EXPERT OPINION

Strategies and treatment alternatives in the management of Erdheim–Chester disease

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Introduction: The treatment of Erdheim–Chester disease (ECD) remains a challenging task. Current opinion corroborates interferon-α as the first-line treatment. Several second-line treatments exist for patients who advance on or who do not tolerate interferon-α. Among them are vemurafenib, anakinra, infliximab and cladribine.

Areas covered: A systematic search of PubMed was employed to identify all the articles relating to the treatment of ECD. The quintessential facts are as follows: Interferon-α increases survival among ECD patients at dosages of as low as 3×10^6 IU × 3/week. Nevertheless, the more resilient cardiovascular and central nervous system (CNS) disease foci necessitate dosage regimens of as high as 9×10^6 IU × 3/week. Anakinra, administered at dosages of 1 – 2 mg/kg/day, should be reserved for patients with mild disease. Infliximab, administered at a dosage of 5 mg/kg/6 weeks induced regression of ECD-related cardiovascular lesions. Vemurafenib, administered at a dosage of 960 mg/day, induced remarkable improvement in the symptoms, CRP levels and PET findings of patients harboring the V600E BRAF mutation. Cladribine may be effective administered at dosages of 0.07 – 0.14 mg/kg/day for five consecutive days. However, it should be reserved for patients with moderate–to-severe disease who failed on or who are not candidates for other second-line treatments.

Expert opinion: Recent advancements in the recognition of biological targets imbued the therapeutic repertoire of ECD with novel personally tailored treatments. As the zealous hunt for future remedies persists, one must always remember that the success of an ongoing treatment is congruent with an assured, well-informed patient.

Keywords: anakinra, cladribine, Erdheim–Chester, infliximab, interferon-α, vemurafenib

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1. Introduction

Erdheim–Chester disease (ECD) is an orphan histiocytic disorder characterized by the infiltration of CD68(+), CD1a(–) histiocytes to various target foci. Only several hundred cases had been reported in the medical literature since its initial description in 1930. ECD affects mainly adults in their fifth through seventh decades of life [1]. Progression of this adamant disease may ultimately result in accumulation of histiocytes in multiple organ systems and consequently impair their function. Organ systems that are frequently involved in ECD are the skeletal system, central nervous system (CNS) and the cardiovascular system as well as the lungs, kidneys and skin [2]. The vast majority of patients are diagnosed with a multisystemic disease [3]. Thus, both a meticulous surveillance program and a multifacet treatment strategy are needed in order to improve the patients' prognosis. Treatment of ECD consists of several fundamental elements. First and foremost, the treatment should aim at

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Article highlights.

- Interferon-α improves survival and is considered to be the first-line treatment in ECD.
- Vemurafenib is an efficacious second line treatment in ECD patients whose histiocytes contain the V600E BRAF mutation.
- Anakinra is reserved as a second-line treatment for ECD patients with mild disease, with no CNS or cardiovascular disease foci.
- Cladribine is a plausible second-/third-line treatment for ECD patients with moderate to severe disease.
- ECD patients treated with corticosteroids may benefit from a transient relief of related symptoms and should used mainly for control of disease flare-ups.
- Radiation therapy may palliate ECD lesions associated bone pain.
- Bisphosphonates decrease bone associated pain and normalize born turnover markers in ECD patients.

This box summarizes key points contained in the article.

