AHFS Final Determination of Medical Acceptance: Off-label Use of Vemurafenib for Relapsed/Refractory Hairy Cell Leukemia

Drug: Vemurafenib

Off-label Use: Relapsed/refractory hairy cell leukemia

Off-label Use for Review:

- Results from phase 2, single-group, multicenter clinical studies

Strength of Evidence: Level 2 (moderate strength/quality)

Grade of Recommendation: Recommended use (accepted)

Narrative Summary:

Hairy cell leukemia is a rarely occurring, indolent, low-grade, B-cell malignancy that has a remitting and relapsing response pattern to sequential treatments.[10001,10002] Watchful waiting is the preferred first-line approach for the estimated 10-20% of patients with hairy cell leukemia who present without clinically significant cytopenias, symptomatic organomegaly, recurrent infections, and constitutional symptoms.[10001] For those patients requiring therapy, purine analogues (i.e., cladribine or pentostatin) are quite effective, resulting in complete remission in approximately 80-90% of patients; administration of rituximab concurrently with or after purine analogues may also be an option.[10001] Despite the high initial response rates observed with purine analogue therapy for hairy cell leukemia, many patients experience relapse.[10001,10002] A variety of treatment options have been evaluated for the treatment of relapsed/refractory disease including the administration of vemurafenib, a BRAF inhibitor.[10001,10002] The *BRAF* V600E kinase-activating mutation is the genetic cause of hairy cell leukemia in ≥95% of cases.[10001]

Two phase 2, single-group, multicenter clinical studies (one in Italy and the other in the United States[US]) evaluated the use of vemurafenib monotherapy in relapsed or refractory hairy cell leukemia.[10003] In the Italian trial, patients with hairy cell leukemia refractory to a purine analogue, early relapse after purine analogue therapy, or severe adverse effects from prior purine analogue treatment were eligible for study enrollment.[10003] Patients were eligible for study

enrollment in the US trial if their disease was refractory to a purine analogue, early relapse occurred after the initial course of purine analogue therapy, or ≥2 relapses occurred more than 2 years after a third or later course of a purine analogue.[10003] In addition, patients in both trials were required to meet certain cytopenic requirements (e.g., hemoglobin level, neutrophil count, or platelet count) and confirm presence of a *BRAF* V600E mutation.[10003] In the Italian study, patients were administered vemurafenib 960 mg orally twice daily for a minimum of 8 weeks; therapy could be continued for a maximum of 16 weeks if a complete response was not achieved at 8 weeks. [10003] In the US study, vemurafenib was administered at a dose of 960 mg orally twice daily on a continuous schedule for 12 weeks.[10003] Up to an additional 12 weeks of vemurafenib therapy was allowed for patients with residual disease.[10003]

In the Italian trial, 28 patients were enrolled, while 26 patients were included in the US trial (at the time of study publication, enrollment in this trial was ongoing with a planned total enrollment of 36 patients).[10003] The median patient age was 57 and 62 years in the Italian and US trials, respectively.[10003] The median number of prior therapies was 3 in both trials; 56% of patients in the Italian trial had disease refractory to the immediate prior therapy compared to 41% of patients in the US trial.[10003] The primary endpoint of the Italian trial was the rate of complete response.[10003] In the US trial, the primary endpoint was the overall response rate after 12 weeks of vemurafenib therapy.[10003] Secondary endpoints varied between the trials.[10003]

