Drugs of the Future 2011, 36(5): 403-408

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.5.1624327

ERDHEIM–CHESTER DISEASE: NEW ADVANCES

K. Haddley

University of Liverpool, School of Biomedical Sciences, Liverpool, Merseyside, UK

CONTENTS

SUMMARY

Erdheim–Chester disease (ECD) is a rare histiocytosis with a typical clinical phenotype of cortical sclerosis of long bones, detected using imaging techniques, and tissue infiltration by immune cells, detected by lesion biopsy. It can be histochemically distinguished from other histiocytoses, although it is often misdiagnosed. The disorder generally effects middle-aged people, with a predominance for males, but on rare occasions it has been reported in children or young adults. Although the major complaint with ECD is long bone pain, it is also associated with extraskeletal manifestations in many other tissues, and it is these manifestations that give rise to a poor prognosis for those with ECD, patients often dying soon after diagnosis, usually due to cardiac, pulmonary or renal failure. The etiology of the disease is unknown and treatment protocols have largely been based on therapies used to treat other histiocytoses, but recent advances point to the involvement of cytokines involved in inflammation. Previous therapies for ECD include radio- and chemotherapy, immunosuppressant drugs and transplantation, all of which have shown poor efficacy. More recently, interferon alfa and interleukin receptor agonists have been used with greater promise, as well as a tyrosine kinase inhibitor, imatinib, which has proven efficacy in treating ECD.

INTRODUCTION

Erdheim–Chester disease (ECD) is a rare, noninherited, multifocal, xanthomatous non-Langerhans cell, lipid-storing histiocytosis characterized by the absence of serum lipid abnormalities. Originally described as lipoid granulomatosis by Chester in 1930, the disease is often clinically misdiagnosed and mistaken for a number of similar diseases, such as xanthogranulomatous inflammation, Langerhans cell granulomatosis, Gaucher's disease and Rosai–Dorfman disease (1, 2).

Correspondence: Kate Haddley, University of Liverpool, School of Biomedical Sciences, Crown St., Liverpool, Merseyside L69 3BX, U.K. E-mail: K.Haddley@liverpool.ac.uk.

The predominant clinical phenotype is bilateral, symmetric, metaphyseal and diaphyseal cortical sclerosis of the long bones associated with inflammatory foamy histiocyte infiltration surrounded by fibrosis (3). In almost half of the cases, long bone abnormalities are present concomitant with pathologies in other tissues, such as pulmonary (4), renal (5), cardiac (3, 6, 7), periorbital (8), central nervous system (9, 10) and breast tissues (11). Such widespread involvement of other tissues and similarities to other diseases often complicate the diagnosis, and the medical field is divided as to whether or not ECD is a distinct disease rather than a collection of other closely related pathologies. The diagnosis of ECD is dependent on observations from clinical, radiological and pathological investigations of the long bones and other tissues involved. The disease usually presents in middle age, showing a slight preponderance in males, and is often fatal, resulting in mortality rates of 60% within 2-3 years of confirmed diagnosis for ECD, especially when manifest with neurological or cardiac symptoms (6-8).

The incidence of ECD was recently reported to be approximately 350 cases worldwide, although the etiology and causative factors involved in the disease are largely unknown. Despite a lack of understanding of the etiology of ECD, it has been suggested that overstimulation of the inflammatory interleukin-1 (IL-1) network and other proinflammatory cytokines may play a central role in the development and progression of ECD (12-14). A number of treatments for ECD have been assessed with poor efficacy and high toxicity, including corticosteroids (8, 15), chemotherapy with cladribine (2-CdA) (13), vinca alkaloids (2, 8, 15), anthracyclines (doxorubicin) (2, 8), immunosuppressive drugs (azathioprine, ciclosporin and cyclophosphamide) (2, 8), interferon alfa (IFN-α) (16-19), radiotherapy and autologous hematopoietic stem cell transplant (20, 21). However, more recently, encouraging results have been seen with the administration of IFN-α in combination with other drugs that have shown efficacy in the treatment of Langerhans cell histiocytoma (LCH), such as vinblastine, prednisone, methotrexate and 6-mercaptopurine (22). In addition, a recombinant IL-1 receptor antagonist (IL-1Ra) has shown promise in treating two ECD patients (12). The success of these treatments points to a role for aberrant IL-1 network processes as a potential causative factor in the development of ECD. Furthermore, recent treatments using imanitib, a potent tyrosine kinase inhibitor that downregulates platelet-derived growth factor (PDGF) by inhibiting its receptor (PDGF-R-β), have demonstrated potential therapeutic benefits for patients with ECD.

