nodes is a ES peculiar clinical feature. The rate of nodal metastases varies from 22% to 45%, clearly higher compared to the 2.6% rate reported for adult patients with all-types soft tissue sarcoma[4-8]. Metastatic spread has been reported in the range of 30-50% of patients, with lung being the most common site[4, 5, 9-11]. Dissemination to the scalp and other skin sites, bone, brain, liver and pleura has also been described.

The classic-variant is encountered nearly twice as often as the proximal-type and tends to occur in adolescents and young adults (age in the range of 10 to 40 years) with a clear male predominance (2:1). Also known as "distal-type", it mainly arise in acral sites, particularly distal upper extremities (60% of cases) followed by distal lower extremities, proximal lower and upper extremities, trunk and lastly head and neck[1, 12]. The proximal-type variant often presents itself as larger and more infiltrative tumor, arising from deep soft tissues. Trunk is the most common primary site, followed by buttock/hip, thigh, head and neck and axilla[1, 3, 13].

The prognosis for patients with proximal-type ES is significantly worse than for patients with classic-type variant[3, 12, 13]. Adverse prognostic factors in both conventional-type and proximal-type ES

include male sex, older age, proximal/axial primary site, large tumor size, involvement of deep soft tissues and lymph-nodes, early distant metastases, high mitotic activity and extensive necrosis[6, 9-12, 14].

1.2 Immunophenotype and genetics

In both ES variants, the immunophenotype is characterized by the positivity for cytokeratins (CK) and the epithelial membrane antigen (EMA). In contrast to carcinoma, CD34 is expressed in more than 50% of all cases[1, 2].

INI1, a subunit of the ATP-dependent SWI/SNF chromatin remodeling complex encoded by the SMARCB1 gene at 22q11, is deficient in approximately 80% of ESs of both classic and proximal-type. Although cytogenetic investigation of ES has proven complex rearrangements, 22q abnormalities have been reported and correlated in the pathogenesis of this sarcoma[15, 16]. Similar alterations were previously described in paediatric rhabdoid tumours of kidney and CNS among other neoplasms[17].

However, the frequency of SMARCB1 mutations in ES is significantly lower compared to malignant rhabdoid tumours and it can only partially account for the high frequency of INI1 deficiency in this disease. The exact mechanisms behind INI1 loss in ES is therefore to be considered still poorly understood[1, 2, 4, 18, 19].

1.3 Treatment

The optimal management of ES remains to be defined. Wide surgical resection is today regarded as the standard treatment for patients with a localized disease. ES local aggressiveness may partially account for the higher amputation rate reported in this sarcoma subtype (up to 50%) compared to patients with all-type soft tissue sarcomas (10%). Also, given the known tendency toward local recurrence, a possible role for postoperative radiotherapy has been suggested[20, 21]. The value of adjuvant chemotherapy in ES is unproven; when the risk of relapse is high, it is an option to be discussed with the patient in conditions of uncertainty.

Data on chemotherapy in ES are currently limited to case reports and small retrospectives series. Anthracycline as single agent or in combination with ifosfamide seems to provide satisfactory palliation in these patients and therefore it is widely used. However, most patients achieve disease stabilization: responses are rare and response duration tends to be short[22]. The combination of gemcitabine and docetaxel has been reported to be active in this sarcoma subtype, but the

experience is limited to a small number of patients[23]. Signs of activity for navelbine and pazopanib, an oral tyrosine kinase inhibitor approved for the treatment of soft tissue sarcoma, have also been described in two distinct case reports and may warrant further investigation[24, 25].

1.4 Outcome

The overall outcome for patients with localized ES is better compared to those with regional disease spreading (5 years overall survival of 75% vs 49%). Prognosis seems to be favourable in paediatric patients (5 years overall survival 92.4%), probably because of a higher incidence of localized distal-type ES and a lower rate of nodal involvement[14]. Despite the administration of palliative chemotherapy, the outcome in patients with metastatic disease is still unsatisfactory: the reported median survival is approximately 50 weeks and the 1- and 5-year survival rates are 46 and 0%, respectively[22, 26].

