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COBIMETINIB FOR TREATING PATIENTS WITH BRAF WILD-TYPE ERDHEIM-CHESTERDISEASE

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ABSTRACT

Erdheim-Chester disease (ECD) is a non-Langerhans histiocytosis that usually affects adults between the fourth and seventh decade of life. Its clinical presentation can vary, the main symptom being bone pain, predominantly in the diaphysis and metaphysis of the long bones; it can even compromise the patient's general condition due to massive multisystemic infiltration. The etiology is still unknown, but is associated with a TH1 type immune response. It is diagnosed using immunohistochemistry based on characteristic markers including S100(+/-), CD68(+) and CD1a (-). The 5-year survival rate is estimated to be just 68%. Mutations activating the MAPK pathway are described in 80% of patients, the most frequent being the BRAFV600E mutation (57% to 70%) of cases, followed by the MAP2K1 mutation (20%). Currently, this disease represents a challenge in terms of both diagnosis and treatment due to the scarce options available to adequately control the disease. Interferon-α is the most commonly used first-line treatment, with cladribine (2CDA), anakinra and vemurafenib recommended as second-line treatments. We present the experience of four patients in our center who were diagnosed with ECD without BRAF mutation and treated due to progression with cobimetinib, a protein kinase 1 inhibitor that inhibits the catalytic activity of MEK1, thereby inhibiting phosphorylation and activating extracellular signal-related kinase 2 (ERK2) while decreasing the proliferation of tumor cells. In our case series, the median response time to cobimetinib was 4.5 months, with all patients achieving at least a partial response. The median treatment duration was 50 months, with a median overall survival of 72.5 months. The most frequent toxicity reported was a skin rash, which occurred in 75% of patients. Cobimetinib may therefore be a viable treatment option in ECD without BRAF mutation, where therapeutic options are scarce and low response rates are achieved.

KEYWORDS: Erdheim Chester disease, histiocytosis, bone pain, targeted therapy, MAPK pathway, BRAFV600E, cobimetinib.

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis by characterized by lipid deposits and CD68p+, CD1a- and S100- histiocytes leading to the disruption of physiological tissue architecture and reactive fibrosis, and thus impairing organ function. Recently ECD was recognized as an inflammatory myeloid neoplasia associated with oncogenic mutations of the kinase signaling pathway including BRAF, NRAS, KRAS, MAP2K1, and PIK3CA in histiocytes.Recent studies have demonstrated that more than 50% cases involve BRAFV600E mutations.[1]

The clinical presentation can vary, from symmetrically distributed sclerosing bone involvement, predominantly in the diaphyses and metaphyses of long bones, to a generalized form with multi- organ involvement and a worse prognosis.[2-3] The disease can infiltrate different organs and particularly affects the CNS. The prognosis depends on the extent and distribution of the disease. It can appear at any age and seems to be slightly more predominant in males; the majority of patients are diagnosed between the ages of 40 and 70 years.[3-4]

The etiology and pathogenesis of ECD is not entirely clear, it is believed that it may be associated with an intense Thelper1 (Th1) immune response. The high levels of IFN-alpha, interleukin-7, interleukin-12, monocyte chemoattractant protein-1, and reduced concentrations of interleukin- 4 found in ECD patients may explain the associated intense systemic TH-1 immune response.[5]

Formerly, there was no effective treatment against this disease; however, given the characteristics of the disease and the variability of symptoms, a number of treatment options are offered, including IFN-alpha, chemotherapy such as Cladribine and Anakinra (IL-1 receptor antagonist), bisphosphonates and, in specific cases, radiotherapy.[5,6]

Second- and third-line treatment with BRAF inhibitors such as vemurafenib is promising in selected patients with the BRAF-V600 mutation. This has paved the way for targeted therapies.[7-8]

We report the excellent response to targeted therapies in our cohort of patients diagnosed with BRAF wild type (BRAF-wt) ECD.

MATERIALS AND METHODS

Study population

This was a descriptive retrospective study that included six patients suffering ECD with systemic involvement, between January 2013 and February 2023 at Virgen del Rocío University Hospital (Seville, Spain). Four of the patients had BRAF-wt ECD and they received cobimetinib as amonotherapy at 40 mg/day (20 mg twice a day) for 21 days in a 28-day cycle.

