Ann Hematol (2014) 93:2087–2089
DOI 10.1007/s00277-014-2104-2

LETTER TO THE EDITOR

Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib

V. Vergote · D. Dierickx · A. Janssens · G. Verhoef · T. Tousseyn · P. Vandenberghe · P. Wolter · M. Delforge

Received: 22 April 2014 / Accepted: 7 May 2014 / Published online: 27 May 2014

Dear Editor,

Hairy cell leukemia (HCL) is a mature B-cell lymphoid cancer that can be treated successfully in the majority of patients with various agents like purine nucleoside analogues, rituximab, interferon-alpha, or splenectomy. Recently, it was reported that BRAF V600E mutations can be found in virtually all patients with HCL, suggesting that this genetic event represents a key driver of the disease. The BRAF protein is part of the RAS-RAF-MAPK signaling pathway, which plays a major role in regulating cell survival, proliferation, and differentiation [1].

Various case reports of successful treatment of refractory HCL with the BRAF inhibitor vemurafenib have recently been published [2–7]. Dabrafenib is a reversible BRAF inhibitor with a shorter half-life compared to vemurafenib. We report a 62-year-old male patient with refractory HCL who achieved a rapid and complete hematological response to treatment with the BRAF inhibitor dabrafenib. To our knowledge, this is the first manuscript of the use of dabrafenib in HCL.

The patient was diagnosed in 2008 with HCL at the age of 57 years. The presented signs and symptoms were fatigue, splenomegaly, and pancytopenia. He was initially treated with one cycle of the purine nucleoside analogue cladribine (0.1 mg/kg for 7 days) resulting in normalization of his blood counts. After 22 months, he relapsed with worsening cytopenia and he was retreated with cladribine, but with incomplete recovery of his white blood cell count followed by progressive pancytopenia. Despite four doses of the anti-CD20 monoclonal antibody rituximab at 375 mg/m^2, he remained pancytopenic due to the infiltration of the bone marrow with hairy cells (Fig. 1). A BRAF V600E mutation was detected in his bone marrow by locked nucleic acid PCR followed by Sanger sequencing. Due to increasing red blood cell and platelet transfusion need and progressive splenomegaly, a splenectomy was performed but with no improvement on his blood counts.

One month later, he was hospitalized with neutropenic fever due to invasive pulmonary aspergillosis. On admission, he had a neutrophil count of 100/μL and a platelet count of 13,000/μL. He received caspofungin followed by posaconazole, G-CSF, and broad-spectrum antibiotics because of persisting neutropenic fever and increasing pulmonary infiltrates. After intensive counseling, we obtained approval from the local ethics committee, and informed consent from the patient to start dabrafenib in compassionate use. Dabrafenib (Tafinlar®) was kindly provided free of charge by GlaxoSmithKline, Belgium. On October 1, 2013, dabrafenib was started at a reduced dose of 100 mg twice daily (day 0) to avoid any drug interaction with his antifungal treatment. On day 14, the dose was increased to 150 mg twice daily, the recommended dose in metastatic melanoma. His neutrophil count started to increase after 23 days of treatment. On day 30, his neutrophil count was 1.100/μl, his fever had resolved, inflammatory parameters normalized, and the patient was discharged from the hospital. Platelet count normalized on day 42, neutrophils on day 79, and hemoglobin by day 100 (Fig. 2). Antifungal treatment was discontinued after 2 months.

Bone marrow aspirate and biopsy performed after 79 days of treatment with dabrafenib revealed only scarce hairy cells by morphological examination (Fig. 1), and <1 % hairy cells by flow cytometry. Dabrafenib was discontinued after 129 days.

