Sirolimus for Patients With Progressive Epithelioid Hemangioendothelioma

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In this issue of *Cancer*, Stacchiotti and colleagues present data from a large retrospective cohort of patients with epithelioid hemangioendothelioma (EHE) who were treated with sirolimus.[1] EHE is a rare type of soft tissue sarcoma that was first described in 1982,[2] with the naming representative of intermediate biologic behavior between epithelioid hemangioma and angiosarcoma.[3] Histologically, EHE is characterized by nests and cords of epithelioid endothelial cells in a myxoid matrix.[2,3] Before the identification of pathognomonic gene fusions, the diagnosis of EHE was challenging because of the histologic overlap with the spectrum of epithelioid vascular tumors, from benign epithelioid hemangioma to epithelioid angiosarcoma.[4] The molecular hallmark of EHE is 2 fusions—*WWTR1-CAMTA1*[4] and *TFE3-YAP1*[5]—with CAMTA1 and YAP1 sharing similar protein level functions in the Hippo signaling pathway.[5] The most common is the recurrent chromosomal translocation *WWTR1-CAMTA1* (t[1;3][p36.3;q25]),[4,6] which has been described across multiple EHE primary sites and grades.[4] The *TFE3-YAP1* fusion has been reported primarily in young adults.[5]

Similar to the findings of Stacchiotti et al, published cohorts of patients with EHE are more often women,[3,7,8] and the median age at diagnosis ranges from 44 to 57 years.[3,7,8] EHE can develop in any vascular area but most commonly occurs in the lung (15%-19%),[7,9] liver (28%-34%),[7,9] extremity (13%-65%),[2,3,6,10] head and neck (12%-21%),[2,3,6,10] trunk (8%-23%),[2,3,10] or mediastinum (2%-8%).[2,3,10] Most patients present with metastatic disease.[7,11] For patients with localized disease, complete surgical resection is the mainstay of treatment. A large primary tumor size (>3 cm) and a high mitotic index (>3 mitoses per 50 high-power fields) have been shown to increase the risk of recurrence and mortality in a retrospective cohort.[3] Although there are multiple case series in the literature, it is difficult to estimate the risk of recurrence given the heterogenous clinical behavior of patients with EHE. Across multiple small studies, the risk of recurrence can range from 21% to 58%,[3,6,10,12] with sites of metastasis including lung, liver, bone, chest wall, peritoneum, and lymph nodes.[6,12]

The natural history of EHE is unpredictable, and there is significant patient variation. Behavior ranges from very indolent disease, with rare cases of spontaneous pulmonary regression,[13] to other patients experiencing rapid disease progression.[14] It has been demonstrated that patients with effusions, either pleural or peritoneal, have worse outcomes.[13,15] In a retrospective combined analysis of 75 published cases, pulmonary disease, weight loss, anemia, and pulmonary hemorrhage were correlated with poorer patient outcomes.[15]

There is very limited literature published related to systemic treatment for EHE. Multidisciplinary input is key given the heterogeneous clinical behavior of EHE. Local treatments should be considered for patients who have indolent disease with oligoprogressing sites.[16] There is biologic rationale for antiangiogenic agents with immunohistochemical analysis from a small cohort of patients with pulmonary EHE who demonstrated expression of vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor 2 (VEGFR2), and VEGFR3.[17] However, in retrospective cohorts, mixed efficacy has been reported with antiangiogenic treatments. Sorafenib, thalidomide, and cyclophosphamide have shown limited activity,[11] whereas responses have been reported using celecoxib[7] and pazopanib.[18] Partial responses (PRs) have also been reported with interferon.[7,19] The single published phase 2 trial of 15 patients who had EHE treated with sorafenib reported a nonprogression rate of 38.4% and an overall response rate of 7.7%.[8] A single-arm phase 2 trial of the MEK inhibitor trametinib for patients with unresectable or metastatic EHE is ongoing, with results expected in 2023.[20] The ultrararity of EHE likely precludes any randomized trials, and the evidence backbone for treatment will remain in robust cohort studies.[7] Consequently, the cohort reported by Stacchiotti et al is an important addition to the limited existing literature.

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Building on their single-enter experience,[21] in their current series of 38 patients across 2 Italian sarcoma centers, Stacchiotti and colleagues examine the effect of sirolimus at plasma levels from 15 to 20 ng/dL in patients with progressive EHE. To our knowledge, this is the largest retrospective cohort to date of patients with EHE who received the same systemic therapy. Sirolimus is a natural product originally isolated from *Streptomyces hygroscopicus* from Easter Island.[22] Sirolimus forms part of a complex that directly binds and inhibits the function of mammalian target of rapamycin (mTOR), which has downstream effects, including cell cycle arrest.[22] In vitro studies have demonstrated that YAP/TAZ, the oncogenic fusions of which are the molecular hallmark of EHE, are involved in activation of mTOR complex 1.[23] This provides biologic rationale for the use of sirolimus in EHE.