THE IL-1 NETWORK

The IL-1 proteins are a family of proinflammatory cytokines that bind to IL-1 receptors expressed on the surface of leukocytes to act as major regulators of the host immune response. The IL-1 proteins are produced and secreted primarily by epithelial cells, and when released into the bloodstream, act to stimulate white blood cells and cause the infiltration of circulating leukocytes into inflamed tissue. Examples of such leukocytes include neutrophils, eosinophils, basophils, B and T lymphocytes and monocytes, which differentiate into macrophages once they have transitioned into the tissue. Binding of IL-1 to the IL-1R activates mitogen-activated protein kinase pathways (p38, p42/p44 and c-Jun *N*-terminal kinase) and nuclear factor NF-κB to induce gene transcription of other proinflammatory cytokines, e.g., IFN-α, which in turn further activates immune cells, such as macrophages (23).

DIAGNOSIS

Patients with ECD commonly present with intense bone pain in the legs and fever, although a large proportion of patients with ECD are asymptomatic (24). Half of all ECD patients display extraskeletal features of ECD in other tissues, such as retroperitoneal (3), pulmonary (3, 4, 25), renal (5), breast (11), cardiac (3, 6, 7), periorbital (exophthalmos-bulging eyes) (8) and central nervous system tissues (10). Diagnosis is made following histological and radiological examination. ECD can often be misdiagnosed as other diseases, such as xanthogranulomatous inflammation, LCH, Gaucher's disease and Rosai–Dorfman disease, and is often present with comorbidities, including diabetes insipidus and hypogonadotropic hypogonadism (1, 25).

Histological

Examination of biopsy tissues from ECD lesions is critical for a correct diagnosis and reveals the presence of a xanthofibromatous reaction with infiltrating inflammatory monocytes, such as lipid-laden foamy histiocytes, lymphocytes and eosinophils. Multinucleate cells such as giant Touton-type cells formed by the fusion of foamy macrophages may also be present (1, 2, 6). Electron micrographs indicate that ECD histiocytes are generally negative for S-100 protein and Birbeck granules, both of which are present in LCH (2, 8 10, 26). In addition, histiocyte nuclei are rounded or oval, unlike the irregular nuclei seen in LCH (25). Immunohistochemically, the histiocytes stain negative for the glycoprotein CD1, which is expressed on the surface of antigen-presenting cells, but positive for the glycoprotein CD68, which is bound to low-density lipoprotein found on the surface of infiltrating macrophages and Touton-type cells. In addition to the characteristic histological profile, constitutive activation of PDGF-R-β is frequently detected in ECD, although the underlying molecular mechanism for such activation is unknown (27). Quantitative polymerase chain reaction (PCR) carried out on peripheral blood from one ECD patient showed a specific pattern of cytokine activation, with increased IL-1α, IL-1β, IL-2 and IL-8, which is indicative of monocyte activation (13). Some patients may present with all of the above profiles; however, others may have only a few further compounding diagnoses, making it essential that radiological examinations be performed together with histological investigations, especially radiological examinations of the long bones and examination of lung infiltration, which appear to be specific to ECD (25).

X-ray

Bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in the long bones, in particular the femur, tibia and fibula, and to a lesser extent the ulnae, radius and humerus, is a major and specific feature of ECD and was observed in an investigation by Veyssier-Belot et al. in 45 of 59 patients. In addition to osteosclerosis, lytic lesions were found in the long bones and bone masses were present on the ribs and knees (n = 3). In the some patients, X-ray also revealed osteosclerosis in the cranial, thoracic, spinal or pelvic bones, which can lead to misdiagnosis, as these are present in other histiocytic disorders. In patients with extraskeletal manifestations of ECD, chest X-rays show diffuse interstitial fibrosis or infiltration of lung parenchyma, and pleural thickening or effusion (8, 25).

Computed tomography (CT) scan

Haroche et al. utilized CT scans in a case study with ECD patients presenting cardiac manifestations of the disease. The scans revealed mild cardiomegaly (n = 2 of 31), right atrial enlargement (n = 3 of 31) and aortic arch enlargement (n = 1 of 31) (7). More recently, Brun et al. examined mediastinal, cardiac, pleural and pulmonary infiltration using CT scans from 40 patients with biopsy-confirmed ECD. Circumferential periaortic infiltration was seen in 85% of patients in the ascending aorta, the aortic arch and the descending aorta (43%, 68% and 75%, respectively), with an associated increase in mean thickness of tissues (7, 12 and 7 mm, respectively). Twenty-four patients with mediastinal involvement also had involvement of the pericardium, myocardium and/or cardiac sulci. In 22 of these patients, the right coronary artery was sheathed by the mediastinal infiltration. Infiltrations were also observed around the left coronary artery (n = 14), the left anterior descending (n = 10) and/or circumflex arteries (n = 10), the right atrial wall (n = 12), causing severe narrowing of the right atrial lumen in 8 patients (mean thickness of 9 mm), and the inferior wall of the right atrium (n = 6). In addition, three patients displayed coronary artery stenosis (~50%). Pericardial involvement was found in 24 patients and was characterized by abnormal thickening (n = 17; mean thickness of 8 mm), effusions (n = 4), or both (n = 3) (3).