generating an objective global response, causing regression of ECD-related lesions from multiple anatomical sites and resolution of related symptoms. However, complete response in ECD is a rare phenomenon, as most patients experience either a partial response, stabilization of their disease or even disease progression on treatment. Local interventions should be attempted as a salvage strategy, in order to preserve potentially compromised organ function. Such are the cases of ureteral stenting due to postrenal obstruction caused by the retroperitoneal involvement of ECD or pericardiocentesis due to ECD-related pericardial effusion. Second, since most patients require long-term treatment, the patients' tolerance to the treatment should be a prime consideration in the formulation of a therapeutic program. Several therapeutic alternatives have been proposed for the treatment of ECD (**Table 1**). It should be noted that these treatments are given without a license for the indication of ECD. Current consensus refers to interferon-α as the agent of choice in the first line treatment of ECD. It appears to facilitate long-term stabilization of the disease in a fair share of the cases [3-5]. Prior to the acceptance of interferon-α, corticosteroids were used for the treatment of ECD. However, this strategy produced transient relief at best for the majority of patients [3,4,6]. Attempts at treating ECD patients involved various cytotoxic agents [6-9], out of which cladribine was considered to be the most promising [9-13]. Other strategies include radiotherapy [4], bisphosphonates [14-16], surgical debulking [17] and hematopoietic stem cell transplantation [18]. Another approach to the treatment of ECD consists mainly of personally tailored targeted therapy. Attempts to inhibit the platelet-derived growth factor (PDGF) signaling pathway in patients with ECD lesions expressing PDGFR-α or PDGFR-β were made [19-21]. However, this approach failed to produce favorable responses. A second attempt focused on inhibiting the interleukin-1 (IL-1) signaling pathway in ECD patients with normal to elevated levels of serum IL-1β [22-25]. This attempt resulted in rather promising results. Latest publications advocate the role of the different pro-inflammatory cytokines in ECD [22,23,26,27]. For example, tumor necrosis factor α (TNFα) plays a pivotal role in the regulation of the pathological processes in ECD [28] and considered a potential therapeutic target. The inhibition of another proinflammatory cytokine, IL-6, is hypothesized to produce a favorable response as well [16,29]. Recent studies accomplished in identifying the BRAF V600E mutation among ECD patients [30-32], leading to treatment attempts with the BRAF inhibitor vemurafenib [33,34]. Pursuant our clinicopathological review of the literature [35], we survey herein the different treatment modalities for ECD.

2. Interferon-α and peginterferon alfa-2a

Interferon-α is an antiviral, antiproliferative, immunoregulatory agent prescribed for the treatment of hairy cell leukemia among other conditions. Peginterferon alfa-2a is a pegylated form of interferon-α, with a prolonged half-life of 80 h as opposed to simple interferon-α which is characterized by a half-life of 3.7 – 8.5 h. Peginterferon alfa-2a should be attempted if the patient does not tolerate interferon-α. Currently interferon-α is considered the most efficacious agent in the management of ECD. It is recommended as the first-line therapy for ECD by numerous recent studies [3,5,36]. Several mechanisms of action have been proposed to explain this agent's action in ECD. First, interferon-α promotes the maturation of dendritic cells and enhances their differentiation by augmenting CD40-ligand-induced cytokine secretion [37,38]. Second, interferon-α is hypothesized to promote immune-mediated killing of histiocytes by natural killer cells [4]. Third, interferon-α exerts direct antiproliferative effects due to protein kinase C down-regulation [39]. Fourth, interferon-α increases both molecular transcription and secretion of IL-1 receptor antagonist, thus decreasing IL-1 signaling [22]. The efficacy of interferon-α varies in concordance with the different sites of disease involvement. ECD skin lesions respond well to high dose (interferon-α: 6 – 9 × 10^6 IU/3 times a week or peginterferon alfa-2a: > 180 μg/week) treatment [40]. ECD-related cardiovascular and CNS manifestations seem to be more resistant to interferon-α [5] and require high-dose treatment with hope to elicit a response [3,40]. Pulmonary involvement was reported to respond poorly to interferon-α [21]. Considerable long-lasting regression of lesions of the skeleton and retro-orbital space was evident in another report of three patients treated with interferon-α [4]. According to accumulated experience of the leading ECD centers of excellence in the world, treatment should be initiated at 3 × 10^6 IU three times a week. Prolongation of survival can be achieved at 3 × 10^6 IU three times a week [3]. When cardiovascular and/or CNS manifestations are apparent, or when the lesions progress despite

Table 1. Therapeutic alternatives for Erdheim Chester disease.