Clinical data, characteristics, treatment received, and follow-up data were obtained from electronic health records: computerized clinical history (Diraya) and pharmacy records (HUVR) specific for oncological treatments in Farmis-Oncofarm 3.0® (V.11.38), which collates the systemic treatments received by patients. The BRAF-wt status was determined by PCR.

The data collected from the patients included their age at diagnosis, histological subtype, BRAF expression, systemic involvement, and the different lines of treatment received. Further patient characteristics were also collected [Table 1].

Statistical analysis

Descriptive statistics were used to analyze the general characteristics of the patients and the response or toxicity presented with the treatment. All the statistical analyses were performed using SPPS 26.0 (Statistical Package for the Social Sciences).

Approval by the ethics committee and informed consent

This research was carried out in accordance with Regulation (EU) 2016/679 on the protection of natural persons with respect to the processing of personal data and on the free movement of such data and Organic Law 3/2018 of 5 December, on the protection of personal data and guarantee of digital rights. All identifying information was removed from the dataset prior to analysis. All the patients signed the informed consent (available as supplementary material).

RESULTS

In our case series, 66.7% (4/6) of patients were male and 33.3% were female and the mean age at diagnosis was 50 years (range 22-60 years). The most frequent presentations at diagnosis wereretroperitoneal fibrosis, lymph node disease and perivascular fibrosis (mainly aortic).

All patients in the BRAF-wt population (4/6 patients) had multiorgan involvement. Bone involvement was present in 100% of patients, 25% had lung involvement, in addition to cutaneous, perivascular and cardiac involvement. 75% of patients developed disease at the lymph node level.

Of the BRAF-wt patients, only one required three lines of treatment while three of these patients received two lines of treatment, the last being cobimetinib at the time of data collection. The first line of treatment was INF-α, with progression-free survival (PFS) of 18 months (range 11-40 months), with treatment interruptions due to associated toxicity. One patient received vincristine and another was given high-dose corticosteroids.

The median cobimetinib treatment duration was 50 months (range 12-56 months) with a medianresponse time of 4.5 months (range 3-7 months); all patients had at least a partial response (according to RECIST 1.1 criteria) [Table 1]. The median survival from diagnosis of these patients was 72.5 months (range 19-104 months), with two patients dying due to disease progression.

Table 1: Clinical expression of ECD at diagnosis and response to cobimetinib treatment of our patients.

	Patient 1 At diagnosis	Patient 1 After treatment	Patient 2 At diagnosis	Patient 2 After treatment	Patient 3 At	Patient 3 After diagnosis treatment	Patient 4 At diagnosis	Patient 4 After treatment
Retroperitoneal fibrosis	+	-	+	+	-	-	-	-
Skeletal involvement	+	+	+	+	+	+	+	+
Skin involvement	+	-	-	-	-	-	-	-
Lung involvement	+	-	-	-	-	-	-	-
Lymph node involvement	-	-	+	-	+	-	+	+
Cardiac involvement	-	-	-	-	+	-	-	-
Thoracic aorta involvement	-	-	-	-	+	-	-	-

The most frequent toxicity reported with cobimetinib was skin rash in 75% of the patients, in only one case this was grade 3, which was resolved by discontinuing the drug for two weeks, followedby reintroduction with a one-step dose

according to the technical data sheet. 50% of the patients presented grade 1 or grade 2 asthenia and 25% presented grade 1 arthralgia. [Table 2]

Table 2: Toxicity associated with cobimetinib treatment.

	Patient 1	Patient 2	Patient 3	Patient 4
Rash	Grade 1	Grade 3 (resolved)	Grade 1	-
Impaired kidneyfunction	-	-	-	-
Asthenia	-	-	Grade 2	Grade 1
Arthralgia	-	-	Grade 1	-

DISCUSSION

Patients with ECD usually need their treatment to be initiated at the time they are diagnosed, except in exceptional asymptomatic cases or those whose only expression is in bone. Historically, these patients have been treated with IFN-alpha, with a response rate of 50-80% at the cardiac or central nervous system level–although high doses were required[9-12] with a response rate of 20% at other disease sites.[9,10] The elevated doses required to obtain a response wereassociated with a high incidence of side effects including cytopenia, asthenia and flu-like syndrome, among other issues.[9-12] For this reason, this treatment is currently used only if no other therapy is available.

