

# Two years progression-free survival under vinorelbine metronomic therapy of a patient with metastatic epithelioid hemangioendothelioma

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## Abstract

Epithelioid hemangioendothelioma (EHE) is a very rare vascular tumor, originating from endothelial cells. The etiology of EHE is unknown, yet at the molecular level, different angiogenic stimulators may act as promoters of endothelial cell proliferation. The tumor affects more commonly the lung, the liver and the bones but it can affect any other organ. Due to its heterogeneous

presentation and rarity, it is often misdiagnosed. No treatment is proved to be efficient in metastatic EHE and the median survival of patients with metastatic pleural disease is generally poor, less than one year. We report a case of a 57-year-old female with multiple metastatic EHE including pleural, diagnosed by medical thoracoscopy, with a progression-free survival of 24 months with oral vinorelbine as maintenance therapy after combination of cisplatin-vinorelbine. We believe that this therapy might be of value to test in this patient population as it has never been tested before.

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## Introduction

Epithelioid hemangioendothelioma (EHE) is a very rare vascular tumor with an epithelioid appearance, originating from endothelial cells, first described by Dail and Liebow in 1975 as an aggressive bronchoalveolar cell carcinoma [1,2]. The term of EHE was introduced in 1982, by Weis and Enzinger [3] to describe a vascular tumor of bone and soft tissues showing features of hemangioma and angiosarcoma. EHE is a very rare tumor with a prevalence rate estimated less than one in 1 million [4]. There is a 4:1 female prevalence, mostly middle aged, but pleural EHE is most common in men [5]. The etiology of EHE is still unknown, yet at the molecular level, different angiogenic stimulators may act as promoters of endothelial cell proliferation, such as monocyte chemo-attractant protein-1 [2]. No treatment is proved to be efficient in metastatic EHE and the median survival of patients with metastatic disease is generally poor, less than one year [2]. Herein we report a case of a patient with multimetastatic EHE, with an overall survival after diagnosis of 36 months, of which 24 months with oral vinorelbine as maintenance metronomic therapy.

## Case Report

A 57-year-old female heavy smoker was referred to our hospital with a right-sided pleural effusion. The clinical examination showed absence of normal vesicular sound in the right hemithorax with dullness and a chest CT showed a large pleural effusion on the right hemithorax with mediastinal lymphadenopathy. Diagnostic thoracentesis was performed and the pleural fluid was an exudative serosanguinous fluid with 80% lymphocytes with negative pleural cytology.

The day after admission we proceeded to medical thoracoscopy under local anaesthesia in order to explore the pleural cavity and to take biopsies. Macroscopically we observed the presence of multiple metastatic nodules with lymphangitis on visceral, parietal and

diaphragmatic pleura (Figure 1A). Microscopic examination (Figure 1B) revealed moderately atypical epithelioid cells with eosinophilic cytoplasm arranged in cords staining for vascular immunohistochemical factors and harboring the *WWTR1*□*CAMTA1* gene fusion confirming the diagnosis of EHE. The patient then underwent a workup for staging the disease, which included a new chest computed tomography after thoracoscopy (free of pleural fluid), bronchoscopy, cranial, abdominal and pelvis computed tomography and bone scan. Multiple metastatic sites were found, such as lung, liver (Figure 1C), and bones (Figure 1D). The patient's ECOG performance status (ps) was at the time 1.

As the patient declined initially chemotherapy, we initiated pazopanib, a tyrosine kinase inhibitor, in the standard dose of 800mg orally once daily, for 4 months. Due to liver toxicity associated to significant fatigue and progressive disease with PS degradation, we had to discontinue pazopanib and we decided to start chemotherapy with cisplatin (80 mg/m<sup>2</sup>, d1) and vinorelbine (30 mg/m<sup>2</sup>, d1,8) for 6 cycles every 21 days. The patient showed stable disease (SD), after 3 cycles. However, due to grade 3 hematological, renal and gastrointestinal toxicity, we were forced to stop this regimen after the completion of the 4<sup>th</sup> cycle and continue with vinorelbine per os as maintenance metronomic therapy 40 mg every second day. Since, the patient is alive with SD, 29 months after the start of cisplatin-vinorelbine, 24 of these months with metronomic oral vinorelbine therapy showing no further toxicity. Her overall survival from diagnosis is 36 months.