Overall, 26 of the 28 patients in the Italian trial completed planned vemurafenib therapy, with one patient discontinuing treatment due to an acute myocardial infarction unrelated to the study drug and another withdrawing consent after experiencing drug-related grade 3 reversible pancreatitis.[10003] In the US trial, 24 of the 26 patients were administered vemurafenib therapy for a median of 18 weeks (range: 12 to 24 weeks).[10003] Of the other 2 enrolled patients, one died from progressive pneumonia deemed unrelated to the study drug and the other withdrew consent due to drug-related grade 3 reversible photosensitivity.[10003] Results revealed an overall response rate of 96% (25 of 26 patient) in the Italian study and 100% (24 of 24 patients) in the US study. [10003] The rates of complete and partial responses were similar between the 2 trials.[10003] At a median follow-up of 23 months in the Italian trial, the median relapse-free survival was 19 months among patients with a complete response and 6 months among those experiencing a partial response.[10003] In addition, the median treatment-free survival was 25 months among those patients with a complete response and 18 months among those experiencing a partial response.[10003] The progression-free survival rate and overall survival rate were 73% and 91%, respectively, in the US trial at 1 year.[10003] Commonly reported vemurafenib-related adverse events in both trials included skin-related toxicity (e.g., rash, photosensitivity), arthralgias or arthritis, pyrexia, and an increased bilirubin level; these events were primarily of grade 1 or 2.[10003] Of note, cutaneous basal cell carcinomas occurred in 2 patients and cutaneous superficial melanoma developed in 1 patient in the Italian study.[10003] In the US trial, 3 patients developed cutaneous squamous cell carcinomas and a single patient experienced a cutaneous basal cell carcinoma.[10003] All tumors were managed via simple excision.[10003] Dosage reduction of vemurafenib was required in 15 of 26 patients in the Italian trial and 13 of 26 patients in the US trial.[10003] Adverse events leading to dose reductions included rash; increased AST/ALT, creatinine, or bilirubin; arthralgia; pancreatitis; photosensitivity; neutropenia; palmar and plantar dysesthesia.[10003]

The complete results of the full cohort of 36 patients in the US trial were subsequently published, with 32 patients completing at least 4 weeks of vemurafenib therapy.[10004] The best overall response rate with vemurafenib in the entire cohort was 86%, with 33% experiencing a complete response and 53% a partial response.[10004] After a median follow-up of 40 months, 21 (68%) of 31 responders experienced relapse with a median relapse-free survival of 19 months.[10004] Of the 21 patients with relapse, 14 were retreated with vemurafenib and 86% achieved a complete hematologic response.[10004] At 4 years, overall survival was 82%, with a significantly reduced overall survival in patients who relapsed within 1 year of initial vemurafenib therapy.[10004]

In another phase 2, single-group, single-center trial, the combination of vemurafenib plus rituximab was evaluated in patients with relapsed or refractory hairy cell leukemia.[10005] Patients eligible for study enrollment had hairy cell leukemia with a confirmed *BRAF* V600E mutation, cytopenia, and any of the following: primary refractoriness to a purine analogue; early relapse after an initial purine analog course or at any time after a second or later course; severe adverse effects related to purine analogue therapy; ineligibility for chemotherapy; and prior *BRAF* inhibitor treatment.[10005] Vemurafenib was administered at a dose of 960 mg orally twice daily for 8 weeks with rituximab 375 mg/m^2 as an IV infusion given 8 times over a period of 18 weeks.[10005] Patients underwent 2 induction cycles, each consisting of 4 weeks of vemurafenib and 2 rituximab infusions on days 1 and 15, followed by 2 weeks of rest and evaluation of response.[10005] After the second induction cycle, the last 4 rituximab infusions were given as consolidation therapy 2 weeks apart from one another.[10005]

Thirty-one patients were enrolled in the study with one patient subsequently withdrawn due to having an unclassified B-cell neoplasm instead of hairy cell leukemia; a majority were male (n=28) with a median age of 61 years.[10005] The median number of prior therapies was 3 (range: 1 to 14); all patients received prior therapy with a purine analogue.[10005] The primary study endpoint was complete response at the end of planned treatment.[10005] Time to response, minimal residual disease status, and survival were also evaluated.[10005] Results revealed occurrence of a complete response in 26 (87%) of 30 patients in the intention-to-treat analysis.[10005] A complete response was seen in all patients who were refractory to chemotherapy or rituximab and all patients who had previously received a *BRAF* inhibitor.[10005] Of those who experienced a complete response, 17 patients were cleared of minimal residual disease.[10005] For all 30 patients, progression-free survival was 78% at a median follow-up of 37 months.[10005] At a median follow-up of 34 months, relapse-free survival was 85% among the 26 patients with a complete response.[10005] Adverse effects were primarily grade 1 or 2, transient, and were reported previously in patients administered vemurafenib and rituximab as monotherapy.[10005] Dosage reduction of vemurafenib occurred in 14 patients due to increases in amylase/lipase, rash, arthralgia, hyperbilirubinemia, potential interaction with an azole antifungal, and hemolytic anemia.[10005]

