EXCEPTIONAL CASE REPORT

blood advances

Classic hairy cell leukemia complicated by pancytopenia and severe infection: a report of 3 cases treated with vemurafenib

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Key Points

- Infections are a major cause of morbidity and mortality in HCL patients, and myelosuppressive therapies increase the risk of poor outcomes.
- Vemurafenib achieves rapid hematologic improvement in HCL and may facilitate management during life-threatening infection.

Introduction

Purine nucleoside analogs (PNAs) remain standard treatment of classical hairy cell leukemia (c-HCL), achieving high rates of complete remission (CR).[1] PNAs are known for causing profound myelosuppression with enduring immunosuppression[2]; however, the studies in which high CR rates were reported after cladribine explicitly excluded patients with active infection.[3,4] A significant proportion of patients with HCL present with infection, and there is a need for effective treatments in this setting.[5]

The BRAF p.V600E mutation, initially recognized as a target in treatment of malignant melanoma, was identified in the majority of c-HCL cases, leading to successful treatment of PNA-refractory HCL with BRAF inhibitors (BRAFi).[6,7] Although several phase 2 studies confirm a high response rate to vemurafenib with different dose levels, doses as low as 240 mg twice daily abrogate the signal from BRAFV600E, interrupting ERK phosphorylation.[8] Unlike PNAs, BRAFi carry less risk of myelosuppression.[9,10] Side effects noted with BRAFi include skeletal pain, photosensitivity, skin tumors, including keratoacanthomas and squamous cell cancers, and renal toxicity. We report 3 cases of patients with c-HCL with life-threatening infections following PNA treatment who received therapy with the BRAFi vemurafenib resulting in the reversal of profound cytopenias.

Case description

Case 1

A 52-year-old man presented with pneumonia. Bone marrow biopsy confirmed a diagnosis of c-HCL by immunohistochemistry and flow cytometry, and BRAF p.V600E mutation was demonstrated. Treatment with pentostatin (4 mg/m^2) was initiated. His absolute neutrophil count (ANC) declined from 0.526 $\times$ 10^9/L to 0 $\times$ 10^9/L upon starting cycle 2. Modifications to treatment included reduced pentostatin dose (2 mg/m^2), delayed schedule of administration (every 3 weeks), and daily filgrastim (480 μg subcutaneously). Following 6 doses of pentostatin, his ANC was 0.13 $\times$ 10^9/L, and bone marrow biopsy demonstrated 50% persistent c-HCL.

The patient was hospitalized for acute cholecystitis, which progressed to severe sepsis. Although his clinical status improved after cholecystostomy and broad-spectrum antibiotics, profound neutropenia (ANC, 0 $\times$ 10^9/L) persisted. Salvage treatment with vemurafenib 240 mg orally twice a day was initiated, and filgrastim was continued. After 1 week, vemurafenib was increased to 480 mg orally twice a day. After 2 weeks, the patient's ANC recovered to $>$3 $\times$ 10^9/L, with durable response despite discontinuation of filgrastim.

Vemurafenib was held for 8 days in preparation for cholecystectomy with subsequent drop in ANC from $>$3 $\times$ 10^9/L to 0.1 $\times$ 10^9/L. Upon reinitiation of vemurafenib, ANC quickly recovered to $>$3 $\times$ 10^9/L. Dose reduction of the vemurafenib was required after 15 weeks due to migratory arthralgias and myalgias, which are well-known adverse reactions.[11] Bone marrow biopsy after treatment revealed 30% to 40% hairy cell involvement, yet the patient has persistently had normal peripheral blood counts for 3.5 years after restarting vemurafenib. Considering the profound initial decline in ANC when vemurafenib was

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temporarily held, he now refuses to consider alternative therapy. Thus, he is maintained on vemurafenib 240 mg orally daily despite complaints of diffuse arthralgia.

Case 2

A 36-year-old man presented with fatigue and dyspnea on exertion. Workup revealed ANC of 0.1×10^9/L and platelet count of 34×10^9/L. A bone marrow biopsy was consistent with c-HCL by immunohistochemistry and flow cytometry and presence of BRAF p.V600E mutation. Treatment was initiated with pentostatin (4 mg/m^2) every 2 weeks.

Eight days after the second pentostatin infusion, the patient presented with severe left buttock pain. He had extensive left buttock and thigh cellulitis, which progressed to septic shock, requiring admission to the medical intensive care unit for vasopressor support. He received broad-spectrum antibiotics and filgrastim for 2 weeks. Once stabilized, the patient began treatment with vemurafenib 480 mg orally twice a day. ANC rapidly improved, rising from 0.402×10^9/L to 1.47×10^9/L after 2 weeks of treatment. Sepsis resolved with recovery from neutropenia.