V. Vergote (✉) · D. Dierickx · A. Janssens · G. Verhoef · P. Vandenberghe · M. Delforge
Department of Hematology, UZ Leuven, UZ Gasthuisberg Herestraat 49, 3000 Leuven, Belgium
e-mail: Vibeke.Vergote@gmail.com

T. Tousseyn
Department of Pathology, UZ Leuven, Leuven, Belgium

P. Wolter
Department of Medical Oncology, UZ Leuven, Leuven, Belgium

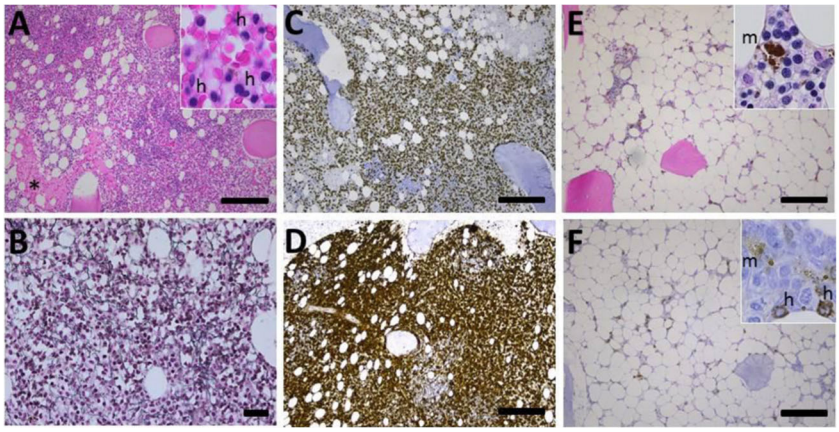

Fig. 1 Histological images from bone marrow trephine pre (**a**–**d**) and post therapy (**e**–**f**). **a** HE staining showing a moderately increased cellularity, caused by the interstitial presence of a lymphocytic infiltrate as well increased red blood cells, including some characteristic "venous lakes" (*asterisk*). The lymphocytes are small, with rounded nucleus and abundant clear cytoplasm (*h* in *inset*). They are surrounded by a delicate pericellular fibrosis (**b** reticulin stain). They express CD20, CD79a (**c**), PAX5, AnnexinV (**d**), and T-bet. **e** HE staining showing a low cellularity mainly composed of regenerating erythroid precursors and iron-loaded macrophages (*m* in *inset*), as well as some myeloid cells and megakaryocytes. Only sparse residual neoplastic hairy cells (*h* in *inset*) can be detected by an anti-CD79a staining (**f**). Pictures were all taken at ×100 (except B at ×200 and *insets* at ×400) with a Leica DFC290 camera. Images were processed using Adobe Photoshop CS5. *Scale bar* 200 μm

Notably, there were no major side effects documented during treatment with dabrafenib, including the absence of any new skin lesions.

Over the past decades, the clinical outcome for patients with HCL has improved significantly because of highly effective therapies, including interferon-alpha, purine nucleoside analogues (cladribine, pentostatin), and rituximab. However, relapse occurs in a significant percentage of patients, with some patients becoming refractory to all currently available agents [4, 8].

Our patient with HCL became refractory to multiple lines of conventional therapy (cladribine, rituximab, splenectomy), and developed severe pancytopenia complicated by a life-threatening invasive pulmonary aspergillosis. As reported by Tiacci et al., a vast majority of HCL cases harbor a V600E mutation of the BRAF gene, suggesting that this genetic event represents a key driver of the disease [1]. Several case reports have been published showing rapid response of refractory HCL to the BRAF inhibitor vemurafenib [2–7]. Both vemurafenib and dabrafenib have been licensed as a treatment for metastatic BRAF V600-mutated melanoma [9]. A recent abstract reported on the successful use of dabrafenib in a patient suffering from metastatic melanoma and HCL [10]. To our knowledge, this is the first full paper of treatment with dabrafenib in a patient with refractory HCL. The patient had a