Similar cardiac abnormalities were found in a retrospective study involving four patients, including pericardial effusions and circumferential periaortic infiltration by solid tissue (28). Furthermore, in the investigation by Brun at el. bilateral pleural involvement was found in 16 patients and was characterized by effusions (n = 8) and smooth pleural thickening (n = 15), 11 of whom showed exclusive right basal paravertebral thickening (mean thickness of 8 mm). Twenty-two patients showed pulmonary involvement, with smooth, symmetrical, interlobular septal thickening (n = 21), subpleural thickening along the fissures (n = 13), small centrilobular nodular opacities (n = 9), ground-glass opacities in lung parenchyma (n = 8) and focal subpleural areas of consolidation (n = 3). Bilateral osteosclerosis of the diaphyses and metaphyses of the clavicles (n =

8, 7 of which were symmetrical) and/or ribs (n = 6, all asymmetrical) was present in 12 thoracic images analyzed. In conclusion, Brun et al. determined that periaortic infiltration was positively associated with coronary sulci involvement (P = 0.0048). Positive correlations were also observed between lung and pleural involvement (P = 0.001), and between lung and mediastinal involvement (P = 0.004), providing a useful paradigm for the diagnosis of ECD (3). Others also examined pulmonary manifestations of ECD in patients and found similar characteristics, namely, scattered fine reticular and centrilobular opacities, thickening of interlobular septa and pleura, and scattered areas of ground glass attenuation (25, 28).

Many patients with confirmed ECD reveal enlarged kidneys with increased cortical density and intrarenal low-density nodules and retroperitoneal fibrosis in perirenal regions (5, 8, 28). CT scans have also been used to identify rare extraskeletal presentations of ECD in breast tissue biopsies in four distinct cases (11, 29).

Bone scintigraphy

Magnetic resonance imaging (MRI) utilizes paramagnetic contrast agents such as gadolinium or radioactivity agents such as technetium 99 to examine bone inflammation or fracture. The reagent is taken up by osteoblasts present and active in response to bone fracture, cancers, infections or inflammation. MRI is generally more sensitive than X-ray, and in the case of using paramagnetic agents is much safer for the patient. Bone scintigraphy is a metabolic measurement considered for functional analysis rather than structural analysis. In patients with ECD, bone scanning with technetium 99 or gadolinium showed increased labeling of the distal ends of the long bones of the lower limbs and, less frequently, the upper limbs (8, 28). In a single case, quantitative bone densitometry revealed that lumbar bone density was increased by eightfold (8).

MRI

MRI is particularly useful for noninvasive, safe, high-contrast examination and functional imaging of soft tissues, such as the components of the central nervous system. An additional investigation in two ECD patients reported to have neurological symptoms identified diffuse hyperintensity in the pons extending to the left middle cerebellar peduncle and lower midbrain in the first patient, and widespread hyperintensity involving the pons and extending to the right middle cerebellar peduncle and lower midbrain in the other. Diffuse hyperintensity of the periventricular white matter and small multiple foci of post-contrast enhancement in the pons and in the left temporal periventricular white matter were also present in the second patient (9). Overall, cerebral MRI findings in ECD patients with associated neurological presentations generally manifest as meningioma-like tumors or thickening of the dura mater, or an infiltrative pattern always located along the falx or the hemispheric, cerebellar or spinal dura (30, 31).

MRI has also been used to investigate cardiac manifestations in 37 ECD patients, 70% of whom displayed abnormal heart imaging, including abnormal pseudotumoral infiltration of the right atrium (n = 11) or the right auriculoventricular sulcus (n = 7), pericardial effusion (n = 9), pericardial thickening (n = 5), periarterial infiltration of the left coronary artery (n = 10) and periarterial infiltration of the right artery (n = 2) (7). In general, retroperitoneal tissue infiltration in ECD patients shows low signal intensity on T1-weighted images and high signal intensity on T2 images (8, 28).

