Cladribine for the Management of Erdheim-Chester Disease in Adults

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Abstract

Erdheim-Chester Disease (ECD) is a rare, non-Langerhans cell histiocytosis characterized by foamy infiltrates of soft tissue and bone, with a histopathology that reveals CD68+, CD1a-, and S100- histiocytes densely infiltrating organ systems such as bone, large vessels, heart, and lungs, and other tissues to name a few. Few chemotherapeutic options exist in the second line, of which one is cladribine. Cladribine (2-chlorodeoxyadenosine) is an anti-metabolite that predominantly affects blood cells by mimicking adenosine nucleosides, inhibiting adenosine deaminase, and thus disrupts the ability of the cell to repair DNA. Here we report three patients with varying sites of disease who achieved a response following treatment with cladribine. Although the efficacy of cladribine has been demonstrated in patients with ECD who primarily exhibited neurological symptoms, we present three patients in whom significant responses were achieved in disease distributed in long bones, pericardium, and retroperitoneum.

Keywords: Cladribine; Erdheim-Chester disease; Non-Langerhans; Histiocytosis

Introduction

Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytosis that was first described as a "lipoid granulomatous" by JakobErdheim and William Chester in 1930. The disease is characterized by infiltration of foamy macrophages into various tissues with associated xanthogranulomas inflammation. ECD is a relatively rare condition with between 550-600 reported cases in the literature. Diagnosis of the disease primarily hinges on imaging, clinical symptoms, and the aforementioned histology [1]. The disease shows preference to males and adults, although it can present in children [2].

The pathophysiology of ECD is yet to be fully understood. There is some debate as to the reactive or malignant nature of the disorder, with favorable data existing for both mechanisms. Stoppacciaro et al. have shown undetectable Ki-67 on ECD histiocytes and the absence of mitosis, which led them to conclude the limited contribution of proliferation to the disease [3]. Furthermore, they found an increase in chemokine receptors for monocyte migration that allows for the possibility that proliferation has a minimal contribution to the pathogenesis of the disease and an autocrine loop of recruitment and accumulation may be the major contributing factor [4,5]. The group was also able to show T-helper lymphocyte infiltration with IFN-γ staining with IL-10 on the histiocytes, pointing to a TH1 or TH2-oriented inflammatory response. The alternative hypothesis, which posits malignancy, cites the incidence of the mutation in the proto-oncogene BRAF, a member in the MAPK pathway [6]. Depending on the study and the method used to evaluate the mutation status, more than 50% of all tested ECD biopsies carry the V600E mutation in BRAF [7-10].

Histologic lesions are characterized by cells staining for CD68 and are CD1a-negative, indicating that the progenitors arise from the macrophage/monocyte cell line rather than the dendritic line characteristic of the more common Langerhans Cell Histiocytosis [1]. In addition, the clones of ECD are S100 negative in 80% of the cases and are further differentiated from LCH by the presence of cytoplasmic Birbeck granules in fewer than 20% of invading histiocytes [11].

The most commonly associated clinical feature of ECD is osteosclerosis of the long bones, centered primarily in the metaphyses and diaphysis. In a large series of 59 cases, 45 had evidence of radiologic disease such as osteosclerosis [11]. Extraskeletal manifestations of the disease are varied, with common presentations included central diabetes insipidus, retroperitoneal fibrosis, exophthalmos, aortic sheathing, pericardial involvement, cutaneous xanthalesmas, and neurological involvement including parasthesias, paraplesias, and ataxia [2,11].

Figure 1: Patient Scans (F, 27) Figure shows the patients PET results before and after treatment with cladribine for the patient in case 2.