Other ECD treatments that were available prior to the development of targeted therapies consisted of cytotoxic chemotherapy, such as cyclophosphamide, high-dose methotrexate or vinblastine, recommended on the basis of case series[13-15] with response rates similar to IFN- alpha but with a higher rate of cytopenia. Cases of treatment involving autologous hematopoietic transplantation were also reported.[16]

Until the emergence of targeted therapies, patients with ECD had a poor prognosis and their quality of life was significantly impaired. In a molecular study of samples from ECD sufferers, somatic mutations were identified in the mitogen-activated protein kinase (MAPK) pathway, the most frequent being the BRAF V600E mutation, present in approximately 50% of patients. This increases cell proliferation and prevents cellular senescence by activating RAS, RAF, MEK and the MAPK signaling pathway.[17-18]

The use of targeted ECD therapies began with the FDA approval of treatment with vemurafenib. This drug, known for its use in BRAF-mutated metastatic melanoma, was used in ECD in the VE Basket trial. This trial included twenty-two ECD sufferers with the BRAF V600E mutation who had progressed to IFN-alpha treatment, with a response rate of 54.5% and a median response time ofeleven months, although its main advantage was the significant clinical response, functional improvement and improved patient quality of life.[19] Subsequent studies on treatment with vemurafenib proposed discontinuing treatment in "long-responders" (results from twenty patients in the LOVE study), with a relapse rate of 75% after six months of follow-up; ten patients were re-treated with vemurafenib and all of them showed a clinical and radiological response.[20]

However, in ECD patients with BRAF-wt there was no evidence of targeted therapies being effective for controlling the disease. The first reference to cobimetinib treatment at progression to IFN-alpha in BRAF-wt patients was published by Cohen Aubart et al.[21], involving a series of three cases, all of which presented a partial response confirmed by FDG PET. However, the treatment duration was short (eight, seven and one months, respectively), so that long-term results were not available, and its validity as a treatment could not be assured.

The LOVE study[20] included twelve BRAF-wt patients of whom eight received cobimetinib together with a BRAF inhibitor; a partial response was obtained in 62.5% of patients at six months while 37.5% had a complete response. The remaining four patients in that study received cobimetinib as monotherapy; 50% presented a partial response and 50% a complete response. However, it is noteworthy that the median treatment duration in the patients who received cobimetinib was 5.5 months (range 0.1-14 months). This last result contrasts strikingly with those in our case series, where the median duration of treatment, while maintaining a clinical and radiological response, was much longer. Toxicity in patients receiving cobimetinib was similar to that reported in our series.

Other treatment options have been proposed for patients with refractory ECD. mTOR inhibitors such as sirolimus were tested together with prednisone in a phase II trial involving 10 patients who expressed by immunohistochemistry histiocytes with phosphorylated forms of the mTOR pathway, with a response rate of 80% at at least one disease site, with a 62.5% response at the retroperitoneal level and 33.3% in bone.[22] The results of a phase II trial with tocilizumab (monoclonal antibody against the IL-6 receptor) administered to three ECD sufferers for whom the use of IFN-alpha was contraindicated or who had progressed to IFN-alpha, were also published.[23] The response at the cardiac level, which is rare with other treatments, was notable, as it was at other disease sites, such as at the retroperitoneal level, although there was progression at the central nervous system level. It should be noted that, although it was not an inclusion criterion, all three of those patients had the BRAF mutation. This implies the activation of oncogenes to prevent senescence, a mechanism characterized by the secretion of cytokines such as IL-6, so its efficacy cannot be extrapolated to BRAF-wt patients.[24]

CONCLUSIONS

The low incidence of ECD makes it difficult to perform clinical trials of drugs for treating these patients, especially in the absence of known driver mutations. The favorable results using cobimetinib treatment in patients with BRAF-wt ECD in our series of patients, who underwent a long treatment and follow-up period, is therefore an important step in the management of thesepatients and provides further insight into their evolution. However, the absence of therapies for successive treatment lines continues to pose a therapeutic challenge.

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