Hairy Cell Leukemia Treatment (PDQ®): Treatment - Health Professional Information [NCI]

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General Information About Hairy Cell Leukemia

Prognostic Factors

Hairy cell leukemia is an indolent, low-grade, B-cell lymphoma usually characterized by the following:

- Circulating B-cells with cytoplasmic projections ("hairy" appearance).
- Splenomegaly.
- Absent lymphadenopathy.
- Pancytopenia.
- Monocytopenia.

Diagnosis

In addition to the B-cell antigens CD19, CD20, and CD22, the cells coexpress CD11c, CD25, and CD103. The BRAF-V600E mutation is a hairy cell leukemia-defining genetic lesion that can be used diagnostically.[1,2] The decision to treat is based on symptomatic cytopenias, massive splenomegaly, or the presence of other complications. About 10% of all patients will never require therapy.

References:


Stage Information for Hairy Cell Leukemia

No generally accepted staging system is useful for both prognosis and therapy.

For the purpose of treatment decisions, it is best to consider this disease in the following two broad categories:

- Untreated hairy cell leukemia.
- Progressive hairy cell leukemia, either postsplenectomy or post-systemic therapy.
Untreated hairy cell leukemia

Untreated hairy cell leukemia is characterized by splenomegaly, varying degrees of leukopenia (occasionally leukocytosis) and/or pancytopenia, and bone marrow infiltration by an atypical cell with prominent cytoplasmic projections (i.e., hairy cells). The bone marrow is usually fibrotic and is not easily aspirated; therefore, bone marrow biopsies are required for diagnosis and evaluation of the degree of hairy cell infiltration.

Progressive hairy cell leukemia

Progressive hairy cell leukemia postsplenectomy (or after any systemic therapy), is characterized by progressive bone marrow replacement by hairy cells with pancytopenia refractory to treatment. For patients with advanced hairy cell leukemia treated with cladribine (2-chlorodeoxyadenosine, 2-CdA), pentostatin, or interferon-alpha, the survival rate appears to be higher than 85% at 5 years after the initiation of any one of these therapies.[1,2]

References:


Treatment Option Overview for Hairy Cell Leukemia

The initial therapies of choice for hairy cell leukemia are either cladribine (2-chlorodeoxyadenosine, 2-CdA) or pentostatin.[1,2] These drugs have comparable response rates but have not been compared in phase III trials. Cladribine is administered as a one-time continuous infusion or series of subcutaneous injections and is associated with a high rate of febrile neutropenia.[3,4,5,6] Rarely, more than one course of treatment is required to induce a desirable response. Treatment should be discontinued once complete remission or stable partial remission with normalization of peripheral blood counts is reached. The presence of residual disease may be predictive of relapse but does not seem to affect survival.[5,7]

The role of consolidation or maintenance therapy in preventing relapse or progression of the disease after treatment with purine analogs has not been evaluated and remains unproven. Pentostatin is administered intermittently for a longer time but may result in a lower incidence of febrile complications.[8,9] While most patients remain disease free 10 years after treatment with these purine analogs, no patient has been monitored long enough to assess cure.[10,11] Both nucleoside analogs cause profound suppression of
CD4 counts, which may last for a year, and a potential increased risk of second malignancies has been reported.[5,12]

A study of 3,104 survivors of hairy cell leukemia from the Surveillance, Epidemiology, and End Results (SEER) database showed an increased risk of second cancers (standardized incidence ratio, 1.24; 95% confidence interval, 1.11-1.37), especially for Hodgkin and non-Hodgkin lymphomas.[13] The increased risk for second cancers was seen even in the two decades before the introduction of purine nucleosides.[13] With the use of cladribine, an increased risk of second malignancies is possible among patients with hairy cell leukemia (observed to expected ratio of about 1.8 in several series after 6 years).[5,12] Several series using pentostatin did not report an increased risk of second malignancies.[8,10,14] For a few patients, such as those with severe thrombocytopenia, splenectomy might be considered.[15] After splenectomy, 50% of patients will require no additional therapy, and long-term survivors are common. Therapy with interferon-alpha is another treatment option, especially for patients with intercurrent infection.[9,16]

The hairy cell leukemia variant has a distinctive phenotype and typically presents with leukocytosis instead of leukopenia.[17,18] Patients with this variant have poorer responses to initial cladribine, have shorter durations of response, and typically do not respond again to purine analogs after relapse. Combinations of rituximab and purine analogs are under evaluation, and further studies are required to define optimal therapies.[19]

References:


**Treatment for Hairy Cell Leukemia**

**Untreated Hairy Cell Leukemia**

Hairy cell leukemia is a highly treatable disease. Because it is easily controlled, many patients have prolonged survival with sequential therapies. The decision to treat is based on cytopenias (especially if symptomatic), increasing splenomegaly, indications that the disease is progressing, or the presence of other, usually infectious, complications. It is reasonable to offer no therapy if the patient is asymptomatic and if blood counts are maintained in an acceptable range.

**Progressive Hairy Cell Leukemia**

**Standard treatment options:**

1. Cladribine (2-chlorodeoxyadenosine, 2-CdA) given intravenously by continuous infusion, by daily subcutaneous injections, or by 2-hour infusions daily for 5 to 7
days results in a complete response rate of 50% to 80% and an overall response rate of 85% to 95%.\[1,2,3\] Level of evidence: 3iiiDiv] The response rate was lower in 979 patients treated with the Group C mechanism of the National Cancer Institute (i.e., 50% complete remission rate, 37% partial remission rate). Responses are durable with this short course of therapy, and patients who relapse often respond to retreatment with cladribine.[4,5,6]

A retrospective review of 83 patients, aged 40 years and younger, reported a median time to first relapse of 54 months for all responders and a median overall survival of 21 years from diagnosis.[7] This drug may cause fever and immunosuppression; documented infection was found in 33% of treated patients. In a retrospective study of patients with cladribine-associated neutropenic fever, filgrastim (G-CSF) did not demonstrate a decrease in the percentage of febrile patients, number of febrile days, or frequency of admissions for antibiotics.[8] (Refer to the PDQ summary on Hot Flashes and Night Sweats for more information about fever.) A potential increased risk of developing second malignancies with this agent remains controversial.

