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Advances in the Treatment of Hairy Cell Leukemia

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Abstract

Hairy cell leukemia is relatively rare, chronic low grade B-cell leukemia. It is characterized morphologically by cells with abundant cytoplasm and “hair”-like projections that can be found within the peripheral blood, bone marrow or splenic pulp. Like many cancers, the treatment for hairy cell leukemia has evolved considerably in the last several years. In the mid 1980s, the acceptable treatment was splenectomy and later interferon therapy, which is quickly falling out of favor with the advent and acceptance of purine analog therapy. In addition, we now have several biologic agents that are coming into favor based on their improved success and favorable toxicity. In addition, several studies are currently looking into the efficacy of purine analogs in conjunction with biologic agents. Rituximab, alemtuzumab and recombinant immunotoxins are being studied with limited success in hairy cell leukemia. The use of kinase inhibition is also being studied at this time. Advances in understanding the biology of hairy cell leukemia could potentially increase more treatment options.

Keywords: Hairy cell leukemia; Purine analog; Immunotherapy; B-cell leukemia

Introduction

Hairy cell leukemia (HCL) is a chronic, low grade, non-Hodgkin lymphoma. This disease is relatively rare and represents 2% of all lymphomas [1]. It is characterized by the accumulation of small, mature B-cell lymphoid cells with abundant cytoplasm and "hairy" projections that are found within the peripheral blood, bone marrow, and splenic red pulp [1,2]. This accumulation results in significant splenomegaly and pancytopenia. Even though HCL is not curable, prognosis for classic HCL is relatively better.

Therapeutic options for HCL include: watchful waiting, splenectomy, purine analogs, and more novel immunotherapies and targeted kinase inhibitors. The majority of patients do not require therapy immediately upon diagnosis. Indications for treatment are symptomatic disease with debilitating fatigue, massive splenomegaly leading to abdominal pain, weight loss secondary to early satiety and bone marrow failure [1]. Most patients show excellent long-term response to treatment with a single-agent purine analog. The increasing number of patients, who either relapse or become refractory to purine analog therapy, led to more studies for a better understanding of the HCL pathobiology and more effective treatment options.

Splenectomy was developed as the first effective therapeutic approach in the history of HCL treatment and was considered as the treatment of choice until 1984 [3]. However, splenectomy did not improve bone marrow infiltration or fibrosis. In 1984, alpha interferon therapy for HCL was proven to be effective in improving cytopenias as well as reducing bone marrow fibrosis. Interferon treatment was associated with about 30% complete response and over 50% partial response rates [4].

Purine Analogues (PA)

The adenosine deaminase (ADA) inhibitor, Pentostatin (2'-deoxycoformycin), was developed in the 1970s and was introduced to treat HCL in late 1980s [5]. It was proved to induce high response rates and long-lasting responses [6]. Generally, Pentostatin is well tolerated [7], however it could cause prolonged myelosuppression, neutropenic fever, skin rash [8], and cardiotoxicity [9]. Cladribine (2-chlorodeoxyadenosine) was developed as another purine analog that became more commonly used as first line therapy [10]. Cladribine has a better side effect profile coupled with ease of administration via a single cycle over 5–7 days. There are no randomized clinical trials to compare Cladribine with Pentostain in the treatment of HCL. A long follow up retrospective study, compared the effects of either PA in the treatment of treatment naïve HCL patients. Complete response rates were similar between patients treated with cladribine (84%) or pentostatin (82%). The 5-Year survival was about 97%, when treated with either PA. The overall response rates and survival rates were similar with no significant difference in toxicity [6,11]. Patients with refractory or relapse disease usually received a further course of either drug.

Novel Therapeutics Approaches

Advanced understanding in HCL pathobiology, over the past decade, has paved the path for developing several new targeted therapies. These include monoclonal antibodies, immunotoxins, and kinase inhibitors [12]. Two characteristics mark the ideal target antigen: an exclusive expression on malignant cells, and the abundant availability on the surface of the malignant cells to supply a sufficient

number of binding sites for the antibody. In HCL, all the leukemia cells are found to be strongly positive for CD20, CD22, and CD25. These abundant cell surface antigens can be used to develop monoclonal antibodies against these antigens or drug delivery targets. Monoclonal antibodies can directly attach to HCL cell surface and activate cell-mediated apoptosis. Recombinant immunotoxins are used to carry and deliver a lethal dose of chemotherapy into the targeted cells. Since the discovery of *V600E BRAF* mutation in HCL, there has been heightened interest in studying the role of kinase-targeted therapy.

Rituximab, a chimeric monoclonal CD 20 antibody

CD20 is a non-glycosylated transmembrane protein, exclusively expressed on mature B-cell lymphocytes (both healthy and malignant) and appears in high density on HCL cells. CD20 is involved in the regulation and proliferation of the B-cell. Rituximab, a chimeric monoclonal CD 20 antibody induces cell death by several mechanisms including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and a direct prompting of internal signaling pathways. Usually the side effects of rituximab result from infusion-related reactions (pyrexia, rigors, flushing, pruritus, bronchospasm, urticaria) or from cytopenias (gastrointestinal bleeding and reactivation of viral infections, particularly hepatitis B virus and cytomegalovirus). Progressive multifocal leukoencephalopathy (PML) was also reported in rare cases [13]. Rituximab is reported to be effective in HCL patients refractory to traditional chemotherapies [14]. Significant synergy was noted, when rituximab was combined with PA in relapsed and refractory HCL patients. This combination strategy achieved a complete response rate of more than 85% with tolerable toxicity [15]. More extensive studies for the efficacy and safety of this combination are required to determine its potential as a first line approach for treating HCL. Currently, a clinical trial is randomizing de novo or first-relapse HCL patients to cladribine or concurrent rituximab and cladribine [ClinicalTrials.gov identifier NCT00923013].