1. Epithelioid sarcoma: unmet needs

Due to its extreme rarity and the variable therapeutic approaches reported in literature, the best management for ES remains uncertain. At present, no on-going clinical trials are available for this rare sarcoma subtype and current knowledge is based on limited retrospective experiences.
As previously successfully done, the co-operation among institutions with expertise in the field of soft tissue sarcoma within the Italian Sarcoma Group will results in the first large prospective effort, aiming to properly describe the population of patients affected by ES and to promote a better understanding of the clinical behaviour and molecular characteristics in this rare disease.

2. Epithelioid sarcoma: the prospective observational analysis.

3.1 Study design – clinical data collection.

An electronic database accessible by all the institutions willing to join the study will be made available on the Italian Sarcoma Group website. Data from all patients diagnosed in Italy with ES from May 2017 to December 2021 (56 months) will be prospectively entered in this national platform. Each patient will be provided with an informational leaflet for his/her general practitioner and asked to sign an informed consent prior to data entry.
The following information will be recorded in the database:

- Demographics – patient name, DOB, gender, date of first consultation, data of diagnosis
- Data on primary tumor – size, site, evidence of multifocality

- Data on histological diagnosis – morphology (classical type, proximal type, mixed), mitotic count, depth
- Data on staging at diagnosis – evidence of lymph-nodal and/or distant metastases
- Data on treatment of primary tumour – surgery, radiotherapy, chemotherapy
- Data on recurrence – type of recurrence, site, date
- Data on treatment of local relapse – surgery, radiotherapy, chemotherapy
- Data on treatment of metastatic disease – pulmonary metastasectomy, radiotherapy
- Data on chemotherapy for metastatic disease – line, regimen, number of cycles, best response, duration of response
- Patient status

3.2 Study design - centralised pathology review and translational optional analysis

For each patient included in the present study, the referring institution will be asked to retrieve pathological specimens (paraffin embedded tissue) in order to perform a centralised pathological review (FFPE should be sent for central within 2 weeks from the study entrance)

The centralised pathology review will be arranged through the electronic platform of the Italian Rare Cancer Network, already in place. The pathological specimen will be centralised at the Pathology Department of Azienda Ospedaliera Universitaria di Padova (Prof. Angelo Paolo Dei Tos).

If the patient will agree and will provide his/her informed consent, an optional translational study will be performed. Immunohistochemical as well as molecular analysis of INI1 and EZH2 status will be assessed. NGS analysis of ES subtypes (classic versus proximal) will be performed in order to elucidate the molecular mechanism underlying the two distinctive morphologies. Immunohistochemical as well as molecular data will be correlated with clinical features and outcome. The expression of immune checkpoint inhibitors along with an immunohistochemical typing of the immune-infiltrate will be performed.

3.3 Study objectives

As a prospective observational effort, this will be a hypothesis generating study. However, it will also provide a valuable opportunity to test existing assumptions coming from everyday clinical practice and from preliminary data currently available in the literature. One of the main objectives of the present analysis will be to identify distinguishing features between the two different ES subtypes (classic versus proximal). The clinical behaviour of the classic and proximal variant, whose

distinction is currently on topographic and morphological bases, is expected to be different, with the proximal-type being apparently more sensitive to chemotherapy but probably more aggressive and associated with a poorer outcome[27]. This clinical observation is currently supported by little data from small retrospective experiences. A validation on a larger prospective cohort of patients is required to provide results, which may guide clinicians toward a better-tailored treatment approach in the two different subtypes. Also, the present study will serve as a platform for tissue collection and NGS testing in selected cases, allowing the elucidation of possible molecular features underlying the distinction of the two variants.

Despite the use of multimodal approaches, the overall outcome in patients with ES remains unsatisfactory and the identification of new strategies is a priority. INI1 loss is recognised as a common finding in ES (approximately 80% of all cases) and this has recently translated in the development of new compounds targeting his downstream effector EZH2[28, 29]. Little is known about the correlation between INI1 and EZH2 status with clinical and pathological characteristics of the disease. Through this study, we also aim to provide an insight into the small proportion of ES showing INI1 preservation, trying to clarify the distinguishing clinical, pathological and molecular features and possibly identify different targets. Finally, as immunotherapy is emerging as a promising treatment approach in several solid human cancers, we will also explore the expression of immune-checkpoint inhibitors and evaluate the immune infiltrate in the two different variants, to eventually identify a subset of ES patients who could potentially benefit from this strategy.