Vemurafenib was continued due to extensive infection and persistence of an open wound, while filgrastim was discontinued. Bone marrow biopsy revealed CR following a 7-month course of vemurafenib. The patient is currently without any evidence of disease recurrence after 18 months.

Case 3

A 46-year-old man presented with fatigue, night sweats, unintentional weight loss, and pancytopenia. A peripheral smear showed hairy cells, and a computed tomographic scan revealed splenomegaly. Bone marrow biopsy confirmed diagnosis of BRAF p.V600E–positive c-HCL with 90% marrow involvement. The patient completed 2 doses of pentostatin, with each dose delayed by a week due to neutropenia. He received 1 dose of filgrastim after the second dose of pentostatin, but he had significant side effects, and filgrastim was discontinued. Dose 3 of pentostatin was held due to concern for infection. The patient presented to the hospital 3 days later with febrile neutropenia and an ANC of $<0.1 \times 10^9$/L and severe sepsis. Workup revealed rhinovirus, and blood cultures grew viridans group streptococci. Once his clinical status stabilized, vemurafenib was begun at 960 mg orally twice a day, with recovery to ANC $>1.5 \times 10^9$/L 26 days later. Vemurafenib was briefly held due to pancytopenia potentially related to the vemurafenib and restarted at 240 mg orally twice a day and continued for a total of 49 days without any subsequent adverse reactions. Pentostatin (4 mg/m^2) was then restarted.

He completed 4 cycles of pentostatin and 2 cycles of consolidation followed by 8 doses of weekly rituximab (375 mg/m^2). Bone marrow biopsy 1 month following rituximab revealed no evidence of HCL, and peripheral counts normalized. The patient is currently with no evidence of disease 1 year later.

Methods

This report was a retrospective chart review of 3 c-HCL patients with severe neutropenia and life-threatening infection following PNA therapy who were offered vemurafenib as salvage therapy for leukemia. This study was approved by the institutional review board, and patients provided written consent for the review of their medical records and publication of the results, per the Declaration of Helsinki.

Results and discussion

PNAs successfully induce durable CR in the majority of c-HCL patients. However, early worsening of myelosuppression and immunosuppression due to therapy greatly amplifies the risk of severe infection. One study evaluating PNA induction for this disease found a 25% incidence of infection or neutropenic fever.[5] BRAFi in refractory c-HCL effect rapid hematological recovery, suggesting a role for these agents in HCL cases where PNAs may be contraindicated due to infection and neutropenia.[12-14] Prior to starting vemurafenib, all 3 patients were profoundly neutropenic. Upon initiation of vemurafenib, all patients had rapid improvement in neutropenia, with ANC rising to $>1 \times 10^9$/L in 5, 2, and 26 days, respectively. This response facilitated recovery from severe infection potentially faster than would be expected with PNA therapy and likely averted fatal outcomes. These cases illustrate 2 strategies in the treatment of HCL with BRAFi complicated by infection. The first 2 cases continued vemurafenib therapy in lieu of resuming standard PNA induction, whereas the final patient used vemurafenib as a bridge to definitive PNA therapy. In patient 1, the continued administration of low-dose vemurafenib has resulted in normal blood counts for an extended period of time.

Although anecdotal reports such as ours support "off-label" case-by-case consideration for BRAFi treatment in c-HCL patients with this mutation and life-threatening infection, several considerations prompt additional investigation. Although rapid, the hematologic recovery may not be durable; in the case of patient 1, ANC declined from $>3 \times 10^9$/L to 0.1×10^9/L when vemurafenib was held for 8 days. The optimal dosing strategy for vemurafenib remains undetermined; 2 patients required dose reductions due to adverse effects. Finally, Dietrich et al found that a median 3-month course of variable low-dose vemurafenib induced hematologic response in a majority of patients; however, median time to relapse after cessation of vemurafenib was just 14 months.[8] Last, vemurafenib is an expensive therapy and not currently approved for use in c-HCL. All 3 patients in our series had vemurafenib covered by their insurance company, but cost may limit the ability of other c-HCL patients with infection from benefiting from this treatment approach.

Tiacci and colleagues report high rates of durable response with the combination of vemurafenib and rituximab in relapsed and refractory c-HCL patients. This regimen was short, safe, and nonmyelotoxic.[15] Recently, moxetumomab pasudotox was approved for use in HCL, but patients with active infection or uncontrolled infection were excluded from the clinical trials with this agent, and the established side effect of capillary leak syndrome would be excessively toxic in patients who are ill from infection.[16] This underscores the need to study novel therapies in this specific population.

These cases demonstrate the need for further research into the role of BRAFi therapy alone and/or in combination with other agents in the treatment of c-HCL patients with infection for whom standard PNA induction may be contraindicated.

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Authorship

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