First-line treatment for ECD consists of either interferon-α or pegylated interferon-α; interferon is thought to cause immune-mediated histiocyte killing and differentiation of immature histiocytes [4]. The efficacy of interferon was debated until a study conducted by Arnaud et al showed an increase in survival with interferon in a 53-patient cohort [2]. Furthermore, a positive correlation between treating with escalated-dose regimen contingent on location of disease (i.e. CNS involvement) has been established as well [12]. More recent studies have shown that the response to IFN-α is variable and again, dependent on the site of disease [13], leading most to cite its lack of efficacy or poor tolerance justifying a search for an alternative [13].

One alternative therapy is cladribine, a purine nucleoside analogue that is selectively toxic to monocytes and lymphocytes [14]. It acts by interfering with single-stranded DNA repair and synthesis of both resting and dividing monocytes and lymphocytes [14]. The proposed treatment dosage for cladribine is 0.1-0.14 mg/kg per day for five days on a twenty-eight day cycle for histiocytic diseases [15], although the dosage is often modulated according to the severity of the disease. Cladribine has several side effects including neutropenia, anemia, thrombocytopenia, headaches, and increased risk of infection, fatigue, pyrexia, optical nerve toxicity, and lymphopenia [15,16].

Cladribine use in the management of ECD is poorly understood, mainly due to insufficient reports. Induction treatment with cladribine isn't initiated until the disease is refractory to multiple treatments, which may contribute to the anecdotal opinions of some clinicians against the drug. Here we present three cases of patients whose disease was successfully managed with cladribine.

Case Presentation

Case 1: Male, Age 58

The patient presented with a history of histiocytic granulomatous disease involving his skin, uveal tract, testis, retroperitoneum, lungs, and diabetes insipidus (ECD), and disseminated nocardiosis. At initial presentation to us the patient had received corticosteroids, vinblastine, IFN-α, and mycophenolate mofetil. Despite these treatments, his disease progressed as evidenced by intertriginous inguinal erosive and ulcerative dermopathy and dermatologic involvement of external auditory canals. The patient had initially been diagnosed via testicular biopsy, which revealed granulomatous infiltration. Upon referral to our clinic, he was treated with local radiotherapy for intertriginous rash but was switched to IV cladribine (0.14 mg/

kg) on the aforementioned schedule due to disease uncontrolled locally and systemically. He received a total of five cycles. There was immediate control of the skin disease. His course was complicated by opportunistic gram-positive disseminated nocardia infection of the wrist, chest, and pleura during his final cycle. (Was that really the timing? Can you provide me with a treatment synopsis?). Since treatment over thirteen years ago, there has been persistent retroperitoneal fibrosis, but no return of cutaneous, ocular, skeletal, lung, or testicular manifestation of ECD since and remains clinically stable. BRAF mutation status is unknown and the patient's disease is followed via CT.

Case 2: Female, Age 27

A 27 year old female presented to clinic with a history of fevers, chills, night sweats, and recently had begun experiencing weight loss attributed to anorexia. Upon physical examination, splenomegaly was noted. A CT at the time revealed osseous lytic bone disease, with a subacute fracture at the posterior 10th rib and femoral neck lesion. A subsequent CT revealed extensive bone disease, with involvement in the right humoral shaft, proximal left radius, a larger fracture in the 10th rib, and thickening of the abdominal aorta and iliac arteries. Pathology was negative for both S100 and CD1a, leading to the diagnosis of ECD after the pathologist noted fibrosis that was inconsistent with Langerhans Cell Histiocytosis. The patient was stated on zoledronic acid (4 mg per 28 days) for the lytic lesions and IV cladribine (0.14 mg/kg) for management of the disease. The patient was treated for three cycles and experienced mild nausea and manageable leukopenia, but bone surveys revealed decrease in lytic lesions in the right humeorous, left radius, bilateral ribs, and was accompanied by increased sclerosis indicative of healing. After being clinically stable for thirteen months, the patient returned with increased bone pain. A subsequent PET showed greater radiographic evidence of extensive disease, with recurrence of disease in the abdominal aorta and iliac arteries. Due to prior treatment with cladribine, the patient was started on IFN-α but had progression of the disease and was switched back to cladribine for six additional cycles. This time leukopenia was mild but the patient developed thrombocytopenia and intermittent bruising on the hands, arms, and legs on the final two days of each cycle. A bone marrow biopsy and PET showed no residual abnormalities (Figure 1), but did show signs of mild reticulin fibrosis and significant megakaryocytopenia. The patient is once again clinically stable with no signs of progression for over fifteen months, although she did develop renovascular hypertension. She, and continues to be followed. BRAF mutation status is undetermined, but under evaluation.

