Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia

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Abstract

Hairy cell leukemia is an uncommon hematologic malignancy characterized by pancytopenia and marked susceptibility to infection. Tremendous progress in the management of patients with this disease has resulted in high response rates and improved survival, yet relapse and an appropriate approach to re-treatment present continuing areas for research. The disease and its effective treatment are associated with immunosuppression. As more patients are being treated with alternative programs, comparison of results will require general agreement on definitions of response, relapse, and methods of determining minimal residual disease. The development of internationally accepted, reproducible criteria is of paramount importance in evaluating and comparing clinical trials to provide optimal care. Despite the success achieved in managing these patients, continued participation in available clinical trials both in the front-line and particularly in the relapse setting is highly recommended. The Hairy Cell Leukemia Foundation convened an international conference to provide common definitions and structure to guide current management. There is substantial opportunity for continued research in this disease. In addition to the importance of optimizing the prevention and management of the serious risk of infection, organized evaluations of minimal residual disease and treatment at relapse offer ample opportunities for clinical research. Finally, a scholarly evaluation of quality of life in the increasing number of survivors of this now manageable, chronic illness merits further study. The development of consensus guidelines for this disease offers a framework for continued enhancement of the outcome for patients.

Consensus Guidelines for the Diagnosis and Management of Patients with Classic Hairy Cell Leukemia

Hairy cell leukemia (HCL) is an uncommon chronic B-cell leukemia initially described by two independent investigators who established this as a distinct clinical entity.[1,2] While the initial term describing this disease was **leukemic reticuloendotheliosis**, the cell of origin was established to be a mature B cell.[3] In 2008, the WHO (World Health Organization) determined that the classic form of hairy cell leukemia (HCLc) should be recognized as separate from the rarer variant of this disease called hairy cell leukemia variant (HCLv).[4] The observation that a specific mutation $BRAF^{V600E}$ is present in the overwhelming majority of patients with HCLc and absent in HCLv validates the clinical observation that HCLv follows a different clinical course and response to therapy.[5,6] Recently, Chung and colleagues showed that hematopoietic stem cells from the bone marrow of patients with HCLc expressing the $BRAF^{V600E}$ mutation have self-renewal potential.[7] The $BRAF^{V600E}$ mutation was also shown to play a key role in shaping the specific molecular signature, morphology and anti-apoptotic behavior of HCL.[8] Molecular and genomic studies identify prognostic factors in HCL that are associated to different responses to therapy.[9-13] The consistent application of these respective prognostic parameters may impact on the optimal management of patients.

The introduction of the purine nucleoside analogs (cladribine and pentostatin) either alone or in combination with an anti-CD20 monoclonal antibody secured durable complete responses.[14-21] Nevertheless, patients relapse and require additional therapy. Substantial variability has been introduced into how these agents are administered.[22-24] Mature data regarding long-term follow-up has shown the effectiveness of the purine analogs delivered either by continuous infusion or subcutaneous injection (e.g. cladribine) or the intravenous administration of pentostatin. [22,25-28]As more patients are treated with alternative programs, comparison of results will require general agreement on definitions of response, relapse, and methods of determining minimal residual disease (MRD). The development of internationally accepted, reproducible criteria is of paramount importance in evaluating and comparing clinical trials.[29] In an effort to clarify the approach to diagnosis, the criteria for initiating therapy, and the selection of therapy followed by an assessment of response, the Hairy Cell Leukemia Foundation convened an international conference to establish consensus on managing patients with HCL. In addition, recommendations for how to approach the patient with relapse who requires re-treatment were considered. The unresolved but important question on how patients should best be managed with active infection and recommendations for incorporating prophylaxis for infection were discussed. Hopefully, the adoption of consensus guidelines will enable international experts to continue making progress toward ever improving quality of life of patients despite the diagnosis of leukemia.

Establishing the Diagnosis

Patients often present with symptoms of fatigue and infection.[1,2,30,31] While patients in the past often presented with an enlarged spleen (approximately 90%), this finding appears to be much less frequent due to earlier detection of disease. More commonly patients present because of incidental findings of pancytopenia.[30,31] The initial evaluation should include careful review of the peripheral blood smear with a differential count; monocytopenia is a relatively sensitive and specific manifestation of HCLc. Leukemic cells are often rare. Hairy cells are medium in size with moderately abundant pale blue cytoplasm, reniform nuclei, open chromatin, absent nucleoli, and a characteristic serrated cytoplasmic border (Figure 1). In Table 1, the recommended initial work-up is presented for HCL, and other clinical entities that may mimic this disease (e.g., HCLv; splenic marginal zone lymphoma; and splenic diffuse red pulp small B-cell lymphoma).

The immunophenotypic profile of the leukemic cells is critical for establishing this diagnosis. Immunophenotypic characterization of the peripheral blood mononuclear cells reveals light chain restriction of either κ or λ expressing populations of B cells. The characteristic immunophenotype of CD19+, CD20+, CD11c+, CD25+, CD103+, CD123+ co-expressing cells confirms the diagnostic features of HCLc. [3,32]These cells are intensely stained for CD200 expression[33,34], but negatively stained for CD27 antigen. In contrast, leukemic cells in patients with the HCLv are most often negative for CD25 and CD123, and most of these patients will not be monocytopenic.[32,35]

A trephine bone marrow biopsy and aspirate are important for understanding the extent of bone marrow infiltration. At diagnosis, a successful bone marrow aspirate is often not attainable because of a “dry tap”, since extensive fibrosis precludes the ability to obtain a cellular aspirate. Approximately 10% of patients will also have a hypocellular bone marrow biopsy at diagnosis reflecting a decrease in normal

hematopoiesis.[36] More often, the extent of bone marrow leukemic cell involvement is more accurately assessed with immunohistochemical stains. Immunohistochemical stains for CD20, Annexin-1[37], and VE1 (a $BRAF^{V600E}$ stain) will assist in establishing the diagnosis and provide an accurate assessment of the degree of bone marrow infiltration with leukemic cells.[36,38,39] Demonstration of the $BRAF^{V600E}$ mutation could also be important for those who do not respond to standard therapy or have multiple relapses.[40-45] Inhibitors of $BRAF^{V600E}$ have provided responses in patients who have been resistant to standard therapy.[46] Consequently, it is now recommended that all patients with HCL be evaluated for this mutation by either a sensitive molecular assay that can detect the often few (<10%) leukemic cells present in the peripheral blood or in bone marrow aspirates diluted with blood due to "dry tap"[47]. It is important to note that, in order to avoid false negative results, highly sensitive techniques (e.g., allele-specific PCR [47] or next generation sequencing) should be preferred over less sensitive ones (e.g., Sanger sequencing, pyrosequencing or melting curve analysis). If access to sufficient leukemic cells or to highly sensitive molecular techniques for genomic profiling is not readily achievable, then application of immunohistochemical stain (e.g., VE1) to the bone marrow biopsy may enable detection of this mutation [38,39].