In addition to the above clinical data, there are several case reports/case series detailing the successful use of vemurafenib (often in a low-dose regimen of 240 mg twice daily) in relapsed/refractory hairy cell leukemia.[10006-10015]

Based on current evidence, vemurafenib, either as monotherapy or in combination with rituximab, as a treatment for relapsed/refractory hairy cell leukemia in patients with a confirmed *BRAF* V600E kinase-activating mutation has Level 2 (moderate strength/quality) evidence supporting its use.[10003,10005] Vemurafenib therapy results in an improvement in response in these patients with a tolerable safety profile.[10003,10005]

Dosage

When vemurafenib is used for the treatment of relapsed/refractory hairy cell leukemia in patients with a confirmed *BRAF* V600E kinase-activating mutation, the usual dosage administered is 960 mg orally twice daily for a minimum of 8 weeks, and if a complete response does not occur, a maximum of 24 weeks.[10003,10005] However, low-dose vemurafenib regimens have been successfully administered in case reports.[10006-10015]

References:

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Oncology Expert Committee Voting Results and Comments:

First-Round Vote (7 of 7 committee members returned the initial ballot):

Proposed Level of Evidence: Level 2 (Moderate strength/quality)

Concur with rating: 7 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 4 votes

Reasonable choice (Accepted, with possible conditions): 3 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Reviewer Comments on Level of Evidence and Grade of Recommendation

There are very few treatment options for hairy cell leukemia, especially after progressing/refractory to the frontline option of the purine analogs. A treatment option like vemurafenib, which has shown such a high response rate in early trials, is a much needed next line of therapy for this patient population. - Also notable is the lack of infectious complications associated with vemurafenib. In a patient population that already has a higher infectious risk due to baseline neutropenia, the ability to give a non-myelosuppressive agent is valuable. Sometimes, the purine analogs are not safe to administer in a patient with an active infection due to their

degree of myelosuppression. Vemurafenib, a non-myelosuppressive option, treats hairy cell leukemia, therefore allowing for neutrophil recovery, and increases the chance of resolving the infection.

Response rates, especially complete responses, were higher when combined with rituximab. Additionally, the duration of response was longer. The optimal dosing of vemurafenib is yet to be determined but appears that full dose (960 mg BID) yields better outcomes. The high number of complete responses in the combination group is similar to that of purine analog, so it would be nice to see a head-to-head comparison for first-line treatment.

The limited scope of relevant trials (phase 2, low sample sizes, non-comparative, surrogate primary endpoints) necessitates only moderate quality level of evidence. The dearth of options in the relapsed/refractory HCL space, particularly for patients who have failed or are not candidates for purine analog therapy, makes it even more important that vemurafenib be recommended and available for use, with or without rituximab, given the optimistic efficacy of these small trials and relatively low toxicity.

Consensus Vote (6 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 2 (Low strength/quality)

Concur with rating: 6 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 6 votes

Reasonable choice (Accepted, with possible conditions): 0 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Recommended use (accepted)

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): Chase Ayres PharmD, BCOP; Sandra Cuellar PharmD, BCOP; Rachel Bubik PharmD, BCOP; Chelsea Gustafson PharmD, BCOP; Isabel Houlzet PharmD, BCOP; Kathleen Wiley MSN, RN; Kate Taucher PharmD, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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