Positron emission tomography (PET)

PET is useful for identifying lytic bone lesions that are not easily detected by MRI. The first reported case using PET as a tool for ECD detection was described by Wright et al. Tomographic images demonstrated increased uptake of ^{18}F-FDG in the pons and normal uptake in the cerebral cortex, suggesting that ECD should be considered in the diagnosis of focal increased glucose metabolism in the brain (10).

TREATMENT AND MANAGEMENT

Corticosteroids

The most commonly used corticosteroid for the treatment of ECD is prednisone; however, the effectiveness of such treatment has so far proved limited. In a study by Sandrock et al., 20 patients received steroids at 1-2 mg/kg/day to control exophthalmos or general ECD symptoms. It was fully effective in two patients, transiently effective in four patients and ineffective in eight patients (8, 32). A 42-year-old female presenting ECD with neurological manifestations was treated with prednisone (60 mg/day p.o. gradually decreasing to every 2 days). After 1 month, her balance, gait ataxia and speech were marginally improved. An MRI detected abnormality in the pons and gadolinium enhancement had decreased. Six weeks post-treatment neurological defects had worsened and a course of radiotherapy was prescribed (10).

Chemotherapy

Vinblastine was given at a dose of 5-6 mg/m^2/week (three patients) with steroids alone or with steroids and doxorubicin (65 mg i.v.) or cyclophosphamide (1000 mg/m^2 i.v.). Vincristine was used once (1.5 mg/m^2/week) combined with adriamycin (25 mg/m^2 fortnightly). In 1 patient, 10 courses of vinblastine induced a 50% reduction in a retroperitoneal mass and a complete disappearance of exophthalmos. In one patient the mediastinal mass, but not the retro-orbital mass, showed a partial response. Chemotherapy had a 50% success rate in improving the status of four of eight ECD patients (8).

Cladribine is a purine analogue that is cytotoxic to monocytes and lymphocytes and which thus has potential for treating inflammatory infiltration. In one case study, a 45-year-old male with ECD was treated with cladribine (0.14 mg/kg/day for 5 days every 4 weeks). After 8 weeks, there was clinical improvement in the proptosis and conjunctival swelling of the eye. After 24 weeks, his elevated monocyte count normalized. Seven months following the onset of treatment, bone scintigraphy showed a great improvement in sclerosis and lung function initially improved, then stabilized. There were no adverse events associated with treatment, and 2 years after cessation of treatment the patient remained well, with an increased tolerance for exercise, an improvement in visual acuity, resolution of proptosis, reduced conjunctival swelling, normal external ocular movement and decreased interlobular septal thickening in the lungs (13).

Autologous bone marrow transplant

An 18-year-old male with ECD who had previously been shown to be refractory to chemotherapy and interferon treatment underwent autologous stem cell marrow transplant. Prior to transplant, high-dose chemotherapy with peripheral blood stem cell rescue was started. Preconditioning consisted of etoposide (60 mg/kg) and melphalan (140 mg/m^2), 4 and 1 day prior to transplant, respectively. One month after transplant, a partial response was observed. After 6 months, a second transplant was performed. Preconditioning consisted of carmustine (300 mg/m^2), etoposide (60 mg/kg) and melphalan (100 mg/m^2) 4, 3 and 2 days prior to transplant, respectively. Two months later, exophthalmometry values improved from 32/28 to 25/23 mm (right/left eye). The volume of a renal mass present prior to transplant had decreased by 90%. There was also a marked reduction in a facial mass present prior to transplant. Two years following treatment, these findings remained stable. The authors concluded that etoposide is effective on neoplastic cells of monocytic lineage and may be useful at high doses in combination with peripheral blood stem cell rescue (20).

Radiotherapy

Low-dose radiation has been used to successfully treat histiocytic lesions such as LCH. Treatment of ECD with radiotherapy has produced conflicting results, especially in patients presenting extraskeletal symptoms of ECD. The rationale behind the use of radiation therapy is the presumed inhibition of xanthogranulomatous proliferation of histiocytes (33). In one study, seven doses of bone irradiation (15 Gy) were transiently effective in all patients with bone pain (n = 3), whereas retro-orbital irradiation in patients with exophthalmos (35 Gy) had no effect (n = 3) (8). Whole brain radiation (16 Gy, 8 fractions over 2 weeks) improved gait and limb coordination (10). In contrast, a protocol of a total dose of 24 Gy in 12 fractions over 2.5 weeks proved ineffective in whole brain radiation (34).

