First-line MAPK inhibition in pediatric histiocytosis: are we ready?

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In this issue of *Haematologica*, Cournoyer *et al*. discuss their experience using first-line mitogen-activated protein kinase (MAPK) inhibitors in childhood Langerhans cell histiocytosis (LCH) and other histiocytic disorders.[1]

LCH, a rare myeloid neoplasm affecting mostly children, is driven by activating mutations in the MAPK pathway, mostly *BRAF*-V600E.[2] It has heterogeneous clinical presentations ranging from limited single-system involvement to severe multisystem or neurodegenerative forms. LCH is defined by the accumulation of CD1a$^+$/CD207$^+$ cells in organs such as bone and skin, and the so-called risk organs (liver, spleen and hematopoietic system); patients with involvement of these organs have a higher risk of mortality.[2] Multisystem LCH is treated with risk-adapted therapy, but many patients require myelosuppressive salvage regimens. MAPK inhibitors, such as dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, are being used to treat refractory LCH and other histiocytic disorders, but most patients relapse after therapy discontinuation.[3,4]

Cournoyer *et al*. treated 14 young patients with relapsed/refractory LCH (13 with proven multisystem disease, one with possible neurodegeneration and diabetes insipidus) and two with relapsed/refractory systemic Rosai-Dorfman-Destomebs disease with dabrafenib, trametinib or inhibitor combination, achieving a 94% favorable response rate; the patient with possible central nervous system (CNS)-LCH had improved neurological symptoms. Eighteen patients received inhibitors first-line, 13 with proven LCH (6 with multisystem and 7 with single-system disease), three with possible CNS-LCH (1 positive for *BRAF*-V600E according to droplet digital polymerase chain reaction [ddPCR]) and two with multisystem juvenile xanthogranuloma. All had sustained favorable responses with a median treatment duration of 2.5 years. The three patients with isolated possible CNS-LCH had improved or stabilized disease. Five LCH patients with single-system disease discontinued therapy and remain well, while four with multisystem LCH who discontinued therapy relapsed and were restarted on inhibitors with rapid response.

Albeit retrospective, the report by Cournoyer *et al.* is important for many reasons. LCH can be almost universally cured with chemotherapy but high rates of treatment failure in patients with multisystem involvement, high toxicity of salvage therapies and long-term morbidity for all relapsed/refractory LCH patients represent major challenges. Therefore, more effective and safer treatment options are warranted. Treatment with MAPK inhibitors is promising due to its ease of administration, less toxicity, the better quality of life it provides and the possibility of it preventing reactivations.

A few studies have shown the effectiveness of MAPK inhibitors in children with relapsed/refractory LCH or neurodegenerative disease.[3,4] However, the efficacy of first-line MAPK inhibitor monotherapy has been unknown, and the paper by Cournoyer *et al*. is the first report of such a strategy in children with LCH or juvenile xanthogranuloma.

A few caveats need discussion. First, not all LCH patients are candidates for first-line inhibitor therapy, which is reasonable in clinical neurodegeneration or infants with risk organ-positive multisystem disease who are at high risk of early treatment failure. In contrast, low-risk patients with relapsed/refractory multifocal bone involvement or risk organ-negative multisystem disease routinely respond to mild chemotherapy and may not need inhibitors, unless they are resistant. This is due to the unknown optimal duration of inhibitor therapy and risk of indefinite and unnecessary treatments for mild disease. Furthermore, these inhibitors are not indicated for unifocal bone LCH, which can resolve spontaneously. Cournoyer *et al*. treated seven patients with single-system LCH (3 multifocal and 4 unifocal bone onvolvement) with inhibitors as first-line therapy with favorable response; however, as they state, it is unknown whether these responses were due to inhibitors or spontaneous LCH remission.