	Agent/modality (Dosage)	Adverse effects	Comments	Refs.
First-line treatments	Interferon-α (3 – 9 × 10^6 IU, 3 times a week) Peginterferon alfa-2a (135 – 200 μg/week)	Asthenia, myalgia, pruritus, neutropenia thrombocytopenia, depression*	Improves survival, however, CV/ CNS localizations require high-dose regimens	[3,40]
Second/third-line treatments	Anakinra (1 – 2 mg/kg/day)	Injection site reaction‡	Suitable for mild disease with no CV/ CNS involvement	[22-24]
	Infliximab (5 mg/kg/6 weeks) + Methotrexate (20 mg/week)	Well-tolerated treatment	Treatment seems effective in controlling CV localizations	[28]
	Vemurafenib (960 – 1920 mg/day)§	Erythema, pruritus, pilar keratosis	Effective treatment in patients harboring the V600E BRAF mutation	[33]
	Cladribine (0.07 – 0.14 mg/kg/day for 5 consecutive days)	Immune suppression, optic nerve toxicity	Suitable for patients with moderate – severe disease, especially with CNS localizations, who are not suitable for other advanced line treatments	[9-12]
Salvage treatments	Vinblastine (5 – 6 mg/m^2/w) OR Vincristine (1.5 mg/m^2/w) OR Cyclophosphamide (1000 mg/m^2/w) OR Doxorubicin (15 – 25 mg/m^2/ 2 weeks)	Chemotherapy-related adverse effects: anemia, neutropenia, alopecia, nausea and vomiting	Chemotherapy should be considered as a salvage therapy in the treatment of ECD	[6]
Palliative treatments	Prednisone¶ (0.5 – 1 mg/kg/d)		Steroids should be used in cases of severe exophthalmos or in order to provide transient control of disease flare-ups	[6]
	Zoledronic acid (4 mg, once per year) OR Pamidronic acid (60 mg every 1 – 3 months) OR Alendronic acid (70 mg, per week)		Bisphosphonates may contribute to the reduction of bone pain in ECD	[14-16]
	Radiation therapy (10 – 35 Gy)		Radiotherapy enables limited, short-term palliation of osseous ECD symptoms	[6]
Other	High dose chemotherapy followed by autologous Stem cell transplantation	Central venous catheter infections	Selected ECD cases who exhibit craniofacial and/or space-occupying brainstem lesions may benefit from this modality	[18,46]

*Treatment with peginterferon alfa-2a is associated with milder adverse effects in comparison to interferon-α.

‡Treatment with anakinra is usually well tolerated.

§Originally, the initial dosage was 1920 mg/day which was later tapered to 960 mg/day due to cutaneous toxicity.

¶Or any other equivalent steroid.

CNS: Central nervous system; CV: Cardiovascular; Gy: Gray; IU: International Unit.

treatment with the regular doses a dosage of 9×10^6 IU three times a week is considered. In a recent comprehensive study performed by Arnaud *et al.* [3], analysis of 53 ECD patients revealed no significant difference in survival between patients receiving regular doses and patients receiving high doses of interferon-α. Thus, they concluded that either regular doses suffice for the average patient, or that high doses are mandatory to improve the prognosis of patients with severe disease [3]. In any case, the patient's tolerance to treatment is a pivotal determinant in the process of tailoring a treatment plan. Most interestingly, while hairy cell leukemia patients tolerate a dosage of 3×10^6 IU three times a week very well, ECD patients seem to tolerate this dosage very poorly. Dosage of peginterferon alfa-2a varies between 135 and 200 μg per week [3]. Among the different adverse effects associated with interferon-α are asthenia, myalgia, pruritus, thrombocytopenia, depression [40] and neutropenia. Although durable responses have been noted, cessation of treatment usually results in disease recurrence.