Treatment

While the majority of patients with HCL require treatment, a small number (about 10%) may not require immediate therapy and may be closely followed until therapy is needed.[48] In general, the therapeutic agents used to treat HCL are quite effective, but they are immunosuppressive. Following the administration of a purine nucleoside analog, there is a further decline in neutrophils before recovery. Initiating therapy before the blood parameters have declined to a dangerous level or before a patient has an active infection is advised.

Patients should be treated if they have symptoms from the disease or if the hematologic parameters are declining. In general, the hematologic parameters indicating a need for treatment include at least one of the following: hemoglobin < 11 g/dL; platelet count <100,000/μL; absolute neutrophil count <1,000/μL.[20,49] While these parameters serve as a guide for therapy, they indicate that bone marrow function is compromised and requires intervention. However, some patients with moderate asymptomatic pancytopenia may remain progression-free for many years without therapy. Others present with profound pancytopenia which may be accompanied by massive splenomegaly. Symptomatic splenomegaly may serve as an indication for treatment.

Primary nucleoside analog induction therapy for HCL involves either cladribine or pentostatin.[20,49] The administration of cladribine has been effective in several different schedules and by different routes (e.g., intravenous continuous infusion for seven days, intravenous infusion over hours on a five-day regimen or alternatively subcutaneously on a daily or weekly regimen). (Table 2) Subcutaneous administration reduces cost as well as the inconvenience and side effects associated with intravenous treatment. Pentostatin is administered intravenously in an outpatient setting every other week to those with near normal renal function.[50] Either agent administered on one of these schedules appears to be equally effective[3,15,51] The choice is determined by physician preference or patient convenience with no benefit to support one versus another.

Cladribine is more myelosuppressive when the entire course of therapy is administered over a week. Pentostatin may also be myelosuppressive, but the schedule of administration enables dose titration to reduce the depth and the duration of myelosuppression. Cladribine is not used in patients with an active infection. In the initial studies of this highly effective agent, patients with uncontrolled infection were excluded[52,53] . In contrast, pentostatin has been used effectively in patients with an active infection[50,54], and reduced doses have been utilized in patients who are likely to have complications from prolonged myelosuppression. In the absence of infection, cladribine is probably uniformly the agent that is most often used. Both pentostatin and cladribine are very immunosuppressive.

Cladribine is administered on a defined schedule, and is most often completed with the initial course of treatment either as a five-day or weekly plan for six weeks or 7-day continuous intravenous infusion. Pentostatin is administered on alternate weeks until the near normalization of hematologic parameters and the disappearance of splenomegaly on physical examination.[20,49,50,55,56] Patients should be followed closely for evidence of fever or active infection, and routine blood counts should be obtained until recovery.

One of the most challenging clinical situations involves the patient with HCL who requires treatment but has an active infection.[3] Attempts to control the infection should be pursued prior to instituting the purine nucleoside analog.[15,55] If it is not possible to control the infection and anti-leukemia therapy is needed, then a decision regarding primary therapy either requires the use of a purine analog or the use of alpha-interferon[57]. Vemurafenib has been reported to be effective in patients with hairy cell leukemia in relapse from primary purine analog therapy. The recent observation of its ability to also increase peripheral blood counts and thus enhance the control of infection is very encouraging, and requires validation in clinical trials for those patients with an active infection.[58]

Assessment of Response

Assessment of response involves inspection of hematologic parameters, complete physical examination including an evaluation of spleen size, and then a bone marrow biopsy to determine whether normal hematopoiesis has been established with eradication of the leukemia. Assessment of the "completeness" of the response may provide guidance as to the future clinical course. Patients who have the longest disease-free interval usually have achieved a complete remission. An assessment of response is an important part of care. In general, it is recommended that a follow-up bone marrow biopsy after cladribine therapy should be delayed for four to six months after completion of drug administration. Following purine analog therapy, there can be delayed and continuing improvement. The bone marrow biopsy following pentostatin therapy is usually performed after a clinical response including near normalization of hematologic parameters. The administration of two consolidation doses of pentostatin following completion of the induction therapy has been the general practice, but this consolidation has not been proven to be necessary. In patients being treated with pentostatin, failure to obtain clinical evidence of an objective response by six months indicates that it is time to select another therapeutic approach. In contrast, patients who show objective evidence of a response by six months were treated up to a year in an attempt to achieve an optimal response.[50]

Complete Response

Accumulated data supports that achievement of a complete response is associated with longer duration of disease free interval.[14,26,27,51] While this disease is not "curable" with current therapy, patients can achieve durable remissions that do not require continued treatment unless symptomatic relapse occurs.[59] Because the achievement of complete remission has been the "goal" of most therapeutic investigations, it is essential that a complete response be carefully defined.[49]

Patients in complete response should have near normalization of peripheral blood counts: hemoglobin >11g/dL (without transfusion), platelets >100,000/µL and an absolute neutrophil count >1,500/µL.[20,49] The lymphocyte count including lymphocyte subsets may be reduced for a long period of time following exposure to the purine analogs.[60] In fact, the bone marrow may require many months before recovery following treatment with a purine analog. Consequently, the standard hematologic parameters required for a complete remission are accepted at values slightly lower than normal. Therefore, it is usually recommended that an assessment for complete response following cladribine be delayed for four to six months after treatment.[20,49]

There should be regression of splenomegaly by physical examination. Notably, most studies have required resolution of palpable splenomegaly but have not recommended treatment extension in an effort to resolve radiographic enlargement of the spleen. While CT scans to assess completeness of response is optional in clinical practice, these studies could be considered in the context of a clinical trial.

