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by Oussama Abla

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

Oussama Abla

Division of Haematology/Oncology, Hospital for Sick Children, Toronto
E-mail: oussama.abla@sickkids.ca

In this issue of Haematologica, Cournoyer et al discuss their experience using first-line MAPK inhibitors in childhood Langerhans cell histiocytosis (LCH) and other histiocytic disorders.

LCH, a rare myeloid neoplasm affecting mostly children, is driven by activating mutations in the mitogen-activated protein kinase (MAPK) pathway, mostly BRAF-V600E. It has heterogeneous clinical presentations ranging from limited single system (SS) to severe multisystem (MS) or neurodeenerative (ND) forms. LCH is defined by the accumulation of CD1a+/CD207+ cells in organs like bone and skin, and patients with risk organ (RO) (liver, spleen or hematopoietic system) involvement have a higher risk of mortality. MS-LCH is treated with risk-adapted therapy, but many patients require myelosuppressive salvage regimens. MAPK inhibitors, like 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.

The authors treated 14 young patients with relapsed/refractory (R/R) LCH (13 proven MS, 1 query ND and diabetes insipidus-DI) and 2 R/R systemic Rosai-Dorfman-Destombe disease with dabrafenib, trametinib or inhibitor combination, achieving a 94% favorable response; the patient with query CNS-LCH had improved neurological symptoms. Eighteen patients received first-line inhibitors, 13 proven LCH (6 MS and 7 SS), 3 query CNS-LCH (1 BRAF-V600E+ ddPCR) and 2 MS-juvenile xanthogranuloma (JXG). All had sustained favorable responses with a median treatment duration of 2.5 years. The 3 patients with isolated query CNS-LCH had improved or stabilized disease. Five SS-LCH patients discontinued therapy and remain well, while 4 MS-LCH patients who discontinued therapy relapsed and were restarted on inhibitors with rapid response.

Albeit retrospective, this paper is important for many reasons. LCH can be almost universally cured with chemotherapy but high rate of treatment failure in MS patients, high toxicity of salvage therapies and long-term morbidity for all R/R LCH patients, represent major challenges. Therefore, more effective and safer
treatment options are warranted. Treatment with MAPK inhibitors is promising due to ease of administration, less toxicity, better quality of life and possibility for preventing reactivations. Few studies have shown the effectiveness of MAPK inhibitors in children with R/R LCH or ND. The efficacy of first-line MAPK inhibition monotherapy has been unknown, and this is the first report of such strategy in children with LCH or JXG.

However, few caveats need discussion. First, not all LCH patients are candidates for first-line inhibitor therapy, which is reasonable in clinical ND or infants with RO+ MS disease who are at high risk of early treatment failure. In contrast, low risk patients with R/R multifocal bone or MS-RO routinely respond to mild chemotherapy and may not need inhibitors, unless they are resistant. This is due to the unknown optimal duration of inhibitors and risk of indefinite and unnecessary treatments for mild disease. Further, these inhibitors are not indicated in unifocal bone LCH that can resolve spontaneously. The authors treated 7 SS-LCH patients (3 multifocal and 4 unifocal bone) with first-line inhibitors with favorable response; however, as they state, it is unknown whether these responses were due to inhibitors or spontaneous LCH remission.

Second, it is controversial whether patients with isolated DI should be treated for LCH. Indeed, few pediatric studies on pituitary stalk thickening showed only 8%-19% to be diagnosed with LCH. It is unknown whether peripheral blood ddPCR might improve the detection rate of LCH diagnosis. Further, a review from Vienna showed only 25% of patients with LCH and radiological ND progressed to clinical ND. Therefore, BRAF inhibitors are reasonable only in patients with presumed LCH, isolated DI and progressive radiological ND with neurological symptoms and with positive ddPCR \textit{BRAF-V600E}. Another issue is the ability of MAPK inhibitors to adequately penetrate the CNS. BRAF/MEK inhibitors are substrates of P-glycoproteins, and their efflux by the blood-brain-barrier leads to limited drug levels within the CNS. Day101 (tovorafenib) is a type II panRAF inhibitor with greater CNS penetration, and less dermatologic, cardiac or ocular toxicities than other MAPK inhibitors. Nevertheless, the authors showed significant improvement in their CNS+ 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 3 patients had sustained responses at smaller doses. Leukemia and cutaneous basal cell carcinoma were seen in adult histiocytosis patients after MAPK
inhibitors. No pediatric reports of second malignancies with MAPK inhibitors exist, and their long-term toxicities in this population is unknown.

Fourth, the most important question is when to stop these inhibitors? An adult study of patients with histiocytosis whose MAPK inhibitors were discontinued after complete or partial response, showed that 77% relapsed after treatment interruption. In the current paper, 11 patients stopped inhibitors with 36% relapsing at a median time of 5 months, all responding after restarting inhibitors. Therefore, in some patients, R/R MS-RO or ND, it may not be safe to stop inhibitors, whereas in others, R/R skin/bone, it might be reasonable to stop inhibitors after 2 years of remission while monitoring ddPCR for circulating BRAF-V600E. However, this question should be answered in a prospective clinical trial.

Additionally, targeted inhibitor therapy does not eradicate the LCH clone, like chemotherapy does; thus, it is possible that combining chemotherapy with inhibitors might help in MAPK inhibitor discontinuation. Evseev et al reported 9 infants receiving vemurafenib and chemotherapy (cytarabine, cladribine) simultaneously as salvage therapy; 8 of them showed response without toxicity. Nevertheless, this combination did not eradicate the clone as 5/8 patients relapsed soon after discontinuing vemurafenib and required vemurafenib maintenance. The long-term safety and efficacy of such 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, this is a promising study of patients with histiocytic disorders receiving first-line and second-line MAPK inhibitor therapy. These inhibitors are well tolerated and have a high response rate, 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 (ddPCR) will help identifying patients where inhibitor discontinuation can be safe.
References

Figure 1 shows a treatment algorithm for relapsed/refractory LCH.
Treatment algorithm for relapsed/refractory LCH

1. Relapsed/refractory LCH
   - Participate in clinical trials with novel agents

   1. RO-
      - Bone only
      - Skin only
      - Pulmonary adult
      - MS-LCH

      a. Bone only
         - Localized:
           - Topical therapy
           - Indomethacin
           - Bisphosphonates
           - Hydroxyurea
           - MTX
         - CR
         - Observation

      b. Skin only
         - Smoking cessation
         - PD
         - Observation

      c. Pulmonary adult
         - Severe resistant:
           - Hydroxyurea
           - 6MP/MTX
           - Thalidomide
           - Inhibitors
         - Cytarabine
         - Inhibitors
         - Observation
         - PD
         - Cytarabine
         - Cladribine +/- cytarabine
         - Clofarabine
         - MEK inhibitor
         - CR

      d. MS-LCH
         - BRAF WT
         - BRAF +ve
         - BRAF +/- MEK inhibitor

2. RO+
   - BRAF WT
   - BRAF +ve
   - MEK inhibitor

3. Children
   - Cytarabine
   - Cladribine
   - Clofarabine
   - Inhibitor

4. Adults
   - < 3 lesions
     - Radiotherapy
     - Cytarabine
     - Inhibitors
   - > 3 lesions
     - Maintenance:
       - 6MP/MTX
       - Observation