Anti-CD52 antibody: Alemtuzumab

CD52 is a cell surface glycoprotein of unknown function expressed on mature lymphocytes and monocytic cells. Alemtuzumab is a fully humanized monoclonal antibody against CD 52. Although attempts to treat HCL using anti-CD52 revealed limited success, there has been better response with treating refractory cases [16]. Its toxicity includes infusion reactions similar to rituximab and prolonged immunosuppression, leading to opportunistic infections.

Recombinant immunotoxins

A recombinant immunotoxin (RIT) is a monoclonal antibody or antibody fragment that is attached to a truncated small toxin. Sources of the cellular toxin component for a recombinant immunotoxin include fungi, bacteria, and plants. These immunotoxins induces apoptosis by inhibition of protein synthesis. Immunotoxins may be used in treating refractory and relapsed HCL patients. Recombinant immunotoxins used in HCL in patients include LMB-2, which targets CD25, and both BL22 and moxetumomab pasudotox, which target CD22.

LMB-2 is an anti-CD25 recombinant immunotoxin, and its role in treating HCL in chemotherapy resistant patients is under evaluation with randomized clinical trials. BL22 is an anti-CD22 RIT. CD22 is a B-cell specific surface antigen of mature B-lymphocytes that is neither found on normal tissues, early progenitor B-cells, nor hematopoietic stem cells [17]. Thus, the anti-CD22 therapeutic effects are targeted directly and specifically towards mature B-cells. Toxicities noted in some patients include a dose-limiting cytokine-release syndrome related to a secondary immune response to BL22 and a marked hemolytic uremic syndrome. Moxetumomab pasudotox is a newer anti-CD22 immunotoxin that was developed from BL22 and displayed a greater affinity for CD22. The role of Moxetumomab pasudotox in the treatment of advanced HCL is currently being assessed in a multicenter Phase III trial [ClinicalTrials.gov identifier NCT01829711].

Targeted kinase inhibition

BRAF inhibition: Using whole-exome sequencing technique, Tiacci et al. discovered V600E BRAF mutation in the activation segment of kinase domain in HCL patients. It is clonally present in 100% of the HCL patients, but not in patients with other B-cell malignancies [18]. Vemurafenib is a novel targeted agent that inhibits tyrosine kinase in cells with *V600E BRAF* mutation. Vemurafinib was used in a patient with HCL harboring V600E BRAF mutation, who failed on traditional chemotherapies. There was rapid reduction in spleen size and improvement in platelet counts [19]. Even after discontinuation of Vemurafinib, there was continued response in that HCL patient. Phase II study is currently recruiting patients with relapsed or refractory HCL to assess both the efficacy of and overall response rates to Vemurafenib following 3 months of treatment [ClinicalTrials.gov identifier NCT01711632]. Recently, Debrafenib, another BRAF inhibitor was successfully used in treating a patient with malignant melanoma and hairy cell leukemia, harboring *V600E BRAF* mutation [20].

Bruton tyrosine kinase (BTK) inhibition: Bruton tyrosine kinase (BTK) is an important molecule in B-cell receptor signaling. It is very important cell proliferation, migration and adhesion. Ibrutinib, an oral irreversible BTK inhibitor was demonstrated to promote apoptosis in B-lymphocytes [21]. Since BTK expression is found to be abundant in HCL cells, recent preclinical models support the idea of using Ibrutinib in treating relapsed HCL patients [22]. A multicenter Phase II trial addressing the role of Ibrutinib in patients with relapsed HCL is currently recruiting patients [ClinicalTrials.gov identifier NCT01841723].

Other Therapies

Radiation therapy was used to treat HCL patient with bony involvement. Several cases were reported with both symptomatic relief as well as resolution of HCL, when treated with radiation. Splenic radiation was also used to decrease the size of spleen, and there by reducing the early satiety, weight loss and cytopenias. Splenectomy could be performed in HCL patients with recurrent and refractory disease.

Conclusion

In conclusion, since the introduction of interferon as a therapeutic option for hairy cell leukemia, the outcome for the HCL patient has significantly improved. The use of PA is considered as the treatment of choice, demonstrating high complete response rates and long-term disease-free survival. Relapse was reported in more than 30% of HCL patients treated with PA [23]. To date, there are no standard consensus or guidelines for treating refractory or relapse HCL patients. Common

therapeutic strategies include: repeating cycles with same or alternative PA, repeating treatment in combination with Rituximab, and clinical trials with immunotoxins or targeted kinase inhibitors. Using the latest technology including high throughput sequencing, OMICS, new targets are being discovered in HCL. This could potentially lead to novel targeted therapies.

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