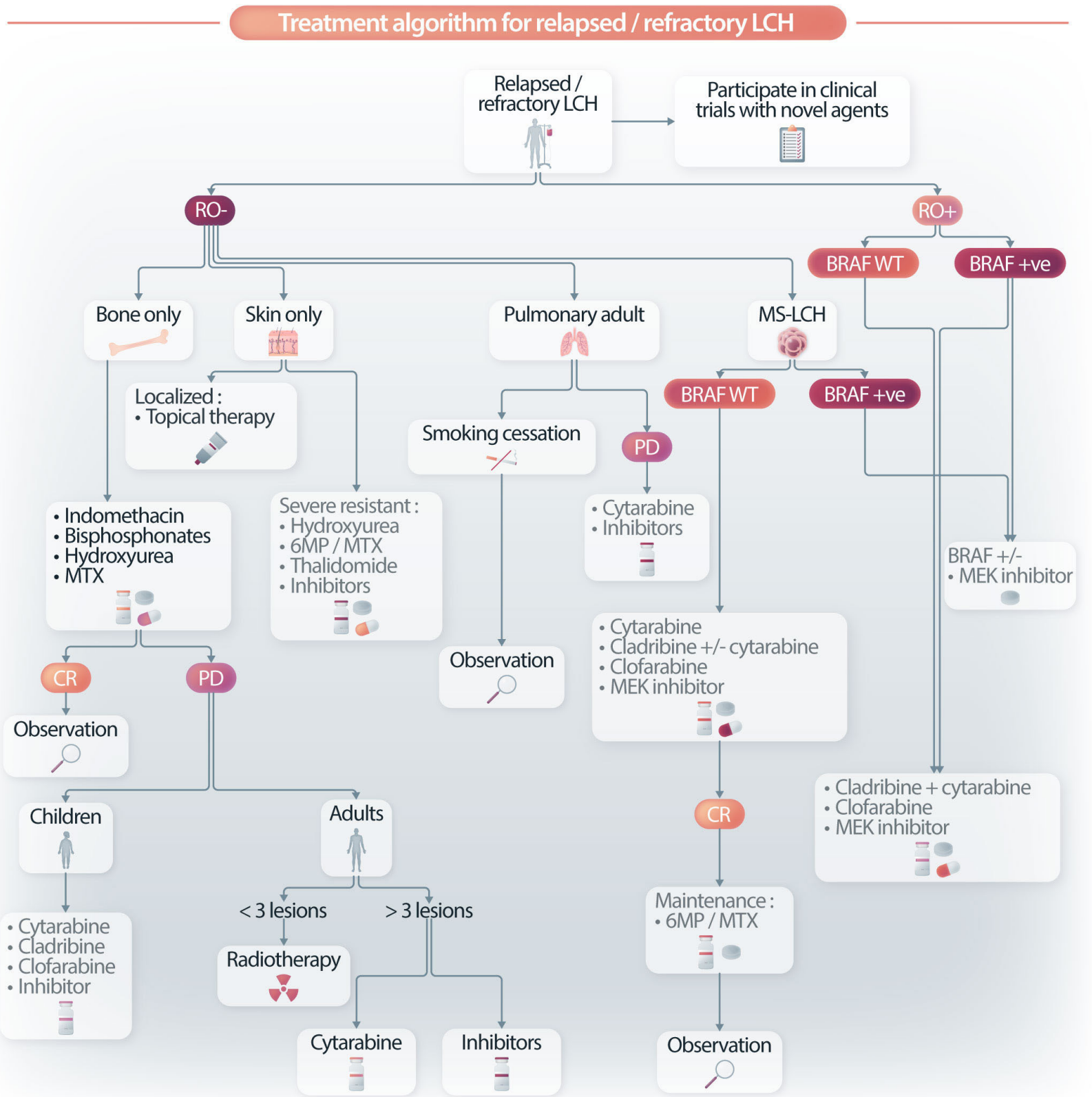

Figure 1. A treatment algorithm for relapsed/refractory Langerhans cell histiocytosis. LCH: Langerhans cell histiocytosis; RO: risk organ; WT: wild-type; MS: multisystem; PD: progressive disease; CR: complete remission; MTX: methotrexate; 6MP: 6-mercapto-purine.