For more than three decades, complete remission was defined by morphologic criteria with the disappearance of the characteristic hairy cells from the bone marrow. Since the demonstration that immunohistochemical stains and flow cytometric techniques are capable of establishing that MRD is quite evident in many patients with a normal hematoxylin and eosin stain, complete remission without MRD is also defined. (Table 3) The criteria for defining a complete remission either with or without MRD now includes the application of immunohistochemical stains (e.g., CD20 and DBA.44) to the bone marrow trephine biopsy to assess presence of residual disease. The use of VE1, as a marker for leukemic cells with the characteristic $BRAF^{V600E}$, has also been reported to be helpful for measuring low volume disease.[39,61]

Partial Response

A partial response is defined by near normalization of the peripheral blood counts with a minimum of 50% improvement in both organomegaly and bone marrow biopsy infiltration with HCL. Such patients may well remain asymptomatic for many years with no further treatment. As an alternative, Dearden and colleagues have administered a second course of cladribine and used rituximab in combination with a purine analog for those not achieving an optimal response with a purine analog alone.[16] Other investigators have not opted for the second course of purine analog, but have either administered an anti-CD20 monoclonal antibody or elected to change to an alternate purine analog in an effort to achieve the optimal response.[21,59,62] While most have acknowledged the benefit of achieving a complete response, many have advised that complete eradication of minimal residual disease, which may

necessitate prolonged administration of immunosuppressive therapies, cannot presently be recommended as a well-established goal of therapy.[49,63,64] Recognition that the extent of remaining MRD may impact on potential for relapse must be balanced by the extent of therapy being employed to achieve this end. Furthermore, some hematologists reserve further attempts at intervention for those who show either progression or persistence of symptomatic disease.

Stable Disease

Patients who have not met the criteria for an objective remission following therapy are called stable disease. Because patients with hairy cell leukemia are treated for specific reasons including either symptoms or a decline in their hematologic parameters, stable disease is not an acceptable goal.

Progression of Disease

Patients who either have an increase in symptoms related to the disease or a 25% decline in their hematologic parameters qualify for progression of disease. Furthermore, a 25% increase in organomegaly based upon the nadir measurements achieved following therapy also suggests progression of disease. An effort must be made to differentiate a decline in blood counts related to the myelosuppressive effects of chemotherapy versus progression of disease. Therapy-induced myelosuppression usually follows treatment, and will recover with observation.

Determination of Minimal Residual Disease Following Therapy

Minimal residual disease is currently defined as HCL infiltrates recognizable by immunohistochemical (IHC) stains, but not by conventional stains.[29] Many hematopathologists estimate the percentage of cells on the bone marrow trephine biopsy using either an anti-CD20 monoclonal antibody or DBA.44. In patients treated with anti-CD20 monoclonal antibody, the use of this stain may be unpredictable. Therefore, application of other pan B cell markers such as CD79a and/or HCL specific markers (e.g., VE1) or DBA.44 will be required to estimate the residual presence of hairy cells that are not detectable by regular histologic stains. One group has recommended that reliable quantitative efforts should include specific instructions for identifying the extent of MRD.[63] These efforts might also be combined with assessing the value of serial soluble IL-2 receptor in determining the need for continuation of therapy.[65,66]

The risk of relapse predicted by MRD has been grouped in one report: Group I <1% positive cells, low risk for relapse; Group II 1 to 5% positive cells by IHC, is designated as intermediate-risk; Group III > 5% positive cells by IHC representing a higher-risk group for relapse. The clinical value of these predictive groups must be validated in future studies.[63]

While flow cytometry has been utilized to quantitate the amount of residual disease in a bone marrow aspirate, these reports depend upon a consistent cellular yield. In contrast, a high-quality bone marrow biopsy provides a platform for potentially more consistent evaluation by IHC staining. Consistency in detection and reporting of MRD will be important given that hematologists may make treatment

decisions based upon these reports. Long term follow-up of patients in complete response will be required to determine the importance of MRD in the biopsy and/or aspirate.

Treatment at Relapse

The introduction of the purine analogs has markedly improved survival in this disease. Some patients with HCL treated with purine nucleoside analogs will achieve very durable remissions lasting years without additional therapy.[26,27,67] Despite this success, many patients will require re-treatment for relapsed disease. In general, the first remission is more durable than subsequent remissions and is associated with a higher percentage of complete responders. [16,68]Nevertheless, achievement of a second or greater complete remission can be accomplished with re-treatment. Review of the previous therapy should be included with consideration of a high-risk grouping. If poor-risk features were identified (e.g., severe anemia, spleen >10 cm below the left costal margin, atypical immunophenotypic profile, mutation of p53, IGHV4-34+ rearrangement, unmutated IGHV, absence of $BRAF^{V600E}$ mutation, etc), identification of an underlying explanation for a less than desired initial response may be helpful in deciding whether to pursue investigational therapies.[3,6,12] While post-treatment bone marrow biopsies are not mandatory outside a trial, they are required to document a complete remission (information which carries considerable prognostic information), and is therefore quite useful even in routine practice. Therefore, a bone marrow biopsy is absolutely necessary to document a complete remission.

Criteria for re-treatment at relapse are equivalent to the initial criteria including symptomatic disease (e.g. splenomegaly) or progressive anemia, thrombocytopenia, or neutropenia.[20,49] In general, patients with an initial remission of < 24 months should consider alternative therapy including investigational agents and regimens after confirming the accuracy of the original diagnosis. Other therapeutic approaches may still offer benefit for selected patients (e.g., alpha-interferon, rituximab, splenectomy). Considering the success of newer agents, enrollment in a clinical trial is also an important option.

Finally, the decision of when to re-treat a patient whose disease is relapsing requires judgment. The mere reappearance of hairy cells either in the peripheral blood or the bone marrow by morphologic or immunophenotypic/immunohistochemical techniques must be carefully weighed considering the potential toxicity of immunosuppressive therapy. The re-demonstration of leukemic cells may indicate that a complete response has ended, but the clinical definition of relapse requiring re-treatment is based upon recurrence of disease-related symptoms (e.g., symptomatic splenomegaly) or deterioration in hematologic parameters (e.g., absolute neutropenia, progressive thrombocytopenia, or anemia) equivalent to the values initially utilized for the initiation of treatment. Establishing the trend of progressive pancytopenia is important, but good clinical judgement would indicate that attempts to re-treat should begin before these values have deteriorated to low levels.

Consideration for Investigational Approaches

Recognition of the presence of the $BRAF^{V600E}$ mutation led to trials showing response to small molecule inhibitors of this target.[5,46] Complete remissions have been reported utilizing the BRAF inhibitor vemurafenib in relapse and refractory disease.[42-45,69] The duration of these remissions is currently being defined in well-designed clinical trials. However, relapse is a frequent finding, and thus strategic

combinations and/or alternative schedules of administration will need to be pursued.[46] Furthermore, newer targeted inhibitors of BRAF (e.g. Dabrafenib) also show promise in relapsed disease meriting study in larger clinical trials.[8,41,70] These agents have enabled improvement in absolute neutrophils showing promise for patients with life-threatening infection. The role of Vemurafenib in treating patients with hairy cell leukemia and infection deserves careful attention.[58] It is important to recognize side effects from the BRAF inhibitors that may include skin rash, arthralgias, arthritis, secondary skin tumors that necessitate follow-up with dermatology. Rarely, vemurafenib has caused abnormal renal function.[46]

Ibrutinib, a first in class oral inhibitor of the Bruton tyrosine kinase (BTK), has recently been approved for the treatment of patients with relapsed and refractory B-cell malignancies.[71] This agent is currently under study in an NCI-sponsored multi-institutional trial for patients with HCL failing to achieve optimal response to standard therapies.