The authors mandated that patients were required to have clinical or radiologic disease progression according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST) before inclusion in the analysis. It is key that this retrospective cohort focuses on a specific, progressing population. This limits heterogeneity, which, in turn, increases the clinical relevance of the results. This cohort is further strengthened by central pathology review and the inclusion of only fusion-positive (*WWTR1* and/or *TFE3* rearrangements) cases. The majority of patients had lung involvement (76.3%). The age and the predominance of women in the cohort were similar to expected values based on published literature.[3,6-8]

The median progression-free survival (mPFS) was 13 months, and the overall survival (mOS) was 18.8 months for the entire cohort. These results are similar to those from the initial cohort of 18 patients.[21] The authors also report results based on the important prognostic feature of serosal effusion.[13,15] Congruent with the published literature,[13,15] patients without serosal effusions fared significantly better, with an mPFS of 47.8 months (interquartile range, 11.4 months to not evaluated) and an mOS of 47.8 months (interquartile range, 15.7 months to not evaluated), compared with patients who did have serosal effusions (mPFS, 4.8 months; mOS, 10.6 months). Thus the results from the entire population should be interpreted with caution given the differing biologic behaviors observed based on the presence of serosal effusions alone. The extent to which the primary site or location of metastasis, independent of the presence of serosal effusions, affected mPFS and mOS is unknown. Given the heterogeneity across primary sites, location of metastasis, and variable clinical behavior, it is difficult to compare these outcomes with those from other published cohorts of patients who received systemic therapy.

In terms of best response, in patients without serosal effusions at baseline, the clinical benefit rate was 88% (PR, 8%; stable disease [SD], 80%) according to RECIST 1.1, compared with 83.3% (PR, 0%; SD, 83.3%) for patients with serosal effusions at baseline. Although the clinical benefit rates were similar for patients with and without serosal effusions, responses were not sustained in patients with serosal effusion, as demonstrated by their much shorter mPFS. At 12 months, only 2 patients (15.3%) with serosal effusions were progression-free, whereas more than one-half of patients (62.8%) without serosal effusions were progression-free at 24 months. Encouragingly, 4 patients who discontinued sirolimus when they were responsive or stable re-achieved stability with sirolimus re-challenge. This suggests that treatment breaks may be possible for patients who have long-term SD, which has important implications for quality of life. However, one must be cautious of overinterpreting response data without parallel information regarding patient symptoms. On the basis of anecdotal observation of patients with extensive EHE, particularly those with pulmonary involvement, treated at The Royal Marsden Hospital, patients may have clinical disease progression without overt changes on imaging. We hypothesize that the mechanism of this discrepancy is poorly understood but may be related to small vessel changes beyond the resolution of conventional imaging. Thus the true response assessment to systemic therapy for EHE may be determined best by using a combination of disease-related symptoms and imaging rather than based purely on imaging alone. Congruently, the authors rightly highlight that it is challenging to interpret the response in EHE using RECIST 1.1 because the response of serosal effusions is not a part of these criteria, and the development of EHE-specific response criteria is indicated.

A significant number of patients required a dose adjustment (42.1%); however, it is not clear why the adjustment was required, although it is likely a combination of side effects and dose titration to a specific plasma level. Relatively few patients discontinued because of toxicities (7.9%), with reported toxicities overall relatively mild, including mucositis, hypercholesterolemia, neutropenia, and thrombocytopenia. No patients had unexpected or grade 4 and 5 toxicities. Infections were common (21%), with grade 3 infections reported in 3 patients. Notably, a significant number of women had menstrual alterations, the clinical significance of which is uncertain given that this is a population with incurable disease; however, such symptoms may be distressing for these patients.

In total, for this ultrarare sarcoma, the current data represent the best quality evidence to date for use of the mTOR inhibitor sirolimus in multifocal EHE. We agree that sirolimus represents a safe and effective treatment option for patients who have EHE without serosal effusions. Outcomes for patients with serosal effusions remain poor, and further thoughtful, multiinstitutional, retrospective cohort studies as well as prospective trials are needed to understand which systemic therapies may be effective for this more aggressive presentation of EHE. In addition, multiinstitutional partnerships focusing on translational work and clinical studies are critical to developing targeted treatments for this ultrarare sarcoma. This approach has implications and relevance for other ultrarare cancers.

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