3. Corticosteroids

Corticosteroids such as prednisone are usually prescribed for the treatment adrenocortical insufficiency, conditions which require immunosuppression and inflammatory conditions among others. Corticosteroids such as prednisone have been administered at dosages of 0.5 – 1 mg/kg/d for the treatment of ECD. This treatment strategy aims at better controlling the symptoms of the disease. One unusual patient had dramatic improvement of his disease with total disappearance of pulmonary lesions while treated with corticosteroids, as opposed to numerous other patients with pulmonary ECD who did not benefit from this treatment [21]. A recent study by Arnaud *et al.* [3] found no significant difference in survival between patients treated with corticosteroids as opposed to those who did not receive such therapy [3]. In summary, accumulated clinical experience proves steroids to have either transient or no effect in the settings of ECD [3,4,6].

4. Cladribine

Cladribine is a purine analogue that impairs DNA repair. It is used primarily for the treatment of hairy cell leukemia. Cladribine is known to be toxic to monocytes and delete both resting and dividing lymphocytes. Because of that, cladribine is considered to be a potent immunosuppressor and although used for the treatment of ECD, some specialists refrain from administering > 3 – 4 courses of this treatment. Cladribine is given at dosages of 0.07 – 0.14 mg/kg/day for five consecutive days. In one case report, an ECD patient was treated with cladribine at a dosage of 0.14 mg/kg/day for five consecutive days due to evidence of increased monocytic activation [9]. The patient exhibited significant recovery and maintained clinical improvement following treatment. Another report described the disappearance of ECD infiltration of the pituitary stalk on MR imaging after four cycles of cladribine, administered at a dosage of 5 mg/m^2 for five consecutive days [11]. It is important to note that in past reports cladribine was found to cause blindness, both transient, and permanent in a different ECD patient with orbital disease [13]. Cladribine is postulated to cause toxic injury to the optic nerves. Thus, if treatment with cladribine is initiated, close monitoring of the degree of exophtahlmos and optic nerve compression as well as close ophthalmological surveillance are absolutely mandatory. In summary, cladribine should be reserved for patients with moderate-to-severe disease with CNS localizations, who are not candidates for vemurafenib or for patients who failed on other second-line treatment modalities.

5. Other cytotoxic agents and combination therapy

Vinca alkaloids, such as vincristine and vinblastine, inhibit microtubule formation. Cyclophosphamide cross-links DNA and interferes with malignant cell growth. Doxorubicin intercalates between DNA base pairs and inhibits the activity of the enzyme topoisomerase II – thus interfering with DNA replication and transcription. These drugs are used mainly for the treatment of various types of cancer. Treatment on the basis of vinca alkaloids was originally proposed by analogy with the first-line treatment in Langerhans cell histiocytosis [41].

Veyssier-Belot *et al.* [6] report the treatment of four ECD cases with combination therapy involving the drugs above, resulting in improvement of their clinical status. Vinblastine was administered at a dose of 5 – 6 mg/m^2/w, Vincristine at 1.5 mg/m^2/w, cyclophosphamide at 1000 mg/m^2/w and doxorubicin at 15 – 25 mg/m^2/2w. Treatment resulted in reduction of the retroperitoneal involvement, improvement in exophtahlmos and partial mediastinal responses. Four other patients treated with chemotherapy gained no benefit and did not respond to the treatment. In some cases, chemotherapy was accompanied by either steroids or interferon-α, generating difficulty in assessing their sole contribution to the course of the disease [6]. Another report enumerates two cases of ECD who responded to treatment with vinblastine (6 mg/m^2/w) and mycophenolate mofetil (1500 mg/d) [7]. Etoposide is known to be effective for the treatment of neoplastic cells of monocytic lineage [8] and is discussed in this article in the context of hematopoietic stem cell transplantation. In respect to combination therapy, one report elaborates on an ECD patient treated with the lymphoma designed VNCOP-B regimen, with satisfactory response and tolerance. The patient experienced regression of orbital disease and significant improvement in vision [8]. In summary, chemotherapy should be considered in the treatment of ECD only pursuant to the failure of several more established treatment lines, namely interferon-α, vemurafenib, anakinra, infliximab and cladribine.