2. Pentostatin given intravenously every other week for 3 to 6 months produces a 50% to 76% complete response rate and an 80% to 87% overall response rate.[9,10] Complete remissions are of substantial duration. In two trials with 9-year median follow-ups, relapse-free survival ranged from 56% to 67%.[11,12] Side effects include fever, immunosuppression, cytopenias, and renal dysfunction. (Refer to the PDQ summary on Hot Flashes and Night Sweats for more information about fever.) A randomized comparison of pentostatin and interferon-alpha demonstrated higher and more durable responses to pentostatin.[9]

3. Interferon-alpha given subcutaneously 3 times per week for 1 year yields a 10% complete response rate and an 80% overall response rate. The drug frequently produces an influenza-like syndrome early in the course of treatment. Late effects include depression and lethargy. (Refer to the PDQ summary on Depression for more information about lethargy; refer to the PDQ summary on Fatigue.) Responding patients who relapse usually react positively to retreatment with interferon-alpha.[13] Remission can be prolonged with a low-dose maintenance regimen.[14] A randomized comparison of pentostatin and interferon-alpha demonstrated significantly higher and more durable responses to pentostatin.[9]

4. Splenectomy will partially or completely normalize the peripheral blood in the vast majority of patients with hairy cell leukemia.[15] Usually little or no change occurs in the bone marrow after splenectomy, and virtually all patients have progressive disease within 12 to 18 months. Therefore, because a number of more effective alternatives are available, splenectomy is playing a decreasing role in the treatment of this disease.

Ongoing trials (including NCT00923013) are studying combinations of cladribine plus the monoclonal antibody rituximab.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with untreated hairy cell leukemia and progressive hairy cell leukemia, initial treatment. The
list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

References:

Relapsed or Refractory Hairy Cell Leukemia

Patients with hairy cell leukemia who relapse after the first course of cladribine or pentostatin often respond well to retreatment with the same or another purine analog.[1,2,3,4,5,6,7] Rituximab can induce durable complete remissions with minimal toxic effects in patients with multiple relapsing or refractory disease after purine analog therapy or after treatment with interferon.[8,9,10,11][Level of evidence: 3iiiDiv] The lack of subsequent immunosuppression with rituximab has made this treatment a common choice among relapsing patients in the absence of a clinical trial.[10] Combinations of rituximab with either cladribine or pentostatin are effective in achieving complete remission and are under clinical evaluation.[6,12,13]

Both anti-CD25 and anti-CD22 recombinant immunotoxins under clinical evaluation can induce complete remissions in patients whose disease is resistant to retreatment with purine analogs or rituximab.[14,15,16] Interferon-alpha and splenectomy are therapeutic options that can be considered when other options have been exhausted.[12,13]

The BRAF-V600E mutation occurs in almost 100% of classic-form hairy cell leukemia patients and almost never in other B-cell lymphomas and leukemias, including hairy cell leukemia variants.[17] Two phase II, multicenter studies in the United States and Italy evaluated the BRAF inhibitor vemurafenib, given orally for 4 months. After a median follow-up of 23 months, the overall response rate for 50 patients was 98%, the complete response rate was 38%, and the median treatment-free survival was 25 months and 18 months in the two studies.[18][Level of Evidence: 3iiiDiv]

Trials (including the ongoing NCT00923013, NCT00321555, and CAT-8015-1001 [NCT00462189] study and NCI-04-C-0014, which is now completed) are in the process of evaluating, or have evaluated, new therapies for this group of patients.

Aggressive, high-dose chemotherapy has been beneficial in some cases, but the associated morbidity and mortality are high. It should not be considered unless other therapies that are more frequently effective have been exhausted.

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials that are now accepting patients with refractory hairy cell leukemia. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.
References:

Changes to This Summary (04 / 08 / 2016)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

**Progressive Hairy Cell Leukemia**

Added level of evidence: 3iiiDiv to data from a multicenter trial about the first treatment option, cladribine.

Added text to state that a retrospective review of 83 patients, aged 40 years and younger, reported a median time to first relapse of 54 months for all responders and a median overall survival of 21 years from diagnosis (cited Rosenberg et al. as reference 7).

**Relapsed or Refractory Hairy Cell Leukemia**

Added Kreitman et al. as reference 16. Added text to state that interferon-alpha and splenectomy are therapeutic options that can be considered when other options have been exhausted.

Added text to state that the BRAF-V600E mutation occurs in almost 100% of classic-form hairy cell leukemia patients and almost never in other B-cell lymphomas and leukemias, including hairy cell leukemia variants (cited Pettirossi et al. as reference 17). Also added that two phase II, multicenter studies in the United States and Italy evaluated the BRAF inhibitor, vemurafenib, given orally for 4 months; after a median follow-up of 23 months, the overall response rate for 50 patients was 98%, the complete response rate was 38%, and the median treatment-free survival was 25 months and 18 months in the two studies (cited Tiacci et al. as reference 18 and level of evidence 3iiiDiv).

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About This PDQ Summary

Purpose of This Summary
This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of hairy cell leukemia. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

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Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Hairy Cell Leukemia Treatment are:

- Eric J. Seifter, MD (Johns Hopkins University)
- Mikkael A. Sekeres, MD, MS (Cleveland Clinic Taussig Cancer Institute)

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