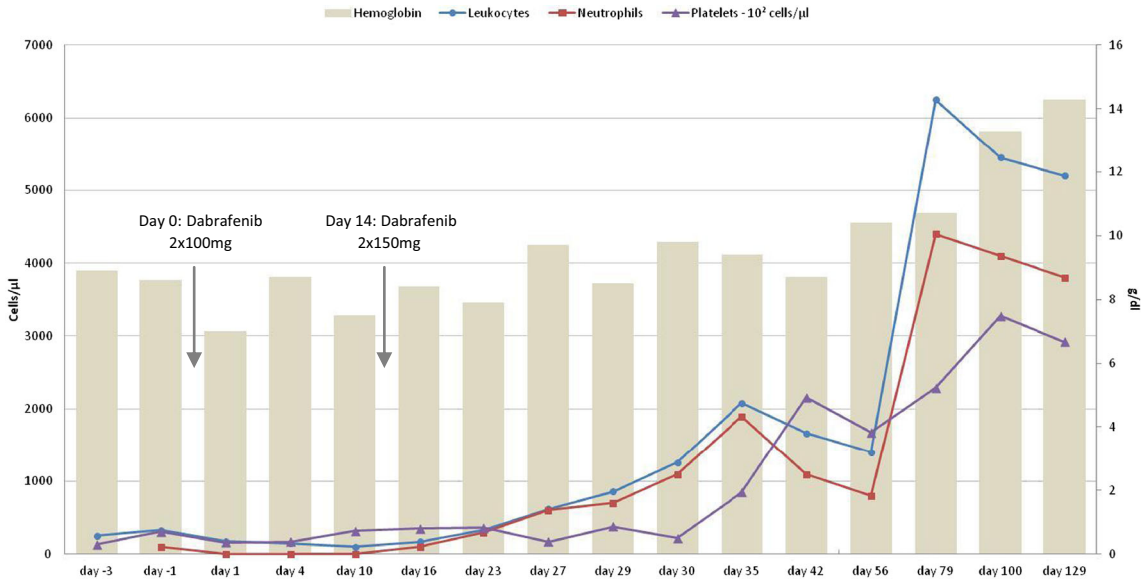

Fig. 2 Plots of serial peripheral blood values from day −3 to day 129 of treatment with dabrafenib. Dabrafenib was started at a reduced dose of 100 mg twice daily on day 0. After 14 days, the dose was escalated to the recommended dose in metastatic melanoma of 150 mg twice daily. Please note that platelet values are displayed as 10^2 cells/μl

rapid and complete hematological and clinical recovery without major treatment-related side effects.

The successful course of this treatment is consistent with previous reports of HCL patients treated with vemurafenib, and supports the therapeutic role of BRAF inhibitors as salvage treatment for refractory HCL. In accordance with the publications on vemurafenib in HCL, we decided to stop treatment when a complete hematological response was reached in order to avoid non-melanoma skin cancer [2–7, 11]. Therefore, additional prospective studies are needed to further optimize the dosing regimen and treatment duration of BRAF inhibitors in hairy cell leukemia.

Acknowledgments We thank GlaxoSmithKline, Belgium for providing dabrafenib (Tafinlar®).

Conflict of interest All authors state that there are no conflicts of interest.

References

1. Tiacci E, Trifonov V, Schiavoni G et al (2011) BRAF mutations in hairy-cell leukemia. N Engl J Med 364:2305–2315
2. Dietrich S, Glimm H, Andrulis M et al (2012) BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med 366: 2038–2040
3. Follows G, Sims H, Bloxham D et al (2013) Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol 161:150–153
4. Munoz J, Schlette E, Kurzrock R (2013) Rapid response to vemurafenib in a heavily pretreated patient with hairy cell leukemia and a BRAF mutation. J Clin Oncol 31:e351–e352
5. Dietrich S, Hüllein S, Hundemer M et al (2013) Continued response off treatment after BRAF inhibition in refractory hairy cell leukemia. J Clin Oncol 31:e300–e303
6. Maurer H, Haas P, Wengenmayer T, Lübbert M, Duyster J, Zeiser R. Successful vemurafenib salvage treatment in a patient with primary refractory hairy cell leukemia and pulmonary aspergillosis. Ann Hematol. 2013; Dec 14. [Epub ahead of print]
7. Peyrade F, Re D, Ginet C et al (2013) Low-dose vemurafenib induces complete remission in a case of hairy-cell leukemia with a V600E mutation. Haematologica 98:e20–e22
8. Grever MR (2010) How I, treat hairy cell leukemia. Blood 115(1): 21–28
9. Jang S, Atkins MB (2013) Which drug, and when, for patients with BRAF-mutant melanoma? Lancet Oncol 14(2):e60–e69. doi:10.1016/S1470-2045(12)70539-9
10. Andritsos L, Blachly J, Kendra K, Lozanski G, Grever M (2013) Co-treatment of hairy cell leukemia and melanoma with the BRAF inhibitor dabrafenib. Blood 122:5311
11. Anforth R, Fernandez-Peñas P, Long GV (2013) Cutaneous toxicities of RAF inhibitors. Lancet Oncol 14(1):e11–e18