6. Radiation therapy

Veyssier-Belot *et al.* [6] report six patients treated with radiation. Three patients underwent bone irradiation (15 Gy), which provided transient relief in bone pain and the other three patients underwent retro-orbital irradiation (35 Gy) which had no effect [6]. Radiation therapy was also found to be ineffective in a case of intracranial ECD [42]. As for the skeleton, one report elaborates on an ECD patient with osseous involvement only, who was treated with external beam radiation therapy. The treatment provided an analgesic effect that lasted for a single year [43]. In another study, the application of radiation therapy was researched in nine ECD patients. Treatments were administered at doses of 10 – 25 Gy. The different sites of treatment included bone, brain and retro-orbital lesions. The bone lesions of six patients proved to be radiosensitive at first and palliation was achieved for a period of up to 1 year at the highest dose. Brain lesions were found to progress 2 months following treatment in two patients. One patient was treated for retro-orbital involvement with mild (25%) reduction of the lesions. Non durable improvement was seen in all patients [44]. In summary, radiotherapy enables limited, short term palliation of osseous ECD symptoms.

7. Bisphosphonates

Bisphosphonates are calcium metabolism modifiers which inhibit bone resorption by blocking the action of osteoclasts. This trait makes them useful for treating bone disorders such as osteoporosis, Paget's disease and malignant hypercalcemia. They are also used for the treatment of osteolytic lesions in Langerhans' cell histiocytosis. Bisphosphonates were proposed for the treatment of ECD. In one report, zoledronic acid was administered to an ECD patient who suffered from bone involvement only. This patient suffered from bilateral knee pain and swelling which completely resolved after a single dose of zoledronic acid (4 mg IV). The clinical effectiveness was maintained for 1 year. The patient subsequently received two additional doses of zoledronic acid in 1-year interval for maintenance purposes and remained symptom free 3 years after the initial presentation [14]. In another report, an ECD patient with skeletal involvement who presented with mild knee and leg pain was treated with alendronic acid at a dosage of 70 mg/week. After 9 months, the treatment resulted in normalization of bone turnover markers. However in that case, imaging studies showed that the bone lesions shifted from sclerotic to lytic lesions [15]. Finally, an additional report describes an ECD patient treated with prednisone and clodronate who responded with a reduction in bone turnover markers, serum IL-6 and IL-6 soluble receptor [16]. In summary, bisphosphonates may contribute to the reduction of bone pain and to the management of the skeletal involvement in ECD.

8. Imatinib mesylate

Imatinib mesylate is a BCR–ABL tyrosine kinase inhibitor which also inhibits c-Kit and platelet-derived growth factor receptors alpha/beta (PDGFR-α/β). It is commonly used for the treatment of Philadelphia chromosome positive chronic myelogenous leukemia (Ph+CML) and gastrointestinal stromal tumors (GISTs) among other indications. Treatment with imatinib mesylate was brought about six ECD patients in a study conducted by Haroche *et al.* [19] following dramatic improvement of two patients treated with this drug for Langerhans' cell histiocytosis and Rosai–Dorfman disease. The study was justified based on the histiocyte expression of PDGFR-β, resistance of 3 patients to interferon-α and overall severity of the disease. Treatment with imatinib was initiated with a starting dose of 100 mg/d per os. The maximal median daily dose was 350 mg/d and the maximal dose reached was 800 mg/d. Two patients responded with a stable disease and four patients responded with worsening of their condition. Progression of CNS symptoms was apparent in 80% of the patients, although 75% exhibited stable cardiovascular disease [19]. Another report describes an ECD patient who was treated with imatinib at a dosage of 400 mg/d. This patient reported significant improvement in dyspnea and fatigue and PET/CT demonstrated improvement in the pulmonary, mesentery and cecal areas. No molecular data exists regarding that patient. Treatment with imatinib was based on the hypothesis that it can act on CD34(+) peripheral blood progenitor cells and inhibit their differentiation to dendritic cells [20]. In both studies, the treatment was tolerable. In summary, limited experience shows that imatinib has a limited potential in treating ECD patients. The anecdotal cases above demonstrate mainly progression of CNS lesions, stabilization of cardiovascular involvement and resolution of pulmonary and abdominal manifestations following treatment with imatinib.