Immunotoxin conjugates have been developed at the NIH, and now are being investigated in multi-institutional clinical trials (e.g., HA-22 or moxetumomab pasudotox).[72,73]

Further opportunities exist to evaluate novel agents both alone or in strategic combinations.[74] Because we have prolonged the projected survival for these patients, recurrent relapse can be anticipated meriting continued investigation.

Infection Prevention and Treatment

The most frequent cause of death among patients with HCL remains infection. Because these patients often present with pre-existing neutropenia/monocytopenia, bacterial, viral, and opportunistic infections can be anticipated. In addition, the primary therapy for HCL is immunosuppressive, and patients may be placed at further risk for infection during treatment. Purine analogs confer prolonged suppression of immune effector cells (e.g., CD4+ T cells), and induce profound and prolonged neutropenia.[75]

Patients must be educated regarding infection prevention and the indications for seeking medical treatment (e.g., fever during periods of neutropenia, rash consistent with varicella zoster). Evidence for the use of specific prevention strategies has not been validated in well-controlled clinical trials. Practice patterns vary between groups, and thus evaluation of both prevention and treatment strategies represent important areas of needed research.[20,49,76]

The use of myeloid growth factors needs to be considered on a case-by-case basis in patients with active infection.[20] Patients may receive vaccinations that utilize killed viral agents, however there are no data that patients with this disease respond to vaccines . Live virus vaccines should be avoided.

Because patients with HCL who have been previously treated with purine analogs have profound and persistent lymphopenia, they should probably receive irradiated blood products if a transfusion is indicated to prevent transfusion-associated graft versus host disease. Furthermore, the hepatitis history should be documented with consideration for suppressive anti-viral treatment for those who are HepB

sAg positive. Patients have had severe liver toxicity following immunosuppressive therapy if there is a chance that reactivation of viral hepatitis should occur. Therefore, screening for previous exposure to hepatitis before therapy for the disease is highly recommended.[77]

Summary

Enormous progress in the management of HCL has resulted in prolonged survival in many patients. HCL cannot be cured with standard chemo-immunotherapy. Patients remain at risk for relapse over time. Because of the tremendous success of standard therapy, many patients are now treated outside of a clinical trial with increasing variability in disease management and monitoring. The Hairy Cell Leukemia Foundation convened an international conference to provide common definitions and structure to guide current management. The development of consensus guidelines for this rare disease offers a framework for continued improvement of the outcome for these patients.

Patients should be encouraged to follow normal recommendations for cancer screening including routine careful follow-up with a dermatologist. Studies in patients with chronic lymphocytic leukemia (CLL) show that an immune response to vaccinations is limited[78]. Because infection is a leading cause of morbidity and mortality in both CLL and HCL, further investigation of the effectiveness of vaccination strategies to prevent illness is warranted. The development of these consensus guidelines is intended to improve the care of patients with this uncommon hematologic malignancy by addressing the most common complications. Patients with HCLc can also have many unusual manifestations of the disease. The guidelines are intended to enhance care of patients, and should not be utilized to deny appropriate and necessary diagnostic or therapeutic interventions.

Author Contributions

All authors participated in the development of these guidelines through extensive discussion at an international meeting with extensive revision of the manuscript following the meeting. The International Hairy Cell Leukemia Research Foundation sponsored the meeting. Michael R. Grever drafted the manuscript. Drs. Michael Grever and Brunangelo Falini revised the manuscript with contributions from each of the authors. All authors contributed revisions and approved this manuscript.

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REFERENCES

1. Gosselin GR, Hanlon DG, Pease GL. Leukaemic reticuloendotheliosis. *Can Med Assoc J*. 1956;74(11):886-891. Prepublished on 1956/06/01 as DOI.
2. Bouroncle B, Wiseman AG, Doan CA. Leukemic Reticuloendotheliosis. *Blood*. 1958;13(7):609-630.
3. Grever MR, Blachly JS, Andritsos LA. Hairy cell leukemia: Update on molecular profiling and therapeutic advances. *Blood Rev*. 2014;28(5):197-203. Prepublished on 2014/08/12 as DOI 10.1016/j.blre.2014.06.003.
4. Piris MA, Foucar, K., Mollejo, M., Campo, E., Falini, B. Splenic B-cell lymphoma/leukaemia, unclassifiable. In: Swerdlow SH, Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J., Vardiman, J.W, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Lyon, France: IARC; 2008:191-193.
5. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364(24):2305-2315. Prepublished on 2011/06/15 as DOI 10.1056/NEJMoa1014209.
6. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. *Blood*. 2012;119(14):3330-3332. Prepublished on 2012/01/03 as DOI 10.1182/blood-2011-09-379339.
7. Chung SS, Kim E, Park JH, et al. Hematopoietic Stem Cell Origin of BRAFV600E Mutations in Hairy Cell Leukemia. *Sci Transl Med*. 2014;6(238):238ra271. Prepublished on 2014/05/30 as DOI 10.1126/scitranslmed.3008004.
8. Pettirossi V, Santi A, Imperi E, et al. BRAF inhibitors reverse the unique molecular signature and phenotype of hairy cell leukemia and exert potent antileukemic activity. *Blood*. 2015;125(8):1207-1216. Prepublished on 2014/12/07 as DOI 10.1182/blood-2014-10-603100.
9. Waterfall JJ, Arons E, Walker RL, et al. High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias. *Nat Genet*. 2014;46(1):8-10. Prepublished on 2013/11/19 as DOI 10.1038/ng.2828.
10. Arons E, Kreitman RJ. Molecular variant of hairy cell leukemia with poor prognosis. *Leuk Lymphoma*. 2011;52 Suppl 2:99-102. Prepublished on 2011/05/27 as DOI 10.3109/10428194.2011.565841.
11. Forconi F, Cencini E, Sozzi E, Sicuranza A, Raspadori D, Lauria F. Insight into the behavior of hairy cell leukemia by immunogenetic analysis. *Leuk Lymphoma*. 2011;52 Suppl 2:103-107. Prepublished on 2011/04/21 as DOI 10.3109/10428194.2011.569620.
12. Forconi F, Sozzi E, Cencini E, et al. Hairy cell leukemias with unmutated IGHV genes define the minor subset refractory to single-agent cladribine and with more aggressive behavior. *Blood*. 2009;114(21):4696-4702. Prepublished on 2009/08/12 as DOI blood-2009-03-212449 [pii]