A mixed response was observed in patients receiving 14-16 Gy for leg bone pain and 35 Gy for periorbital lesions (35). A 33-year-old female with ECD was given radiation therapy of 1,600 rads over 5 weeks to the cranium and upper and lower body; however, no improvement in her symptoms occurred and her condition remained stable (26). In one case, a 42-year-old woman diagnosed with ECD and presenting with fever and pain in the lower limbs was given a total dose of 18 Gy to the right distal femur in 10 fractions over 2 weeks. There were no reported adverse events and the patient showed a gradual symptomatic response, with a decrease in pain score, albeit in the absence of radiological changes. The patient also received a regimen of an oral dose of prednisone (30 mg). On 2-year follow-up, the initial pain experienced by the patient was controllable (33).

IFN-α

IFN-α administration is currently one of the most promising avenues available for treating ECD, although it does vary in efficacy depending on the severity of symptoms and the extraskeletal manifestations present. The mechanism(s) underlying the effects of interferon in ECD treatment are unknown. Several authors have suggested that its efficacy could be due to maturation and activation of dendritic cells, immune-mediated destruction of histiocytes or direct antiproliferative effects (14, 16, 27). The rationale behind using IFN-α to treat ECD lies in its effectiveness in treating other histiocytoses, such as LCH (36).

The first reported case of using IFN-α to treat ECD involved a patient receiving IFN-α-2a (18 million units [MU] s.c. 3 times weekly for 24 months) in combination with vinblastine (5 mg monthly), who demonstrated a partial response (~50%) of orbital and mediastinal infiltration after 6 months (8). A second case involving a 55-year-old male patient with orbital ECD also demonstrated the effectiveness of IFN-β (3 MU/day). The patient had been receiving oral prednisone (100 mg/day p.o. for 2 weeks), which failed to produce any beneficial response, and this medication was gradually discontinued. When assessed at 4 weeks, improvement in visual acuity (from 20/80 to 20/25 in the right eye and from 20/200 to 20/30 in the left eye) and visual fields was noted, in addition to ablation of orbital pain. Four months after commencing treatment, MRI findings indicated an improvement in the orbital infiltration. Nine months following commencement of treatment, the patient was asymptomatic, with stable visual acuity and minimal exophthalmos. No serious adverse events were noted in either of the above cases (37).

In 2005, Braiteh et al. reported on findings using IFN-α to treat three patients with ECD. The first of these was the patient in the previous study described by Esmaeli et al. in 2001. After 4 years of treatment, the patient remains asymptomatic and MRI scans show a further decrease in his retro-orbital mass size and infiltration. The second patient to receive IFN-α (3 MU s.c. x 3 weekly) was a 58-year-old male who was unresponsive to previous treatment with radiotherapy and high-dose prednisone and was receiving opiates for severe pain. Due to mild adverse effects of fatigue, the dose of IFN-α was reduced in this patient (1 MU). Treatment was effective in decreasing bone pain within 3 months, and after 2.5 years of treatment there was significant improvement in bone scans and the patient is pain-free and no longer taking analgesics. The third patient was a 53-year-old male with orbital and retroperitoneal ECD symptoms. The patient's symptoms had worsened following treatment with methotrexate, cyclophosphamide, etoposide and high-dose prednisone and vincristine. This patient also received the higher dose of IFN-α, which was later reduced to the lower dose due to patient fatigue. After 16 months, eye function had normalized and therapy was discontinued; however, on an 8-month follow-up, new lesions had appeared and the patient tested positive for ECD. IFN-α therapy was reinstated and the patient once again responded (16).

It is clear that IFN-α can be used to treat some forms of ECD with success, although the response of patients greatly depends upon the site at which extraskeletal symptoms are manifest. This was demonstrated in a case study by Haroche et al. (17). Eight patients with ECD symptoms (age range: 18-72 years) at various sites, 5 of whom were known to be refractory to steroid treatment, were given IFN-α (3-9 MU x 3 weekly for 23 months [median]). Mild adverse events included fever following injection; one patient was withdrawn due to depression and later died from cardiac complications related to ECD. Another patient died due to pulmonary infection (unrelated to treatment). General improvements were seen overall in six patients, including disappearance of exophthalmos (n = 1), disappearance of xanthelasma (n = 2), regression of hydronephrosis allowing removal of ureteral stents (n = 2), disappearance of

papilledema (n = 1) and improvement in intracranial hypertension (n = 1). Two patients with multifocal ECD showed improvements in renal function, and periaortic fibrosis showed a 50% decrease in the maximum diameter in both patients. One patient with multifocal ECD manifestations developed ataxia and underwent autologous hematopoietic stem cell transplant. Eighteen months later, this patient remained unresponsive to IFN-α treatment. The youngest patient was unresponsive to previous treatment with steroids and treatment with IFN-α at the higher dose, but was treated successfully with autologous hematopoietic stem cell transplant.

