Comment on "MEK inhibition with trametinib and tyrosine kinase inhibition with imatinib in multifocal histiocytic sarcoma"

We would like to follow up on the above-mentioned paper[1] to complete the history of our patient following publication of the case.

After he progressed under imatinib treatment, as already planned and mentioned in the paper, the patient started a 6th line of therapy with nivolumab in June 2017, 16 months after the initial diagnosis. He had a good performance status Eastern Cooperative Oncology Group (ECOG 1) and no specific complaint apart from occasional abdominal pain and grade 1 fatigue. Programmed death-ligand 1 (PD-L1) expression in the initial diagnostic tissue sample was heterogeneous in 15-20% of the tumor. Because of the lack of any treatment guidelines, our decision was based on the overexpression of the programmed death 1 (PD1)-PDL1 axis. PD-L1 expression is frequently found in histiocytic tumors,[2] and the rate of clinical response reached up to 50% in a sarcoma study on 38 patients.[3] After three doses of nivolumab 3mg/kg every other week, progressive disease was documented on positron emission tomography–computed tomography (PET-CT) with peritoneal, pulmonary, bone and lymph nodes hypercaptation.

We thus decided to switch treatment to lenalidomide as administered in an ongoing phase 2 clinical trial,[4] with 25 mg per day, 21 days out of 28. The patient experienced grade 2 skin toxicity needing dose adjustments. One month later, he suffered a pulmonary embolism despite prophylaxis with aspirin and also presented a progression of peritoneal disease and liver metastases, hence lenalidomide treatment was also interrupted. Of note, the only patient with histiocytic sarcoma included in the above-mentioned trial also developed a deep venous thrombosis.

During this time lapse, the patient's daughter was diagnosed with *BRCA1*-related early breast cancer at 34 years of age. After genetic counseling, the same hereditary mutation in this base excision repair gene was detected in our patient, which occurred after our paper was accepted for publication. A DNA sequencing analysis on the tumor found neither a biallelic mutation nor a loss of heterozygosity (LOH), which could have indicated a hereditary origin of this rare disease. However, preclinical data did suggest that *BRCA1* haploinsufficiency may contribute to genomic instability.[5] To our knowledge, this is the first reported case of histiocytic sarcoma in a *BRCA1* carrier.

The patient died in October 2017 from progressive disease with bowel obstruction, two months into his 7th treatment line. His 20 months survival was unexpectedly long according to recent epidemiologic data showing a median overall survival of only six months for histiocytic sarcomas.[6]

Sophie Voruz,[1] Filipe Martins,[1] Anne Cairoli,[1] Olaia Naveiras,[1] Krisztian Homicsko,[2] Edoardo Missiaglia,[3] Laurence de Leval,[3] Bettina Bisig,[3] Olivier Michielin[2] and Sabine Blum[1]

[1]Service and Central Laboratory of Hematology; [2]Department of Oncology and [3]Institute of Pathology, CHUV, University Hospital of Lausanne, Switzerland

Correspondence: sophie.voruz@chuv.ch

doi:10.3324/haematol.2017.186932

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Voruz S, Cairoli A, Naveiras O, et al. Response to MEK inhibition with trametinib and tyrosine kinase inhibition with imatinib in multifocal histiocytic sarcoma. Haematologica. 2018;103(1):e39-e41.
2. Gatalica Z, Bilalovic N, Palazzo JP, et al. Disseminated histiocytosis biomarkers beyond BRAFV600E: frequent expression of PD-L1. Oncotarget. 2015:6(23):19819-19825.
3. Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res. 2016;6:24.
4. Jacobsen E. A phase II trial of lenalidomide in adults with histiocyte disorders. ClinicalTrials.gov Identifier: NCT02523040.
5. Sedic M, Skibinski A, Brown N, et al. Haploinsuffisiency for BRCA1 leads to cell-type-specific genomic instability and premature senescence. Nat Commun. 2015;6:7505
6. Kommalapati A, Tella SH, Durkin M, Go RS, Goyal G. Histiocytic Sarcoma: a population-based analysis of incidence, demographic disparities, and long-term outcomes. Blood. 2017 Nov 28. [Epub ahead of print]