10.1182/blood-2009-03-212449.
13. Arons E, Roth L, Sapolsky J, Suntum T, Stetler-Stevenson M, Kreitman RJ. Evidence of canonical somatic hypermutation in hairy cell leukemia. *Blood*. 2011;117(18):4844-4851. Prepublished on 2011/03/04 as DOI 10.1182/blood-2010-11-316737.
14. Rosenberg JD, Burian C, Waalen J, Saven A. Clinical characteristics and long-term outcome of young hairy cell leukemia patients treated with cladribine: a single-institution series. *Blood*. 2014;123(2):177-183. Prepublished on 2013/11/07 as DOI 10.1182/blood-2013-06-508754.
15. Grever MR, Lozanski G. Modern strategies for hairy cell leukemia. *J Clin Oncol*. 2011;29(5):583-590. Prepublished on 2011/01/12 as DOI 10.1200/JCO.2010.31.7016.

16. Dearden CE, Matutes E, Hilditch BL, Swansbury GJ, Catovsky D. Long-term follow-up of patients with hairy cell leukaemia after treatment with pentostatin or cladribine. *Br J Haematol*. 1999;106(2):515-519. Prepublished on 1999/08/25 as DOI bjh1546 [pii].
17. Cornet E, Tomowiak C, Tanguy-Schmidt A, et al. Long-term follow-up and second malignancies in 487 patients with hairy cell leukaemia. *Br J Haematol*. 2014;166(3):390-400. Prepublished on 2014/04/23 as DOI 10.1111/bjh.12908.
18. Johnston JB, Eisenhauer E, Corbett WE, Scott JG, Zaentz SD. Efficacy of 2'-deoxycoformycin in hairy-cell leukemia: a study of the National Cancer Institute of Canada Clinical Trials Group. *J Natl Cancer Inst*. 1988;80(10):765-769.
19. Chandran R, Gardiner SK, Smith SD, Spurgeon SE. Improved survival in hairy cell leukaemia over three decades: a SEER database analysis of prognostic factors. *Br J Haematol*. 2013;163(3):407-409. Prepublished on 2013/07/31 as DOI 10.1111/bjh.12490.
20. Cornet E, Delmer A, Feugier P, et al. Recommendations of the SFH (French Society of Haematology) for the diagnosis, treatment and follow-up of hairy cell leukaemia. *Ann Hematol*. 2014. Prepublished on 2014/07/06 as DOI 10.1007/s00277-014-2140-y.
21. Ravandi F, O'Brien S, Jorgensen J, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. *Blood*. 2011;118(14):3818-3823. Prepublished on 2011/08/09 as DOI 10.1182/blood-2011-04-351502.
22. Lauria F, Cencini E, Forconi F. Alternative methods of cladribine administration. *Leuk Lymphoma*. 2011;52 Suppl 2:34-37. Prepublished on 2011/04/21 as DOI 10.3109/10428194.2011.570395.
23. von Rohr A, Schmitz SF, Tichelli A, et al. Treatment of hairy cell leukemia with cladribine (2-chlorodeoxyadenosine) by subcutaneous bolus injection: a phase II study. *Ann Oncol*. 2002;13(10):1641-1649. Prepublished on 2002/10/16 as DOI.
24. Juliusson G, Heldal D, Hippe E, et al. Subcutaneous injections of 2-chlorodeoxyadenosine for symptomatic hairy cell leukemia. *J Clin Oncol*. 1995;13(4):989-995. Prepublished on 1995/04/01 as DOI.
25. Sigal DS, Sharpe R, Burian C, Saven A. Very long-term eradication of minimal residual disease in patients with hairy cell leukemia after a single course of cladribine. *Blood*. 2010;115(10):1893-1896. Prepublished on 2010/01/09 as DOI blood-2009-10-251645 [pii]

10.1182/blood-2009-10-251645.
26. Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol*. 2009;145(6):733-740. Prepublished on 2009/04/07 as DOI BJH7668 [pii]

10.1111/j.1365-2141.2009.07668.x.
27. Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. *Blood*. 2000;96(9):2981-2986. Prepublished on 2000/10/26 as DOI.
28. Juliusson G, Samuelsson H. Hairy cell leukemia: epidemiology, pharmacokinetics of cladribine, and long-term follow-up of subcutaneous therapy. *Leuk Lymphoma*. 2011;52 Suppl 2:46-49. Prepublished on 2011/05/27 as DOI 10.3109/10428194.2011.565842.
29. Noel P. Definition of remission, minimal residual disease, and relapse in hairy cell leukemia bone marrow biopsy histology and immunohistology specimens. *Leuk Lymphoma*. 2011;52 Suppl 2:62-64. Prepublished on 2011/04/06 as DOI 10.3109/10428194.2011.565098.
30. Frassoldati A, Lamparelli T, Federico M, et al. Hairy cell leukemia: a clinical review based on 725 cases of the Italian Cooperative Group (ICGHCL). Italian Cooperative Group for Hairy Cell Leukemia. *Leuk Lymphoma*. 1994;13(3-4):307-316. Prepublished on 1994/04/01 as DOI 10.3109/10428199409056295.