Case 3: Female, Age 66

This patient presented for consultation after being evaluated for idiopathic cardiac tamponade. Before coming to our clinic, she experienced upper respiratory symptoms that were due to pericardial effusions diagnosed via echocardiogram. The management of her disease prior to presentation at our clinic consisted of two pericardial drainages, placement of a pericardial window, pericardial stripping, empiric trail of corticosteroids, bronchodilators, and a trial of indomethacin; none showed any improvement. The patient then presented to our hospital with dyspnea, chronic cough, fatigue, chronic shoulder pain, and exertional dyspnea. Pathology of the pericardial tissue revealed infiltrates that were positive for CD68 and CD163, and negative for S100 and CD1a, leading to her ECD diagnosis. She started her treatment with cladribine (0.14mg/kg) that was continued for four cycles. Her course was complicated by neutropenia attributed to the treatment, but did not result in any significant infections. The patient noted a significant improvement in energy, alleviation of her fatigue, and no recurrent pericardial effusion. Her disease has been clinically stable for over four years and follow-up ECHOs have revealed no abnormalities. Her BRAF mutation status is undetermined.

Discussion

Erdheim-Chester disease is a rare, non-Langerhans cell histiocytosis marked by CD68positive, CD1anegative, and S100-negativehistiocytes densely infiltrating bone, lymph nodes, retroperitoneum, and systemic vasculature. Despite consensus guidelines put in place in 2014 by Diamond et al. clinicians often have difficulty in diagnosing ECD and therefore turn to more well-known treatment options for management. Fortunately multiple drugs are now being evaluated for treating ECD, which is changing the outlook for the disease and providing clinicians with study data to aid their treatment decisions. ECD most commonly presents with osteosclerosis of the long bones, centering primarily in the metaphysis diaphysis. There is a large variance in the extra skeletal manifestations, with common presentations in the form of diabetes insipidus, retroperitoneal fibrosis, aortic sheathing, pericardial involvement, and spectrum of neurological manifestations.

Despite an advantage for IFN-α in survival, it has not shown been shown to be curative. With this in mind, more targeted therapies have been used to treat the disease. One such drug is vemurafenib, a BRAF-V600E inhibitor, has been used to successfully treat patients with ECD [1,13]. In the most recent study of eight patients with proven V600E mutations showed weakened metabolic uptake as seen by PET scan at six months, partial cardiac response in all but one patient, and objective decreases in the size of neurological lesions when treated with vemurafenib [6]. In one patient, treatment with vemurafenib following IFN-α resulted in dramatic improvement of functional capacity as well as a reduction in bone, renal, and orbital involvement of disease [17]. Lastly, in a trial of three patients with refractory ECD and mutated BRAF, a substantial reduction in clinical symptoms, regression of aortic and orbital involvement and disappearance of skin lesions was observed [13]. Other treatment methods used include cytotoxic agents, radiation therapy, bisphosphonates, imatinibmesylate, infliximab, anakinra, and hematopoietic stem cell transplantation, each with variable efficacy [17].