9. Infliximab

Infliximab is a recombinant humanized monoclonal antibody to TNFα indicated for the treatment of rheumatoid arthritis and Crohn's disease among other conditions. Dagna *et al.* report two ECD patients who were treated with an infliximab-based regimen. Both patients suffered from extensive cardiovascular involvement of their disease, promoting recurrent pericardial effusions and cardiac failure. These two patients were treated with infliximab (at a dosage of 5 mg/kg every 6 weeks) and methotrexate (at a dosage of 20 mg/week). The treatment was well tolerated by both patients and resulted in the considerable improvement of symptoms and cardiac function. A 30 months follow-up for the first patient, and 12 months follow-up for the second one revealed both of them to be clinically stable and asymptomatic [28]. We also report, by means of personal

communication, a patient who was treated with a combination of steroids, high dose methotrexate and infliximab. The patient originally presented with bilateral orbital, pulmonary, salivary gland and lymph node involvement. This patient had gone into complete remission pursuant the treatment mentioned above, yet, we propose the effect to occur mainly due to inhibition of TNFα signaling. In summary, infliximab may be a promising second line treatment for ECD patients who suffer from cardiovascular involvement.

10. Anakinra

Anakinra is a recombinant IL-1 receptor antagonist (IL-1RA) mainly used for the treatment of rheumatoid arthritis. Binding of IL-1RA to the interleukin-1 receptor results in anti-inflammatory activity. Furthermore, injection of interferon-α/β stimulates increased molecular transcription and secretion of IL-1RA, further substantiating the impact of interferon-α treatment on interleukin-1 network modulation. One report discusses the treatment of two ECD patients with anakinra based on the above. The treatment initiated at 1.06 – 1.5 mg/kg/day by subcutaneous injection and ultimately resulted in one patient's complete response and in the other patient's partial response. Both experienced rapid decrease in bone pain, normalization of fever, regression of retroperitoneal fibrosis and normalization of CRP, IL-6 and membranous IL-1α [22]. Anakinra also appears in the medical literature in the context of a pediatric patient. In this case the treatment with anakinra was initiated pursuant detection of abnormally high levels of IL-1β, IL-6 and TNFα compared to healthy controls. Treatment at a dosage of 2 mg/kg/day yielded resolution of pain and fever and later on normalization of C-reactive protein (CRP) and erythrocyte sedimentation rates. During the following 10 months, the child gained weight and height. The bone lesions and retroperitoneal fibrosis remained stable [23]. Another report details a single patient treated with anakinra at a daily dosage of 100 mg subcutaneously. This patient's PET/CT scan indicated a marked reduction in the bone tracer uptake 1 year pursuant to the initiation of treatment [24]. Yet another report elaborates on an ECD patient who was treated daily with 100 mg of anakinra. In this case, treatment led to normalization of CRP levels as well as significant reduction in the degree of the constitutional symptoms upon 6 months of anti-IL-1 treatment [25]. In all the studies described, the treatment was well tolerated. Opposing evidence can also be found in the medical literature. Haroche *et al.* report an overall poor efficacy of anakinra in the treatment of 10 ECD patients [45]. In summary, these reports demonstrate anakinra to be a plausible agent in the treatment of ECD. However, it should be reserved for patients with mild disease as it is not efficacious in the severe forms of ECD which are associated with CNS and\or cardiovascular localizations.