31. Kraut E. Infectious complications in hairy cell leukemia. *Leuk Lymphoma*. 2011;52 Suppl 2:50-52. Prepublished on 2011/04/21 as DOI 10.3109/10428194.2011.570819.
32. Venkataraman G, Aguhar C, Kreitman RJ, Yuan CM, Stetler-Stevenson M. Characteristic CD103 and CD123 expression pattern defines hairy cell leukemia: usefulness of CD123 and CD103 in the diagnosis of mature B-cell lymphoproliferative disorders. *Am J Clin Pathol*. 2011;136(4):625-630. Prepublished on 2011/09/16 as DOI 10.1309/AJCPKUM9J4IXCWEU.
33. Sandes AF, de Lourdes Chauffaille M, Oliveira CR, et al. CD200 has an important role in the differential diagnosis of mature B-cell neoplasms by multiparameter flow cytometry. *Cytometry B Clin Cytom*. 2014;86(2):98-105. Prepublished on 2013/11/19 as DOI 10.1002/cyto.b.21128.
34. Pillai V, Pozdnyakova O, Charest K, Li B, Shahsafaei A, Dorfman DM. CD200 flow cytometric assessment and semiquantitative immunohistochemical staining distinguishes hairy cell leukemia from hairy cell leukemia-variant and other B-cell lymphoproliferative disorders. *Am J Clin Pathol*. 2013;140(4):536-543. Prepublished on 2013/09/21 as DOI 10.1309/AJCPEBK31VQQNDDR.
35. Sherman MJ, Hanson CA, Hoyer JD. An assessment of the usefulness of immunohistochemical stains in the diagnosis of hairy cell leukemia. *Am J Clin Pathol*. 2011;136(3):390-399. Prepublished on 2011/08/19 as DOI 10.1309/AJCP5GE1PSBMBZTW.
36. Foucar K, Falini, B., Catovsky, D., Stein, H. Hairy Cell Leukaemia. In: Swerdlow SH, Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J., Vardiman, J.W, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Lyon, France: IARC; 2008.
37. Falini B, Tiacci E, Liso A, et al. Simple diagnostic assay for hairy cell leukaemia by immunocytochemical detection of annexin A1 (ANXA1). *Lancet*. 2004;363(9424):1869-1870.
38. Uppal G, Ly V, Wang ZX, et al. The utility of BRAF V600E mutation-specific antibody VE1 for the diagnosis of hairy cell leukemia. *Am J Clin Pathol*. 2015;143(1):120-125. Prepublished on 2014/12/17 as DOI 10.1309/AJCPQLQ89VXTVWKN.
39. Andrulis M, Penzel R, Weichert W, von Deimling A, Capper D. Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. *Am J Surg Pathol*. 2012;36(12):1796-1800. Prepublished on 2012/04/26 as DOI 10.1097/PAS.0b013e3182549b50.
40. Bailleux C, Robert G, Ginet C, et al. Successful re-treatment of a relapsed V600E mutated HCL patient with low-dose vemurafenib. *Oncoscience*. 2015;2(1):44-49. Prepublished on 2015/03/31 as DOI.
41. Blachly JS, Lozanski G, Lucas DM, Grever MR, Kendra K, Andritsos LA. Cotreatment of hairy cell leukemia and melanoma with the BRAF inhibitor dabrafenib. *J Natl Compr Canc Netw*. 2015;13(1):9-13; quiz 13. Prepublished on 2015/01/15 as DOI.
42. Samuel J, Macip S, Dyer MJ. Efficacy of vemurafenib in hairy-cell leukemia. *N Engl J Med*. 2014;370(3):286-288. Prepublished on 2014/01/17 as DOI 10.1056/NEJMc1310849.
43. Munoz J, Schlette E, Kurzrock R. Rapid response to vemurafenib in a heavily pretreated patient with hairy cell leukemia and a BRAF mutation. *J Clin Oncol*. 2013;31(20):e351-352. Prepublished on 2013/06/05 as DOI 10.1200/JCO.2012.45.7739.
44. Follows GA, Sims H, Bloxham DM, et al. Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. *Br J Haematol*. 2013;161(1):150-153. Prepublished on 2013/01/03 as DOI 10.1111/bjh.12201.
45. Dietrich S, Glimm H, Andrulis M, von Kalle C, Ho AD, Zenz T. BRAF inhibition in refractory hairy-cell leukemia. *N Engl J Med*. 2012;366(21):2038-2040. Prepublished on 2012/05/25 as DOI 10.1056/NEJMc1202124.
46. Tiacci E, Park JH, De Carolis L, et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. *N Engl J Med*. 2015;373(18):1733-1747. Prepublished on 2015/09/10 as DOI 10.1056/NEJMoa1506583.

47. Tiacci E, Schiavoni G, Forconi F, et al. Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. *Blood*. 2012;119(1):192-195. Prepublished on 2011/10/27 as DOI 10.1182/blood-2011-08-371179.
48. Golomb HM. Hairy cell leukemia: lessons learned in twenty-five years. *J Clin Oncol*. 1983;1(10):652-656.
49. Jones G, Parry-Jones N, Wilkins B, Else M, Catovsky D. Revised guidelines for the diagnosis and management of hairy cell leukaemia and hairy cell leukaemia variant*. *Br J Haematol*. 2012;156(2):186-195. Prepublished on 2011/11/25 as DOI 10.1111/j.1365-2141.2011.08931.x.
50. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. *J Clin Oncol*. 1995;13(4):974-982. Prepublished on 1995/04/01 as DOI.
51. Golomb HM. Fifty years of hairy cell leukemia treatments. *Leuk Lymphoma*. 2011;52 Suppl 2:3-5. Prepublished on 2011/05/27 as DOI 10.3109/10428194.2011.565094.
52. Piro LD, Carrera CJ, Carson DA, Beutler E. Lasting remissions in hairy-cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine. *N Engl J Med*. 1990;322(16):1117-1121. Prepublished on 1990/04/19 as DOI 10.1056/NEJM199004193221605.
53. Tallman MS, Hakimian D, Variakojis D, et al. A single cycle of 2-chlorodeoxyadenosine results in complete remission in the majority of patients with hairy cell leukemia. *Blood*. 1992;80(9):2203-2209. Prepublished on 1992/11/01 as DOI.
54. Andritsos LA, Dunavin N, Lozanski G, et al. Reduced dose pentostatin for initial management of hairy cell leukemia patients who have active infection or risk of hemorrhage is safe and effective. *Haematologica*. 2015;100(1):e18-20. Prepublished on 2014/11/02 as DOI 10.3324/haematol.2014.113290.
55. Grever MR. How I treat hairy cell leukemia. *Blood*. 2010;115(1):21-28. Prepublished on 2009/10/22 as DOI 10.1182/blood-2009-06-195370.
56. Naik RR, Saven A. My treatment approach to hairy cell leukemia. *Mayo Clin Proc*. 2012;87(1):67-76. Prepublished on 2012/01/04 as DOI 10.1016/j.mayocp.2011.09.001.
57. Habermann TM, Andersen JW, Cassileth PA, Bennett JM, Oken MM. Sequential administration of recombinant interferon alpha and deoxycoformycin in the treatment of hairy cell leukaemia. *Br J Haematol*. 1992;80(4):466-471.
58. Dietrich S, Zenz T. BRAF inhibitor therapy in HCL. *Best Pract Res Clin Haematol*. 2015;28(4):246-252. Prepublished on 2015/11/29 as DOI 10.1016/j.beha.2015.10.001.
59. Grever MR. Hairy cell: young living longer but not cured. *Blood*. 2014;123(2):150-151. Prepublished on 2014/01/11 as DOI 10.1182/blood-2013-11-538280.
60. Seymour JF, Kurzrock R, Freireich EJ, Estey EH. 2-chlorodeoxyadenosine induces durable remissions and prolonged suppression of CD4+ lymphocyte counts in patients with hairy cell leukemia. *Blood*. 1994;83(10):2906-2911. Prepublished on 1994/05/15 as DOI.
61. Brown NA, Betz BL, Weigelin HC, Elenitoba-Johnson KS, Lim MS, Bailey NG. Evaluation of allele-specific PCR and immunohistochemistry for the detection of BRAF V600E mutations in hairy cell leukemia. *Am J Clin Pathol*. 2015;143(1):89-99. Prepublished on 2014/12/17 as DOI 10.1309/AJCPDN4Q1JTFGCFC.
62. Else M, Dearden CE, Matutes E, et al. Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukemia after disease recurrence. *Leuk Lymphoma*. 2011;52 Suppl 2:75-78. Prepublished on 2011/04/21 as DOI 10.3109/10428194.2011.568650.
63. Mhawech-Fauceglia P, Oberholzer M, Aschenafi S, et al. Potential predictive patterns of minimal residual disease detected by immunohistochemistry on bone marrow biopsy specimens during a long-term follow-up in patients treated with cladribine for hairy cell leukemia. *Arch Pathol Lab Med*. 2006;130(3):374-377. Prepublished on 2006/03/08 as DOI OA-5-561 [pii].