An additional case study reported a lack of efficacy for IFN-α in treating ECD. A 31-year-old male who was refractory to previous treatment with a battery of chemotherapeutic agents was given IFN-α (5 MU x 3 weekly, later reduced to 3 MU twice weekly for 6 months). During this period, bone pain, general symptoms and cutaneous lesions improved, while an ECD-related mesenteric mass was unaffected, which eventually led to duodenal occlusion, infection and death (19). It appears that IFN-α treatment has some benefits for treating ECD, but is not equally effective at all sites. Recently, a male patient with renal and cardiac ECD symptoms was treated with IFN-α (3 MU s.c. x 3 weekly). No adverse events were noted and treatment improved xanthelasmas and attenuated the substantial progression of pericardial effusion. After 32 months, the patient's general condition remained stable except for the slow progression of renal dysfunction (18).

Despite these inconsistencies, IFN-α is now considered the first line of defense for patients with ECD. More recently, IFN-α (3 MU weekly) in combination with chemotherapy using vinblastine, prednisone, methotrexate and 6-mercaptopurine was shown to be effective in abolishing ECD symptoms and lesions in a 17-year-old female patient in a 2-year follow-up (22).

Recombinant IL-1Ra

Since IFN-α treatment has demonstrated some level of success in the treatment of ECD, Aouba et al. postulated that an IL-1Ra, anakinra, may be therapeutically beneficial because IL-1R synthesis is a downstream event of IFN-α upregulation. Two patients, one who had previously shown a poor response to IFN-α and one who could not be given IFN-α due to other concomitant medications, were given anakinra (100 mg/day s.c.). Both patients responded well, with improvement of pain (with a cessation of analgesics), fever and fatigue within the first week of treatment. The first patient, a female with a history of mood disorder, displayed complete resolution of exophthalmos and a general improvement in mental health. Within 3 months, she showed regression of both bilateral fibrotic and stenosing periureteral infiltration and hydronephrosis. At 6 months, tissue infiltration was abolished and bone scans showed that previous sites of increased technetium 99 uptake were no longer present, renal function returned to normal, but long bone lesions remained unchanged. The patient discontinued treatment twice but showed signs of relapse, and treatment was reinstated. After 10 months of anakinra treatment, the second patient showed similar good results and renal stenosis had totally subsided, although other renal abnormalities persisted. No change in skeletal scintigraphy or periaortic infiltrate was noted. No serious adverse events were reported and the authors concluded that anakinra might be a safe and effective treatment for ECD, although further investigation is warranted, particularly in terms of dose and duration of treatment (12).

Imatinib mesylate

Imatinib is a competitive inhibitor of tyrosine kinases associated with ABL, ARG, Kit, PDGF-R-α and PDGF-R-β (27), and has been used successfully to treat other non-LCH histiocytoses, such as Rosai–Dorfman disease (38). Recently, imatinib mesylate demonstrated that it can act on normal CD34-positive peripheral blood progenitor cells and inhibit their differentiation to infiltrative dendritic cells (39, 40). Since recent investigations by Aouba et al. indicate that the IL-1 network may play a role in the pathogenesis of ECD and that a major phenotype of the disease is infiltration by CD34-positive cells, it has been postulated that imatinib may be successful in the treatment of ECD (12). A 65-year-old female with ECD received imatinib (400 mg/day for 11+ months). Prior to treatment, CT scan revealed bilateral lung infiltrates, mediastinal and hilar lymphadenopathy, infiltration of the second cervical vertebra, enlargement of the left adrenal gland and ^{18}F-FDG uptake in the mesentery and cecum. Three months after treatment onset, general symptoms such as fatigue and dyspnea were improved, and on a 6-month follow-up, CT scan improvements in the lungs, mesentery and cecal area were apparent. Haroche et al. published the outcome of six patients with ECD and characteristic PDGF-R-β expression who were treated with imatinib. Two patients treated for over 12 months had stable disease, while 4 progressed (27).

FUTURE OUTLOOK

ECD is a rare disease with a very poor prognosis. Past therapies have been largely unsuccessful and of the cases reported in the literature, most patients have not survived. Recent advances have moved IFN-α and IL-1Ra to the forefront of treatment as the first line of defense. With a better understanding of the underlying mechanisms of the disease, especially in relation to IL-1 signaling and cytokine involvement, combined with a set guideline for diagnosis based on radiological and histological findings, more effective targeting is hopefully likely in the near future.

DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Bisceglia, M., Cammisa, M., Suster, S., Colby, T.V. *Erdheim-Chester disease: Clinical and pathologic spectrum of four cases from the Arkadi M. Rywlin slide seminars*. Adv Anat Pathol 2003, 10(3): 160-71.
2. Shamburek, R.D., Brewer, H.B. Jr., Gochuico, B.R. *Erdheim-Chester disease: A rare multisystem histiocytic disorder associated with interstitial lung disease.* Am J Med Sci 2001, 321(1): 66-75.
3. Brun, A.L., Touitou-Gottenberg, D., Haroche, J. et al. *Erdheim-Chester disease: CT findings of thoracic involvement*. Eur Radiol 2010, 20(11): 2579-87.
4. Arnaud, L., Pierre, I., Beigelman-Aubry, C. et al. *Pulmonary involvement in Erdheim-Chester disease: A single-center study of thirty-four patients and a review of the literature.* Arthritis Rheum 2010, 62(11): 3504-12.

5. Sanchez, J.E., Mora, C., Macia, M., Navarro, J.F. *Erdheim-Chester disease as a cause of end-stage renal failure: A case report and review of the literature*. Int Urol Nephrol 2010, 42(4): 1107-12.
6. Haroche, J., Amoura, Z., Dion, E. et al. *Cardiovascular involvement, an overlooked feature of Erdheim-Chester disease: Report of 6 new cases and a literature review*. Medicine (Baltimore) 2004, 83(6): 371-92.
7. Haroche, J., Cluzel, P., Toledano, D. et al. *Cardiac involvement in Erdheim-Chester disease magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients.* Circulation 2009, 119(25): E597-8.
8. Veyssier-Belot, C., Cacoub, P., Caparros-Lefebvre, D. et al *Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases.* Medicine (Baltimore) 1996, 75(3): 157-69.
9. Bianco, F., Iacovelli, E., Tinelli, E., Locuratolo, N., Pauri, F., Fattapposta, F. *Characteristic brain MRI appearance of Erdheim-Chester disease*. Neurology 2009, 73(24): 2120.
10. Wright, R.A., Hermann, R.C., Parisi, J.E. *Neurological manifestations of Erdheim-Chester disease*. J Neurol Neurosurg Psychiatry 1999, 66(1): 72-5.
11. Barnes, P.J., Foyle, A., Dakin-Hache, K.A., Langley, R.G.B., Burrel, S., Juskevicius, R. *Erdheim-Chester disease of the breast: A case report and review of the literature.* Breast J 2005, 11(6): 462-7.
12. Aouba, A., Georgin-Lavialle, S., Pagnoux, C. et al. *Rationale and efficacy of interleukin-1 targeting in Erdheim-Chester disease.* Blood 2010, 116(20): 4070-6.
13. Myra, C., Sloper, L., Tighe, P.J. et al. *Treatment of Erdheim–Chester disease with cladribine: A rational approach.* Br J Ophthalmol 2004, 88(6): 844-7.
14. Stoppacciaro, A., Ferrarini, M., Salmaggi, C. et al. *Immunohistochemical evidence of a cytokine and chemokine network in three patients with Erdheim–Chester disease: Implications for pathogenesis.* Arthritis Rheum 2006, 54(12): 4018-22.
15. Martinez, R. *Erdheim-Chester disease. MR of intraaxial and extraaxial brain stem lesions.* Am J Neuroradiol 1995, 16(9): 1787-90.
16. Braiteh, F., Boxrud, C., Esmaeli, B., Kurzrock, R. *Successful treatment of Erdheim-Chester disease, a non-Langerhans-cell histiocytosis, with interferon-alpha*. Blood 2005, 106(9): 2992-4.
17. Haroche, J., Amoura, Z., Trad, S.G., Wechsler, B., Cluzel, P., Grenier, P.A., Piette, J.C. *Variability in the efficacy of interferon-alpha in Erdheim–Chester disease by patient and site of involvement: Results in eight patients*. Arthritis Rheum 2006, 54(10): 3330-6.
18. Suzuki, H.I., Hosoya, N., Miyagawa, K. et al. *Erdheim–Chester disease: Multisystem involvement and management with interferon-alpha.* Leukemia Res 2010, 34: e21-4.
19. Perlat, A., Decaux, O., Sebillot, M., Grosbois, B., Desfourneaux, V., Meadeb, J. *Erdheim–Chester disease with predominant mesenteric localization: Lack of efficacy of interferon alpha*. Joint Bone Spine 2009, 76(3): 315-7.
