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Commentary

A Tale of Two Histiocytic Disorders

FILIP JANKU,[a] JAVIER MUNOZ,[a] VIVEK SUBBIAH,[a] RAZELLE KURZROCK[b]

[a]Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [b]Moores Cancer Center, The University of California San Diego, San Diego, California, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Histiocytosis is a group of rare disorders of unknown etiology characterized by proliferation and accumulation of histiocytes [1]. Histiocytosis is subclassified as Langerhans cell histiocytosis (LCH) and non-LCH. Non-LCH includes Rosai-Dorfman disease, Erdheim-Chester disease (ECD), interdigitating dendritic cell sarcoma, and histiocytic sarcomas [2]. Both LCH and ECD are caused by accumulation and proliferation of histiocytic cells, but each entity has distinct clinical and pathological features, although rarely both diseases can coexist [3, 4]. LCH is associated with accumulation of dendritic cells and typically presents in children, but less often in adults, with an incidence of nine cases per million per year. ECD is a disease of adults, which is associated with xanthogranulomatous infiltration of foamy macrophages. Only about 500 cases have been reported in the literature to date [3, 5]. It remains unclear whether LCH and ECD are neoplastic or reactive, but in many patients they behave like neoplasms. Advances in genome sequencing technologies led to the identification of *BRAF* V600E mutations in 57% (35 of 61) of patients with LCH and 54% (13 of 24) of patients with ECD [6, 7].

Both LCH and ECD can vary in clinical presentation and prognosis depending on the extent of disease and organ involvement [8]. Therapeutic options include surgery, radiation, vinblastine, prednisone, 6-mercaptopurine, cladribine, and cytarabine for LCH and corticosteroids, vinca alkaloids, anthracyclines, cladribine, interferon-α, anakinra, imatinib, and, most recently, infliximab for ECD [3, 5, 8–18]. Whereas the treatment of LCH has been defined based on the results of prospective studies, including randomized trials, ECD is currently treated on the basis of information from published case series, mostly from Europe and North America [8–21].

Yin et al. [22] are to be commended for presenting a patient with simultaneous LCH (Hand-Schuller-Christian disease) and ECD and their subsequent retrospective review of an additional 54 patients with LCH and six patients with ECD treated in a single tertiary referral center in China. The coexistence of these two entities is consistent with other previously published reports [4]. The patient presented by Yin et al. [22] had a relatively typical disease course over several years (currently 14 years from diagnosis), with symptoms including central diabetes insipidus, hyperprolactinemia, bone involvement, exophthalmus, and underactive thyroid. The patient had a favorable response to external-beam radiation therapy and systemic therapy with interferon-α. In their analysis of the 54 patients with LCH (eosinophilic granuloma, $n = 49$; Hand-Schuller-Christian disease, $n = 5$) and six patients with ECD, they [22] demonstrated that all 35 patients with unifocal eosinophilic granuloma were cured with surgery, and all patients with multifocal eosinophilic granuloma, Hand-Schuller-Christian disease, or ECD were alive, except for one woman who died from unspecified toxicity of chemotherapy.

As mentioned, there is some agreement on how LCH should be managed; however, the treatment of patients with ECD remains empiric, based on evidence from case reports and case series [8–21]. The rarity of this entity makes the feasibility of conducting a prospective trial challenging [5]. Traditionally, patients with ECD were deemed to have a poor prognosis, and most patients succumbed to the disease within 3 years. In contrast, our experience suggests that, given the newer therapeutic options, including, but not limited to, interferon-α, imatinib, anakinra, and infliximab, patients can do well for a long period of time [8, 9, 12–14, 16, 17, 23]. These observations are consistent with the experience of Yin et al. [22], and it is also known that interferon-α is associated with a longer survival time than in historical controls [8]. The individual prognosis depends on the degree of organ involvement, infiltration of the central nervous system (CNS) or infiltration of critical visceral organs, and treatment, which can affect outcome [8]. A recent retrospective analysis of 53 patients treated in western European countries and Israel demonstrated 1-year and 5-year survival rates of 96% and 68%, respectively, which is in line with our experience [8, 9, 12]. Factors selected on multivariate analysis that predicted a poor survival outcome included CNS involvement and not being treated with interferon-α [8]. There is no systemic therapy that has been approved by regulatory agencies, and the available treatments are deemed to be not curative; however, they can lead to disease regression accompanied by symptom improvement and, at least for interferon, perhaps even to a longer survival duration. Despite the absence of randomized trials, our treatment options have nevertheless expanded substantially within the last several years. Interferon-α is often used as a frontline therapy for ECD [5, 8, 12]. Unfortunately, patients with ECD can have a poor tolerance to classic doses of interferon-α, such as three million units s.c. three times per week, although doses of one million units s.c. three times per week are usually well tolerated and, in our experience, are effective in about half the patients treated [12]. Interferon-α can be replaced by its pegylated form, which is