64. Akarca AU, Shende VH, Ramsay AD, et al. BRAF V600E mutation-specific antibody, a sensitive diagnostic marker revealing minimal residual disease in hairy cell leukaemia. *Br J Haematol*. 2013;162(6):848-851. Prepublished on 2013/07/16 as DOI 10.1111/bjh.12429.
65. Lauria F, Raspadori D, Benfenati D, Rondelli D, Pallotti A, Tura S. Biological markers and minimal residual disease in hairy cell leukemia. *Leukemia*. 1992;6 Suppl 4:149-151. Prepublished on 1992/11/01 as DOI.
66. Richards JM, Mick R, Latta JM, et al. Serum soluble interleukin-2 receptor is associated with clinical and pathologic disease status in hairy cell leukemia. *Blood*. 1990;76(10):1941-1945. Prepublished on 1990/11/15 as DOI.
67. Chadha P, Rademaker AW, Mendiratta P, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA): long-term follow-up of the Northwestern University experience. *Blood*. 2005;106(1):241-246. Prepublished on 2005/03/12 as DOI 2005-01-0173 [pii]

10.1182/blood-2005-01-0173.
68. Zinzani PL, Pellegrini C, Stefoni V, et al. Hairy cell leukemia: evaluation of the long-term outcome in 121 patients. *Cancer*. 2010;116(20):4788-4792. Prepublished on 2010/07/03 as DOI 10.1002/cncr.25243.
69. Maurer H, Haas P, Wengenmayer T, Lubbert M, Duyster J, Zeiser R. Successful vemurafenib salvage treatment in a patient with primary refractory hairy cell leukemia and pulmonary aspergillosis. *Ann Hematol*. 2014;93(8):1439-1440. Prepublished on 2013/12/18 as DOI 10.1007/s00277-013-1987-7.
70. Vergote V, Dierickx D, Janssens A, et al. Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib. *Ann Hematol*. 2014;93(12):2087-2089. Prepublished on 2014/05/28 as DOI 10.1007/s00277-014-2104-2.
71. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood*. 2015;125(16):2497-2506. Prepublished on 2015/02/24 as DOI 10.1182/blood-2014-10-606038.
72. Kreitman RJ, Tallman MS, Robak T, et al. Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015 or HA22) in patients with hairy cell leukemia. *J Clin Oncol*. 2012;30(15):1822-1828. Prepublished on 2012/02/23 as DOI 10.1200/JCO.2011.38.1756.
73. Kreitman RJ, Wilson WH, Robbins D, et al. Responses in refractory hairy cell leukemia to a recombinant immunotoxin. *Blood*. 1999;94(10):3340-3348. Prepublished on 1999/11/24 as DOI.
74. Burotto M, Stetler-Stevenson M, Arons E, Zhou H, Wilson W, Kreitman RJ. Bendamustine and rituximab in relapsed and refractory hairy cell leukemia. *Clin Cancer Res*. 2013;19(22):6313-6321. Prepublished on 2013/10/08 as DOI 10.1158/1078-0432.CCR-13-1848.
75. Tadmor T. Purine analog toxicity in patients with hairy cell leukemia. *Leuk Lymphoma*. 2011;52 Suppl 2:38-42. Prepublished on 2011/04/06 as DOI 10.3109/10428194.2011.565097.
76. Cooley L, Dendle C, Wolf J, et al. Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies, 2014. *Intern Med J*. 2014;44(12b):1350-1363. Prepublished on 2014/12/09 as DOI 10.1111/imj.12599.
77. Lok AS, Ward JW, Perrillo RP, McMahon BJ, Liang TJ. Reactivation of hepatitis B during immunosuppressive therapy: potentially fatal yet preventable. *Ann Intern Med*. 2012;156(10):743-745. Prepublished on 2012/05/16 as DOI 10.7326/0003-4819-156-10-201205150-00013.
78. Whitaker JA, Shanafelt TD, Poland GA, Kay NE. Room for improvement: immunizations for patients with monoclonal B-cell lymphocytosis or chronic lymphocytic leukemia. *Clin Adv Hematol Oncol*. 2014;12(7):440-450. Prepublished on 2014/10/17 as DOI.
79. Robak T, Jamroziak K, Gora-Tybor J, et al. Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a

prospective, randomized, multicenter trial. *Blood*. 2007;109(9):3672-3675. Prepublished on 2007/01/09 as DOI blood-2006-08-042929 [pii] 10.1182/blood-2006-08-042929.

80. Goodman GR, Burian C, Koziol JA, Saven A. Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. *J Clin Oncol*. 2003;21(5):891-896. Prepublished on 2003/03/01 as DOI.