20. Boissel, N., Wechsler, B., Leblond, V. *Treatment of refractory Erdheim–Chester disease with double autologous hematopoietic stem-cell transplantation*. Ann Intern Med 2001, 135(9): 844-5.
21. Sheidow, T.G., Nicolle, D.A., Heathcote, J.G. *Erdheim–Chester disease: Two cases of orbital involvement.* Eye (Lond) 2000, 14(4): 606-12.
22. Jeon, I., Lee, S.S., Lee, M.K. *Chemotherapy and interferon-alpha treatment of Erdheim-Chester disease*. Pediatr Blood Cancer 2010, 55(4): 745-7.
23. Brikos, C., O'Neill, L.A. *Signaling of toll-like receptors*. Handb Exp Pharmacol 2008, 183: 21-50.
24. Gomez, C., Diard, F., Chateil, J.F., Moinard, M., Dousset, V., Rivel, J. [*Imaging of Erdheim-Chester disease] (in French)*. J Radiol 1996, 77(12): 1213-21.
25. Egan, A.J., Boardman, L.A., Tazelaar, H.D., Swensen, S.J., Jett, J.R., Yousem, S.A., Myers, J.L. *Erdheim-Chester disease: Clinical, radiologic, and histopathologic findings in five patients with interstitial lung disease.* Am J Surg Pathol 1999, 22(1): 17-26,
26. Bohlega, S., Alwatban, J., Tulbah, A., Bakheet, S.M., Powe, J. *Cerebral manifestation of Erdheim-Chester disease: Clinical and radiologic findings.* Neurology 1997, 49(6): 1702-5.
27. Haroche, J., Amoura, Z., Charlotte, F. et al. *Imatinib mesylate for platelet-derived growth factor receptor-beta-positive Erdheim-Chester histiocytosis*. Blood 2008, 111(11): 5413-5.
28. De Filippo, M., Ingegnoli, A., Carloni, A. et al. *Erdheim-Chester disease: Clinical and radiological findings.* Radiol Med 2009, 114(8): 1319-29.
29. Ferrozzi, F., Bova, D., Tognini, G., Zuccoli, G. *Pseudotumoral bilateral involvement of the breast in Erdheim-Chester disease: CT appearance*. J Comput Assist Tomogr 2000, 24(2): 281-3.
30. Caparros-Lefebvre, D., Pruvo, J.P., Remy, M., Wallaert, B., Petit, H. *Neuroradiologic aspects of Erdheim-Chester disease.* Am J Neuroradiol 1995, 16(4): 735-40.
31. Lachenal, F., Cotton, F., Desmurs-Clavel, H. et al. *Neurological manifestations and neuroradiological presentation of Erdheim-Chester disease: Report of 6 cases and systematic review of the literature.* J Neurol 2006, 253(10): 1267-77.
32. Sandrock, D., Merino, M.J., Scheffknecht, B.H., Neumann, R.D. *Scintigraphic findings and follow up in Erdheim-Chester disease.* Eur J Nucl Med 1990, 16(1): 55-60.
33. Matsui, K., Nagata, Y., Hiraoka, M. *Radiotherapy for Erdhem-Chester disease.* Int J Clin Oncol 2007, 12(3): 238-41.
34. Mascalchi, M., Nencini, P., Nistri, M., Sarti, C., Santoni, R. *Failure of radiation therapy for brain involvement in Erdheim Chester disease*. J Neurooncol 2002, 59(2): 169-72.
35. Kujat, C., Martin, J., Puschel, W. [*Erdheim-Chester disease] (in German).* Radiologe 1991, 31(6): 297-306.
36. Jakobson, A.M., Kreuger, A., Hagberg, H., Sundstrom, C. *Treatment of Langerhans cell histiocytosis with alpha-interferon.* Lancet 1987, 2(8574): 1520-1.
37. Esmaeli, B., Ahmadi, A., Tang, R., Schiffman, J., Kurzrock, R. *Interferon therapy for orbital infiltration secondary to Erdheim-Chester disease.* Am J Ophthalmol 2001, 132(6): 945-7.
38. Utikal, J., Ugurel, S., Kurzen, H. et al. *Imatinib as a treatment option for systemic non-Langerhans cell histiocytoses.* Arch Dermatol 2007, 143(6): 736-40.
39. Janku, F., Amin, H.M., Yang, D., Garrido-Laguna, I., Trent, J.C., Kurzrock, R. *Response of histiocytoses to imatinib mesylate: Fire to ashes.* J Clin Oncol 2010, 28(31): E633-6.
40. Appel, S., Boehmler, A.M., Grunebach, F. et al. *Imatinib mesylate affects the development and function of dendritic cells generated from CD34+peripheral blood progenitor cells.* Blood 2004, 103(2): 538-44.