Correspondence: Filip Janku, M.D., Ph.D., The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), 1515 Holcombe Boulevard, Unit 455, Houston, Texas 77030, USA. Telephone: 713-563-2632; Fax: 713-745-8056; e-mail: fjanku@mdanderson.org Received November 14, 2012; accepted for publication November 20, 2012; first published online in *The Oncologist Express* on January 8, 2013. ©AlphaMed Press 1083-7159/2013/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0440

more costly but has a more convenient weekly dosing schedule [14].

Anecdotal reports have also demonstrated therapeutic responses with the BCR-ABL, KIT, and platelet-derived growth factor receptor tyrosine kinase inhibitor imatinib [9, 13, 24–26]. It has been hypothesized that imatinib can inhibit $CD34^+$ peripheral blood progenitor cells from differentiating into histiocytes; however, beyond that the mechanistic explanation for the activity of imatinib remains unclear [27]. Because natural interleukin-1 receptor antagonist synthesis is induced after stimulation by interferon-α, anakinra, a recombinant human interleukin-1 receptor antagonist approved for rheumatoid arthritis in Europe and the U.S., was anecdotally tested in ECD patients, with encouraging results reported by several investigators [15, 18]. Anakinra mimics the function of a natural inhibitor of interleukin-1 receptor and is well tolerated, with immunosuppression and injection site tenderness being among its very few side effects. Therefore, anakinra can be a reasonable alternative for patients who cannot tolerate interferon-α or who are at risk for suffering deleterious side effects from interferon. The latest potential addition to the therapeutic armamentarium for ECD is the tumor necrosis factor (TNF)-α antibody infliximab [17]. In ECD patients, TNF-α is deemed to regulate the recruitment of histiocytes, and thus, its blockade can lead to disease control. To date, two patients with severe cardiovascular complications of ECD were treated with infliximab in a single institution setting and both showed improvement, with resolution of pericardial effusion and increased cardiac function [17].

Recently, *BRAF* V600E mutations were found in 57% (35 of 61) and 38% (11 of 29) of patients with LCH and in 54% (13 of 24) of patients with ECD [6, 7, 28]. This mutation predicts a positive response to BRAF kinase inhibitors in patients with advanced melanoma [29, 30]. Recently, we showed that a patient with hairy cell leukemia and a *BRAF* mutation achieved a remarkable response after only 3 weeks of the BRAF inhibitor vemurafenib [31]. However, treatment of patients with LCH and ECD with *BRAF* mutations has not been reported.

Despite many therapeutic advances, LCH and ECD remain difficult to eradicate. The arrival of new genotyping technologies, such as next-generation sequencing, has the potential to further explicate the molecular background of these disorders. Furthermore, the heterogeneity of these diseases may have biologic and therapeutic implications. It is known that LCH and ECD can coexist, and Yin et al. [22] reported simultaneously occurring Hand-Schuller-Christian disease and ECD. Furthermore, they also described potentially important clinical characteristics to differentiate these entities. Diabetes insipidus and pituitary stalk thickening point to Hand-Schuller-Christian disease; however, diabetes insipidus can also be found in ECD and osteosclerosis may also support an ECD diagnosis. The advent of advanced molecular technologies may help determine if specific molecular aberrations can differentiate these entities and predict therapeutic response.

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