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COMMENTARY

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The evolving management of epithelioid sarcoma

Anneke Alves[1] | Anastasia Constantinidou[2] | Khin Thway[1,4] | Cyril Fisher[3] | Paul Huang[4] | Robin L. Jones[1,5]

[1]Sarcoma Unit, Royal Marsden Hospital, London, UK

[2]Medical School University of Cyprus and BoC Oncology Centre, Nicosia, Cyprus

[3]Department of Musculoskeletal Pathology, Robert Aitken Institute for Clinical Research, Birmingham, UK

[4]Division of Molecular Pathology, Institute of Cancer Research, London, UK

[5]Division of Clinical Studies, Institute of Cancer Research, London, UK

Correspondence
Robin L. Jones, Sarcoma Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK.
Email: robin.jones4@nhs.net

1 | INTRODUCTION

Epithelioid sarcoma (ES) is an aggressive malignant soft-tissue tumour which was first named in the 1970s by Franz Enzinger (Enzinger, 1970). ES is rare, accounting for less than 1% of all sarcomas, and predominantly occurs in younger adults and males. The aetiology of ES is unknown, but some studies have suggested an association with previous trauma, potentially originating within scar tissue (Jashnani et al., 2011; Kaddu et al., 2008). There are two variants of ES that have been identified according to their anatomical location; it is likely that there is a spectrum of disease between the two variants (Rakheja et al., 2005). Histologically, both classical and proximal-type ES are composed of sheets of uniform epithelioid cells, although they have morphologic/architectural differences.

Nearly half of patients with ES present with localised disease, which is often multifocal (Jawad et al., 2009; Spillane et al., 2000). In classic-type ES, there are often successive lesions with high rates of local recurrence (Baratti et al., 2007). Unlike other soft tissue sarcomas, ES has the propensity to spread via the lymphatic system. In 30–50% of cases, it can metastasise to regional lymph nodes and to distant sites, in particular the lung (Chase & Enzinger, 1985; Ross et al., 1997). Proximal-type ES tends to metastasise earlier than the classic type therefore carrying a poorer prognosis (Guillou et al., 1997). The 5-year overall survival has been reported as 70% with better rates seen in localised disease compared to regional disease (75% vs. 49%, respectively) (Spillane et al., 2000). Adverse prognostic factors include deep, large tumours that are proximally sited, male sex, older age, a history of local recurrence and the presence of regional metastases (Chase & Enzinger, 1985; Spillane et al., 2000). Standard treatment for localised disease consists of complete surgical resection with or without radiation to reduce the risk of relapse (Livi et al., 2003).

Medical management for locally advanced or metastatic disease remains to be precisely defined but includes palliative systemic therapy. However, due to the rarity of the disease, there have been few published studies on the efficacy of chemotherapy (Casanova et al., 2006; Jones et al., 2012). INI1 loss was first reported in malignant rhabdoid tumours but has since been demonstrated in over 90% of ES therefore improving diagnosis through immunohistochemistry (Biegel et al., 1999; Brenca et al., 2013; Hornick et al., 2009; Modena et al., 2005). INI1 is ubiquitously expressed in the nuclei of all normal cells. *INI1* is a tumour suppressor gene located on chromosome 22 and encodes a subunit of the SWI/SNF complex which regulates genes, the cell cycle and signalling pathways (Wang et al., 2014). Therefore, the loss of INI1 leads to genomic instability, cell cycle progression and abnormal signalling pathway activation, including Hedgehog signalling pathway, permitting tumourgenesis (Jagani et al., 2010; Mora-Blanco et al., 2014). Loss of INI1 permits unopposed activation of EZH2 leading to oncogenic dependency and is consequently a therapeutic target in this disease (Phelan et al., 1999; Wilson et al., 2010).

Recently, the Food and Drug Administration (FDA) has approved tazemetostat, an EZH2 inhibitor, which has demonstrated clinical activity and good tolerability in patients with ES in a phase 2 trial (NCT02601950) and has provided promise in expanding the management options for this rare sarcoma subtype (Gounder et al., 2020). Within the phase 2 tazemetostat basket trial, all patients received the

EZH2 inhibitor, and the objective response rate (ORR) was 15%; 26% had disease control at 32 weeks, and 21% remained progression-free at 1 year. ORR was mainly demonstrated when tazemetostat was used in the first-line setting (25% in the first-line and 8% in second-line and beyond). The drug was well tolerated with the majority of toxicities being grade 1–2 events meaning few patients had dose reductions or discontinuation of the drug. Importantly, tazemetostat did not cause grade 3 or worse toxicity such as nausea, neutropenia or thrombocytopenia, which are often seen with conventional chemotherapies used to manage ES (Gounder et al., 2020). These data have led to a phase 1b/randomised phase 3 trial (NCT04204941). The trial will randomise ES patients to receive doxorubicin plus tazemetostat or single agent doxorubicin.