11. Vemurafenib

Vemurafenib is a BRAF inhibitor prescribed for the treatment of advanced melanoma. At first, a single ECD patient was reported to harbor the BRAF V600E mutation. This discovery led to a discussion regarding the plausibility of this mutated kinase as a therapeutic target [31]. Shortly after, Haroche *et al.* [30] reported the BRAF V600E mutation was found to be present among 54% of the 24 ECD patients they have examined [30]. This was further substantiated pursuant examination of histiocytes harvested from additional ECD patients [32]. Recently, Haroche *et al.* [33] reported three ECD patients who were treated with vemurafenib. These three patients carried the BRAF V600E mutation and suffered from multi-systemic ECD which was refractory to treatment with interferon-α. Vemurafenib was initiated at a dosage of 1920 mg/day. 20 – 30 days later, the dosage was tapered to 960 mg/day in all patients mainly due to cutaneous-related adverse effects. Among these adverse effects were erythema, pruritus and pilar keratosis. All three patients, who initially suffered from life threatening manifestations of their disease, experienced dramatic improvement of their disease. This was evident by improvement of the clinical symptoms, normalization of CRP and substantial regression of all the pathologic uptakes on PET [33]. In summary, vemurafenib may serve as a rapid and efficacious treatment modality in the settings of life threatening, multisystemic ECD among patients harboring the BRAF V600E mutation. However, further follow up is needed for the evaluation of long term efficacy of vemurafenib, as well as assessment of its efficacy among larger groups of patients.

12. Hematopoietic stem cell transplantation

Boissel *et al.* report an ECD patient treated with double autologous hematopoietic stem cell transplantation [18]. The patient was diagnosed at the age of 18. 13×10^6 CD34(+) cells were collected at steady state G-CSF mobilization. Conditioning consisted of etoposide administered at a dosage of 60 mg/kg for four days and melphalan at a dosage of 140 mg/m^2 one day prior to transplantation. One month pursuant transplantation, a partial reponse was observed. A second transplantation was initiated with conditioning including carmustine at 300 mg/m^2 4 days before transplantation and etoposide at 60 mg/kg for 3 days and melphalan at a dosage of 100 mg/m^2 2 days before transplantation. Overall, impressive response was recorded with marked improvement of orbital lesions, 90% reduction in the renal mass and marked reduction of facial tumor. The longest follow-up regarding this patient is offered by Gaspar *et al.*, who report this patient to have suffered a local orbital recurrence 84 months pursuant his stem cell transplantation [46]. The patient was also reported to be alive with progressive disease 97 months following his transplantation. In their study,

Gaspar *et al.* also report two additional ECD patients who had undergone high dose chemotherapy based regimens (carmustine 300 mg/m^2 on day -4, etoposide 60 mg/kg on day -3 and melphalan 140 mg/m^2 on day -1) followed by an autologous hematopoietic stem cell transplantation. Although a partial regression of the CNS lesions of one patient was observed, both patients ultimately progressed and were noted to be alive with progressive disease on 8 and 14 months follow-ups. In summary, craniofacial and space-occupying brainstem lesions may respond to high dose chemotherapy followed by an autologous stem cell transplant, however, no response was noted in respect to neurodegenerative lesions.