Cladribine, the purine analog that is cytotoxic to monocytes, has been advocated as a second-line therapy for ECD. Originally approved for the treatment of Hairy Cell Leukemia, a hematologic malignancy characterized by proliferation of cells from the mononuclear cell line, it is believed that its effects may extend from plasma monocytes to tissue histiocytes [18]. Evidence for its efficacy are scattered throughout the literature. Cladribine has been used successfully along with cyclophosphamide and dexamethasone to achieve partial remissions in two patients with CNS and bone symptoms [19]. In another case study, treatment with cladrabine resulted in remission of orbital, pulmonary, bone, and ocular manifestations of the disease with normalization of macrophage counts [20]. Finally, partial remission of CNS lesions following treatment of cladribine was consolidated with lenalidomide and resulted in a complete remission [21].

Mutations in the proto-oncogene BRAF have been found in as few as 50% and as many as 100% of cases, with the variability dependent on the method of detection used. A member of the Raf kinase family, BRAF plays a role in cell proliferation via the RAS MAPK pathway [6]. An activating mutation, BRAF-V600E, may play a role in the proliferation of cells derived from the mononuclear cell line [22]. The BRAF-V600E inhibitor vemurafenib has been successfully used in treatment of patients, most recently in a cohort of eight patients with proven V600E mutations whose reduction in disease was measure via reduced metabolic activity observed on PET scans [6]. Two single case studies in which Mazor et al. [17] and Tzoulis et al. [23] noted an excellent response in intramedullary disease, both of whom treated with vemurafenib [23]. Lastly a study of three patients with V600E mutated refractory ECD observed substantial reduction in clinical symptoms, regression of aortic and orbital involvement, and the disappearance of skin lesions when treated with vemurafenib [13].

Another targeted therapy that is gaining momentum with ECD is sirolimus. Sirolimus is mammalian target of rapamycin (mTOR)-inhibitor and has antiproliferative and immunosuppressive properties [24]. If the previously presented hypothesis of ECD's pathogenesis is correct, mTOR inhibition would manage both paths of the disease. In a study conducted by Gianfreda and Nicastro et al ten patients were treated with sirolimus, of whom eight were able to achieve stable disease or an objective response with mild treatment related toxicities [24]. Additional immunohistochemistry and immunofluorescence done by the group on the ECD biopsies revealed mTOR pathway activation via phosphorylated forms of mTOR and its downstream kinase p70S6K. Other studies have also shown PIK3CA and NRAS mutations, which are mTOR pathway activating mutations [22].

Here we presented three patients who presented in our clinic for the management of their ECD. One of the patients presented after extensive treatments (corticosteroids, vinblastine, IFN-α, and mycophenolate mofetil); the other two had no other systemic therapies. Each of the three patients was treated with cladribine (0.14 mg/kg) via IV infusion for two hours a day for five days on a twenty-eight day cycle. All patients have sustained disease regression after treatments spanning five, nine, and four cycles respectively. All three patients received anti-PCP, anti-viral, and anti-fungal prophylaxis for one year after the completion of their therapy. The first and third patient required no further treatment; patient two required further treatment whose disease is now clinically stable.

Current trials include a Phase II study with dabrafenib and trametinib in patients with the BRAF mutation (NCT02281760), lenalidomide (NCT02523040), sirolimus with prednisone (ACTRN12613001321730), tocilizumab (NCT01727206), and a long-term outcome after vemurafenib inhibitor interruption study (NCT02089724).

Here we have presented our experience with three ECD patients with varying sites of disease whose disease was successfully managed with cladribine. Despite this, there is a patient population who are ineligible for investigational treatments and who would benefit from an alternate therapy. It is here we suggest cladribine to be used as an initial or early therapeutic option based on our experience with the drug and the success our patients have had. Beyond this, it would be interesting to see a larger study with cladribine or a study that compares it to one of the targeted therapies.

Ethics Approval

Ethics approval was obtained from the IRB at UCLA. The reference number for the study is 14-001051.

Ethics, Consent, and Permissions/Consent to Publish

All participants were consented via an IRB approved consent form and were consented by Dr. Gary Schiller. They were notified that their consent would mean that they are participating in this study and the results would be published.

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