Second, it is controversial whether patients with isolated diabetes insipidus should be treated for LCH. Indeed, in a few pediatric studies on pituitary stalk thickening, only 8-19% were diagnosed with LCH.[5] It is unknown whether peripheral blood ddPCR anaysis might improve the detection rate of LCH diagnosis. Furthermore, a review from Vienna showed that only 25% of patients with LCH and radiological signs of neurodegeneration progressed to clinical neuorde-generation.[6] Therefore, BRAF inhibitors are reasonable only in patients with presumed LCH, isolated diabetes insipidus and progressive radiological neurodegeneration who have neurological symptoms and are positive by ddPCR for the *BRAF*-V600E mutation. Another issue is the ability of MAPK inhibitors to penetrate the CNS adequately. BRAF/MEK in-hibitors are substrates of P-glycoproteins, and their efflux by the blood-brain barrier leads to limited drug levels within the CNS.[7] Day101 (tovorafenib) is a type II pan-RAF inhibitor with greater CNS penetration, and less dermatological, cardiac and ocular toxicities than other MAPK inhibitors. Nevertheless, the authors showed significant improvement in their CNS-positive patients treated with MEK inhibition. Third, although MAPK inhibitors are better tolerated than

chemotherapy, they are not harmless. However, the authors showed that inhibitors were well tolerated, and that three patients had sustained responses at smaller doses. Leukemia and cutaneous basal cell carcinoma have been seen in adults with histiocytosis following treatment with MAPK inhibitors.[8] No pediatric reports of second malignancies after MAPK inhibitors exist, and the long-term toxicities of these drugs in this population is unknown.

Fourth, the most important question is when to stop these inhibitors? A study of adult patients with histiocytosis whose MAPK inhibitors were discontinued after complete or partial response had been obtained, showed that 77% relapsed after treatment interruption.[9] In the study by Cournoyer *et al.*, 11 patients stopped inhibitors: 36% relapsed at a median time of 5 months and all responded after restarting inhibitors. Therefore, in some patients, such as those with relapsed/refractory, multisystem risk organ-positive disease or neurodegeneration, it may not be safe to stop inhibitors, whereas in others, with relapsed/refractory skin/bone involvement, it might be reasonable to stop inhibitors after 2 years of remission while using ddPCR to monitor for the presence of circulating *BRAF*-V600E. This question should be answered in a prospective clinical trial.

Additionally, targeted inhibitor therapy does not eradicate the LCH clone, whereas chemotherapy does; thus, it is possible that combining chemotherapy with inhibitors might help in MAPK inhibitor discontinuation. Evseev *et al.* reported on nine infants who received vemurafenib and chemotherapy (cytarabine, cladribine) simultaneously as salvage therapy; eight of them showed response without toxicity. Nevertheless, this combination did not eradicate the clone as five of the eight patients relapsed soon after discontinuing vemurafenib and required vemurafenib maintenance therapy.[10] The long-term safety and efficacy of such a combination will need to be validated in prospective trials. Lastly, although effective, MAPK inhibitors carry a high price tag and may not be affordable in countries with limited resources.

In summary, Cournoyer *et al.* have presented a promising study of patients with histiocytic disorders receiving first-line and second-line MAPK inhibitor therapy. These inhibitors are well tolerated and the rate of response to them is high, but they do not prevent relapses after their discontinuation. Prospective trials are needed to determine the long-term efficacy and safety of inhibitors as first-line therapy and optimal therapy duration in children. Validating the sensitivity of minimal disease markers (monitored by ddPCR) will help in the identification of patients in whom inhibitor discontinuation can be safe. Figure 1 shows a possible algorithm for the treatment of LCH, including the potential role of MEK inhibition.

Disclosures

OA is a consultant for Spring Works.

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