The response rate identified in retrospective studies for anthracycline- or gemcitabine-based chemotherapy in ES is similar to tazemetostat. An ORR of 15% was documented in a case series of 21 patients with first-line chemotherapy of anthracycline alone or in combination with ifosfamide, and one patient received trabectedin (Jones et al., 2012). A later retrospective multi-institutional analysis by Pink et al. demonstrated responses with the use of gemcitabine in combination with docetaxel regardless of the line of treatment with seven out of 12 patients achieving at least a partial response (PR). One patient achieved PR with second line treatment and subsequently had stable disease for more than 6 months with third-line treatment (Pink et al., 2014). Additionally, an analysis by Touati et al. of patients with ES who were treated with systemic therapy in previous prospective European Organisation for Research and Treatment of Cancer (EORTC) clinical trials demonstrated an ORR of 22.2% with first-line treatment (which included either doxorubicin, doxorubicin and ifosfamide, pazopanib or trabectedin) (Touati et al., 2018). Similarly, a multi-institutional case series analysed 115 patients with advanced or metastatic disease and identified a response rate of 22% with anthracycline-based regimens and 27% with gemcitabine-based regimens (Frezza et al., 2018). The median progression-free survival (PFS) was 6 and 4 months, respectively, which is similar to the study by Jones et al. which demonstrated a median PFS of 7.3 months with first-line chemotherapy which included anthracycline-based regimens (Frezza et al., 2018; Jones et al., 2012).

The recent retrospective multicentre analysis of 74 patients by Gounder et al. provided real-world data on the effectiveness of conventional chemotherapy (Gounder et al., 2021). In this real-world study, the ORR was 14.9% and 9.4% for patients who received first- and second-line treatment and beyond, respectively. Of note, 51.4% of patients experienced a clinically significant adverse event during treatment (Gounder et al., 2021). This study provided a valuable benchmark regarding the activity and safety of chemotherapy schedules in advanced ES. Overall, it is clear that some patients can derive benefit from systemic therapy, but this must be weighed against the potential toxicity of these treatments.

Other treatment options for locally advanced or metastatic ES include pazopanib and vinorelbine. In the study by Frezza et al., the median PFS was 3 months with pazopanib, but there were no radiological responses (Frezza et al., 2018). There have also been reports of benefit with vinorelbine with one patient with metastatic ES achieving a radiological complete response and one patient achieving a PR (Anderson et al., 2006; Tariq et al., 2012). Therefore, vinorelbine could be considered as a relatively well-tolerated systemic therapy option for patients with metastatic disease.

There are also a number of promising therapeutic targets in ES. Certain signalling pathways have been associated with the pathogenesis of ES and hence are possible targets for identifying novel treatments. One study identified that the AKT/mTOR pathway is hyperactivated in cells that are SMARCB1 deficient (Imura et al., 2014). As a consequence, a reduction in cell proliferation was seen when mTOR was silenced using anti-mTOR-specific siRNAs. This led to the investigation of whether everolimus, an mTOR inhibitor, could be of use in ES. However, inhibiting the mTOR pathway with everolimus caused an increase in AKT via c-MET activation. This indicates the need to block multiple pathways with different agents as targeting a single pathway may be insufficient.

Studies have also identified a high level of epidermal growth factor receptor (EGFR) expression in both types of ES (Cascio et al., 2010; Xie et al., 2011). Investigation was carried out to assess the use of erlotinib, a tyrosine kinase inhibitor to EGFR, which demonstrates tumour growth delay. Actual tumour arrest was not demonstrated with erlotinib alone however, and this was due to the mTOR pathway sustaining AKT (Xie et al., 2011). The investigators subsequently investigated the effects of erlotinib combined with mTOR inhibition with rapamycin and demonstrated a significant benefit with blockade of both pathways compared to inhibition of a single pathway.

Dysadherin is a cell membrane glycoprotein that downregulates E-cadherin cell-mediated adhesion and therefore promotes metastasis. Higher levels of dysadherin have been found in cell lines from proximal-type ES compared to distal-type ES and might explain the poorer prognosis associated with proximal-type ES (Izumi et al., 2006). In breast cancer, dysadherin expression promotes the motility of cancer cells via AKT activation and therefore inhibiting AKT reduced cell mobility (Lee et al., 2012). Similarly, studies have identified a complete loss of E-cadherin, another glycoprotein responsible for cell–cell adhesion which also permits metastasis (Sakharpe et al., 2011). Therefore, dysadherin and E-cadherin are potential targets to manage tumour progression in ES.

In conclusion, ES is a rare type of soft tissue sarcoma with heterogeneity in presentation and clinical behaviour. Diagnosis has become easier through loss of expression of INI1; however, optimal management of advanced ES remains difficult with limited response to chemotherapy. Tazemetostat, an EZH2 inhibitor, provides patients with advanced ES a well-tolerated oral systemic therapy. The results of a randomised phase 3 trial comparing doxorubicin to doxorubicin plus tazemetostat are eagerly awaited. Ongoing translational studies from the phase 2 tazemetostat trial will hopefully provide more information regarding the mechanisms of response and resistance. More investigation is required to identify potential novel targets to help optimise management in this extremely rare condition that predominantly affects younger adults.

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CONFLICT OF INTEREST

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Anneke Alves https://orcid.org/0000-0001-9968-3099
Robin L. Jones https://orcid.org/0000-0003-4173-3844

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