3.3.1 Clinical objectives

The present prospective national study aims to provide a description of the population affected by ES, an insight into the natural history of the disease and an answer some on the outstanding questions on its management. Also, it will focus on enhancing any differences between the two ES variants (classical-type and proximal-type) in order gain a better understanding of the disease, tailor the treatment and lastly improve outcome.

The clinical objectives of the study will be the following:

- Demographic description of the population affected by ES (as a whole and according to subtypes)
- Description of disease presentation and natural history (as a whole and according to subtype)
- Identification of reliable pathological and clinical predictive factors (in the whole population and according to subtype)

- Description of current treatment approach for localised disease across Italian institutions
- Assessment of radiation therapy and chemotherapy value in the management of localised disease (in the whole population and according to subtype)
- Description of recurrence pattern (in the whole population and according to subtype)
- Description of current treatment approach for local recurrence across Italian institutions
- Description of current treatment approach for metastatic disease across Italian institutions
- Assessment of disease response to different chemotherapy regimens and currently available tyrosine kinase inhibitors (i.e. pazopanib) (in the whole population and according to subtype)
- Description of outcome

3.3.2 Translational objectives

- Elucidation of molecular differences underlying the two different morphologies of ES (classic versus proximal)
- Description of INI1 and EZH2 status in ES
- Correlation of INI1 status with clinical, pathological and molecular features
- Evaluation of the molecular bases of INI1 loss in ES
- Evaluation of checkpoint inhibitors in ES
- Immunohistochemical typing of the immune-infiltrate in ES

4. Study population

We plan to include approximately 60 patients (range: 50-70) in 36 months.

Inclusion criteria

- Histological diagnosis of epithelioid sarcoma according to 2014 WHO classification, performed on biopsy or surgical specimen
- Signed informed consent
- Adequate patient compliance to treatment or follow up
- No age limits

Exclusion criteria

- Other malignancies within past 5 years, with exception of carcinoma in situ of the cervix and basocellular skin cancers treated with eradicating intent
- Impossibility to ensure adequate compliance

5. Retrospective, collaborative analysis on localised, primary, resected epithelioid sarcoma: natural history, treatment and outcome.

Together with the prospective observational study, a retrospective analysis including patients with localised, primary epithelioid sarcoma treated with surgery at three referring Italian sarcoma centres belonging to the Italian Sarcoma Group will be performed.

The joining institutions will include:

Fondazione IRCCS Istituto Nazionale dei Tumori (Milan),
IRCCS Istituto Ortopedico Rizzoli (Bologna) and
Ospedale Careggi (Florence).

This study will promote a better understanding of the natural history of this rare condition and will allow to improve the current knowledge on the clinical behaviour of the two morphological variants ("classic or "distal" versus "proximal").

Inclusion criteria

- Histologically confirmed diagnosis of epithelioid sarcoma. The morphological subtype ("classic" versus "distal") needs to be defined according to WHO criteria. All cases will be reviewed by a pathologist dedicated to soft tissue sarcoma.
- Primary, localised disease
- Curative surgery performed at the Fondazione IRCCS Istituto Nazionale dei Tumori, Fondazione IRCCS Istituto Ortopedico Rizzoli or Ospedale Careggi within January 1995 and December 2015.

Exclusion criteria

- Evidence of metastatic disease at presentation

6. Timeframe

Between January 1995 and December 2015

7. Population size

All consecutive patients treated with surgery between January 1995 and December 2015 will be included in the analysis. Through the collaboration of the three joining institutions, we plan to include approximately 60-80 patients.

8. Data collection

The data will be extracted retrospectively from prospectively maintained institutional database and will be checked through a revision of patient records. The following data will be collected:

demographics (gender, date of birth, age at diagnosis), disease characteristics (morphological subtype, dimension, primary site, INI1 status), treatment received (date of surgery, surgical margins, radiation therapy, timing of radiation therapy, chemotherapy, timing of chemotherapy, type of regimen used, best response according to RECIST 1.1) and outcome (recurrence type and timing, patient status).

9. Study end-point

The following end points will be evaluated as outcome indicators: - local recurrence-free survival, distant metastasis-free survival, disease-free survival, and overall survival. The possible correlation between the morphological subtype, primary site, treatment and outcome will be explored.

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