FIGURE I Histologic image of a hairy cell. Wright- Giemsa stained smear of peripheral blood. These images were obtained using an UPlanFL 100_ Olympus objective in oil immersion. The image was collected using an MTI 3 CCD camera (DAGE-MTI Inc) with PAX-it 2.0 acquisition software (MIS)

Figure I

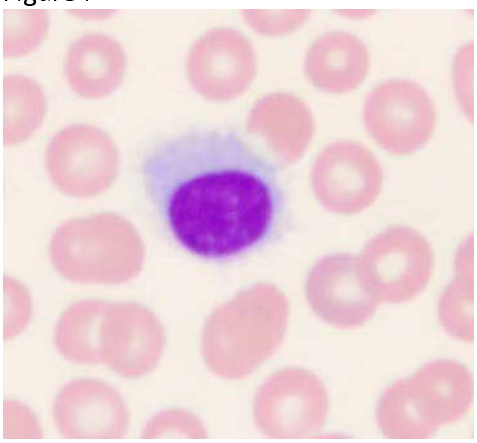

Table I Recommended Initial Work-Up for Patient Suspected of Hairy Cell Leukemia

Diagnosis and Initial Evaluation

- Obtain complete blood count
- Review peripheral blood smear: Wright's stain, do differential, identify leukemic cells
- Immunophenotypic analysis by flow cytometry: positivity for CD19, CD20, CD11c, CD25, CD103, CD123, CD200 , immunoglobulin light chain restriction of the circulating mononuclear cells
- Bone marrow aspiration and trephine biopsy – H& E stain, reticulin stain, and immunohistochemistry for CD20, Annexin-1, DBA-44, BRAF V600E (VE1); identify BRAF V600E mutation by allele-specific PCR, sequence analysis or immunohistochemical stain
- Complete history & physical examination, including assessment of renal function for patients in whom nucleoside analogue is planned
- Optional Imaging studies: Chest x-ray to assess for infection, CT or ultrasound scan of abdomen to evaluate organomegaly, and lymphadenopathy. Should be considered for those patients either on a clinical trial or with associated symptoms referable to these systems.
- Serology for hepatitis if planning on using an anti-CD20 monoclonal antibody
- Differential diagnosis to consider: hairy cell leukemia; hairy cell leukemia variant; splenic marginal zone lymphoma; splenic diffuse red pulp small B-cell lymphoma (Specific immunophenotypic profiles of differential entities is outlined in references 33 through 36.)

Indications for Treatment

- Hematologic parameters consistent with initiating treatment include at least one of the following: hemoglobin less than 11 gram/dL, platelet count less than 100,000/uL, or absolute neutrophil count less than 1,000 uL
- Clinical features or symptoms for which therapy may be considered include: symptomatic organomegaly, progressive lymphocytosis or lymphadenopathy , unexplained weight loss (Greater than 10% within prior six months, excessive fatigue (NCI CTCAE Grade greater than 2)

Table II Recommendations for Frontline Therapy

- In the absence of renal impairment or active infection: Purine nucleoside analogue utilizing a standard regimen of either cladribine or pentostatin
  - Cladribine administered as continuous intravenous infusion 0.1mg/kg/day for 7 days; or, cladribine 0.14mg/kg/day intravenous over 2 hours for 5 days; or cladribine 0.1 - 0.14mg/kg/day subcutaneously for 5 days[22,23,55,56,79]
  - Pentostatin 4mg/m^2 intravenous every 2 weeks [50,55]
- If active infection is present, attempts to control infection should be pursued prior to instituting the purine nucleoside regimen
- If not possible to control infection, alternative therapy with alpha interferon, low dose pentostatin, or newer agents (e.g., Vemurafenib) not associated with worsening myelosuppression may be utilized to improve the absolute neutrophil count in an attempt to control infection before using regular dose purine analogues to secure a durable response.
- Response should be formally assessed at the conclusion of primary therapy.

Table III Assessment of Response in Hairy Cell Leukemia

Complete Response

- Near normalization of peripheral blood counts: hemoglobin greater than 11 gram/dL (without transfusion); platelets greater than 100,000/uL; and absolute neutrophil count greater than 1,500/uL
- Regression of splenomegaly on physical examination
- Absence of morphologic evidence of hairy cell leukemia both on the peripheral blood smear and the bone marrow examination
- Timing of Response Assessment - The bone marrow examination for evaluating response in patients treated with cladribine should not be done before 4 to 6 months following therapy. In those patients being treated with pentostatin, the bone marrow can be evaluated after the blood counts have near normalized and the physical examination shows no splenomegaly
- Complete Remission with or without Minimal Residual Disease (MRD): In patients who achieved a complete remission, an immunohistochemical assessment of the percent of minimal residual disease will enable separation into those with complete remission either with or without evidence of minimal residual disease.

Partial Remission

- A partial response requires near normalization of the peripheral blood count (as in CR) with a minimum of 50% improvement in both the organomegaly and bone marrow biopsy infiltration with hairy cell leukemia.

Stable Disease

- Patients who have not met the criteria for an objective remission following therapy are called stable disease. Because patients with hairy cell leukemia are treated for specific reasons including either disease-related symptoms or decline in their hematologic parameters, stable disease is not an acceptable response.

Progression of Disease

- Patients who have either an increase in symptoms related to disease, or a 25% increase in organomegaly ,or a 25% decline in their hematologic parameters qualify for progression of disease. An effort must be made to differentiate a decline in blood counts related to myelosuppression effects of therapy versus progression of disease.

Hairy Cell Leukemia in Relapse

- Morphological relapse is defined as the reappearance of hairy cell leukemia in either the peripheral blood or the bone marrow biopsy or both by morphological stains, in the absence of hematological relapse. Hematological relapse is defined as reappearance of cytopenia(s) below the thresholds defined above for complete and partial response. Whereas no treatment is necessarily needed in case of morphological relapse, treatment decisions for a hematological relapse are based upon several parameters (e.g., hematologic parameters warranting intervention; reoccurrence of disease-related symptoms)

Table IV Treatment of Hairy Cell Leukemia

Initial Treatment:

- Cladribine administered as continuous intravenous infusion days 1 through 7[55,80] , or daily for five days intravenously over two hours[56,79]; or intravenous weekly over two hours for six weeks[55]; or subcutaneous administration daily for 5 days[22,23,55].
- Pentostatin administered intravenously every two weeks to patients with attention to renal function.[48,49] Lower doses have been utilized under special circumstances.

Treatment at Relapse:

- Confirmation of the initial diagnosis is important including review of data to determine if previous therapy was correct and if poor risk features were identified (e.g., severe anemia, spleen >10 cm below the left costal margin, abnormal immunophenotypic profile, absence of BRAF V600E mutation, etc.).
- Determination of the indication for re-treatment equivalent to the initial criteria including symptomatic disease (e.g., splenomegaly) or progressive anemia, thrombocytopenia, or neutropenia.
- If previous remission greater than 24 months, then consider re-treatment with purine analogue possibly combined with an anti-CD20 monoclonal antibody, or a clinical trial
- If previous remission greater than 60 months, consider re-treat with initial therapy
- If previous remission less than 24 months, consider alternative therapy including investigational agents after confirming accuracy of diagnosis
- Older therapeutic approaches may still offer benefit (e.g., alpha interferon, splenectomy, rituximab, etc)

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Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia

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