13. Conclusion

In conclusion, current data advocates the use of interferon-α as the first-line treatment in ECD. It is a proven treatment modality that provides durable responses in some disease foci and the only treatment that objectively improves the survival of ECD patients. Peginterferon alfa-2a is an equivalent to interferon-α and may reduce the occurrence of adverse effects. As for second-line treatments, several alternatives exist: Anakinra is a promising agent in the treatment of mild ECD. However, it is not recommended in face of CNS and\or cardiovascular localizations of the disease. Conversely, vemurafenib seems as an efficacious treatment alternative for patients with multifocal disease, whose histiocytes are characterized by the V600E BRAF mutation. Another agent, infliximab, has shown potency in the treatment of the cardiovascular manifestations of ECD. Although it seldom appears in the medical literature, cladribine is considered to be yet another alternative in the treatment of moderate to severe ECD. However, this agent should be reserved as a second-line treatment for patients who are not candidates for other treatment modalities in that group, or as a third line treatment for patients who failed on prior second line treatments. Also, cladribine associated immune suppression should be a consideration in the ongoing planning of treatment. It should be noted that imatinib mesylate does not produce an adequate response in the treatment of ECD. Ultimately, other cytotoxic agents should be recommended as a salvage strategy only pursuant exhaustion of all other treatment alternatives at the discretion of the experienced physician. Among these agents, vinca alkaloids are an optional addition to an interferon-α-based regimen. High dose chemotherapy followed by an autologous stem cell transplantation may induce regression of ECD related craniofacial and space-occupying brainstem lesions. However, this radical approach may suit only selected patients whose physical constitution can withstand such an intensive regimen. In respect to palliation, corticosteroids can be supplementary to the fundamental treatment modality and should be used in cases of severe exophthalmos or in order to provide transient control of disease flare-ups. Bisphosphonates can also complement the basic treatment and aid in the control of bone turnover and bone pain. Radiation should be considered on a case-by-case basis and for palliative purposes only.

14. Expert opinion

The treatment of orphan diseases in general, and of ECD in particular, comprises a complex mission for both the patient and the physician. The patients' experience of uncertainty and distress does not contribute to the adherence required by long-term therapy, as it is necessitated in such instances. Patients tend to wander between different medical centers seeking for a physician that would alleviate their plight, a poor strategy in most cases. The physician himself faces a predicament. As opposed to evidence based medicine, the basis for treatment in ECD is not founded on randomized controlled trials. The scarcity of patients impedes the formulation of large prospective studies. At the disposal of the treating physician are case series, retrospective analyses and various therapeutic theories based on biological rationale. As a result, long-term treatment evolves and alters in concert with the patient. The therapeutic roadmap should serve the primary objectives: increasing survival and maintaining the quality of life. However, response to a pharmaceutical agent is not the sole parameter in the selection of treatment. The patients' compliance and tolerance to treatment are important considerations as well. Patient education and alignment of expectations are cardinal components of long term treatment, especially when much is unknown. This serves to provide a fundamental sense of security and assurance to a patient who may face a difficult path to stride. Concrete decisions regarding therapeutic alternatives should be weighed closely for their risk and benefits, taking into consideration the extent and distribution of the disease, presumed impact of therapy and prognosis. A single drug versus combination therapy, alteration of dosage, alteration of treatment, preemptive intervention – these are but a handful of questions that should be addressed in a personally tailored fashion. An ongoing zealous, effort must be maintained in the research of new treatment venues in ECD. Improved understanding of the pathogenesis of this disease is absolutely mandatory, although not always fruitful. Such was the case of the identification of PDGFR as a therapeutic target in ECD: it was found to be prevalent in a group of ECD patients. However, inhibition of this target by imatinib mesylate yielded no substantial results. On the other hand, promising results began accumulating in respect to anakinra (although some failures were also reported). This treatment was originally based on the immunological understanding that ECD involves a prominent Th1 immune response, that is based among other cytokines, on IL-1. Another recent finding was in the field of molecular biology, as the V600E BRAF mutation was identified in 54% of ECD patients. This resulted in an attempt to inhibit the mutated kinase via the small-molecule vemurafenib – an attempt that was reported to induce dramatic responses in three patients. Many questions emanate

regarding new possible therapeutic targets. How would ECD patients respond to the inhibition of interleukin-6? Is a dual cytokine block, a possible efficacious strategy? Will treatment with abatacept yield favorable outcomes via a mechanism of T-cell costimulation inhibition? What other potentially mutated cellular elements play a pivotal role in the propagation of this disease? Ultimately, only a handful of discoveries may traverse the gap between the bench and the bedside. Then again, it takes one meaningful discovery for one substantial leap.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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