## Discussion

Our patient was diagnosed with pleural disease, which is considered of poor prognosis for this tumor compared to the patients without pleural disease [5]. Anderson and collaborators [6] confirmed diagnosis of EHE in 27 out of 30 (90%) tumors showing the

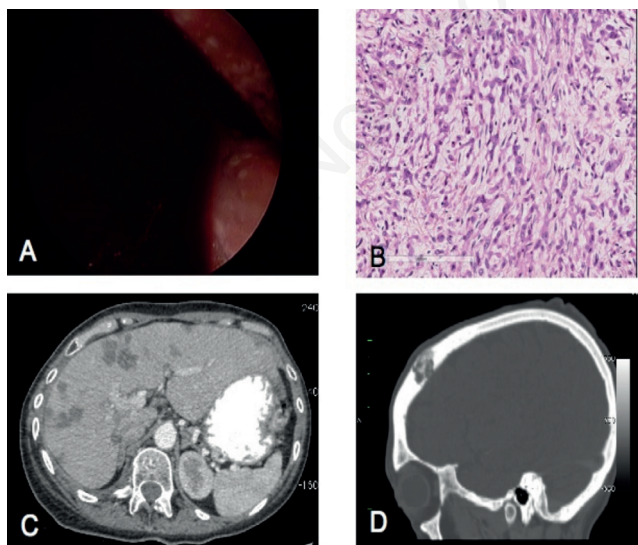
*WWTR1*□*CAMTA1* gene fusion, as was the case of our patient, and in patients with pleural metastasis the 3-year survival was poor (16%-24%). Lin *et al.* [7] described six pleural EHE rapidly progressive and fatal in all cases. In his cohort of seventeen patients treated by sirolimus, an mTOR inhibitor, Stachiotti and collaborators [8] noted that pleural disease had a much worse PFS (4.5 months) and survival (7.7 months) comparing to the non-pleural patients [8]. Our patient had also other metastatic sites such as lung, bones and liver, and yet a significant prolonged survival was observed with metronomic vinorelbine therapy used as maintenance therapy.

EHE is categorized as a malignant vascular neoplasm, and as such, pro-angiogenic factors are believed to promote the growth of these vascular tumors [9]. Therefore, angiogenesis inhibition is a reasonable approach to manage patients with metastatic EHE [10], as was the case of our patient. Pazopanib is a synthetic indazolyl pyrimidine multitarget tyrosine kinase inhibitor (TKI) against VEGFR-1/2/3. Pazopanib was approved for the treatment of soft tissue sarcomas after showing improved PFS vs placebo in a phase III trial (PALETTE) [11]. However, in our case it did not prove to be efficient and at the same time our patient presented with grade 3 hepatotoxicity and fatigue, which are classic adverse effects together with diarrhea, nausea, weight loss and hypertension [11].

Many chemotherapeutic agents have been tested for pleural cases of EHE, yet showing overall results of survival less than one year in patients with metastatic EHE [12]. Our patient was treated with a combination of cisplatin and vinorelbine after failing to pazopanib. She presented SD after 3 cycles, but continuation was compromised due to hematological, renal and gastrointestinal toxicity after the 4<sup>th</sup> cycle. We then decided to further continue with metronomic vinorelbine oral therapy with success. This is the first report of a patient with EHE treated by vinorelbine metronomic therapy.

Metronomic therapy stands in the antipode of classic systemic chemotherapy [13], referring to dense uninterrupted administration of sub-toxic doses of chemotherapy over protracted periods of time, with no prolonged drug-free intervals, with the aim of altering the tumor microenvironment by inhibiting tumor supporting vasculature (angiogenesis) [14], inducing tumor dormancy, restoring immune surveillance [13]. It has the advantage to gently treat low ps patients at risk for severe toxicity as was the case of our patient [15]. Vinorelbine, a semi-synthetic vinca-alkaloid, has an oral formulation and a good safety profile and therefore, it is a good candidate for metronomic therapy [14]. Briasoulis *et al.* [16] assigned seventy patients with recurrent solid tumors, for metronomic vinorelbine in a dose selection randomized trial comparing 50 to 40 and to 30 mg every second day, with the primary end point the time to treatment failure (TTF). The median TTF in all three arms was 8 weeks with no significant difference between the three groups after 6 months. The side effects observed were mild [16]. In a recent individual data meta-analysis from different European centers treating NSCLC with metronomic oral vinorelbine higher than 30 mg, Pujol and collaborators [17] included 418 patients with advanced NSCLC. Most of the patients were old (73 years), ECOG 2 (43%), with adenocarcinoma (48.8%). Median OS was 8.7 months, with OS rates at 6 months, one-year and at two years being 64%, 30.3% and 8.9%, respectively. Median PFS was 4.2 months with rates at 6 months and at one year after treatment initiation, set at 35% and 11.9%, respectively. Forty percent of the patients experienced no toxicity at all. The authors concluded that metronomic oral vinorelbine was an active and well-tolerated regimen in frail patients with metastatic NSCLC [17].

To conclude, our patient with EHE and multiple organ involve-



1. A) Thoracoscopy view of our patient with EHE: bloody effusion with multiple nodules and lymphangitic spread of the pleura. B) Microscopic examination of the patient's pleural biopsy revealed epithelioid tumor cells with abundant eosinophilic cytoplasm arranged in cords inside a loose connective stroma. C) Metastases of the liver and (D) of the skull on computed tomography.

ment is actually stable for more than two years after second line combination of cisplatin-vinorelbine followed by metronomic oral vinorelbine as maintenance therapy. We believe that this therapy might be of value to test in this patient population.

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