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New Therapies for Hairy Cell Leukemia

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Hairy Cell Leukemia (HCL) is a B-cell chronic lymphoproliferative disorder characterized by marked splenomegaly, progressive pancytopenia and reactive marrow fibrosis [1]. The annual incidence of HCL is estimated to be 0.3 cases per 100 000 [2]. Hairy cells characteristically stain strongly positive for tartrate-resistant acid phosphatase, a typical pattern of B-cell antigen expression (CD19, CD20) and coexpression of CD11c, CD25 and CD103. Cell surface markers which are associated with normal B-cell activation, especially CD22, CD25, CD72 and CD40, are strongly expressed by leukemic cells [3]. Recently, the BRAF V600E mutation has been found in all evaluated patients with HCL and has been described as a disease-defining genetic event [4]. Hairy Cell Leukemia Variant (HCL-V) is a rare and indolent form of small, mature, B-cell leukemia comprising about 2% of leukemias [5]. The World Health Organization (WHO) now recognizes HCL-V as a provisional entity distinct from classic HCL.

Over the last decades, the clinical outcome for patients with HCL has been significantly improved because of effective therapies with interferon-alfa and purine nucleoside analogs, pentostatin and cladribine [6]. Cladribine and pentostatin are the drugs of choice in the treatment of HCL [7]. These drugs induce durable and unmaintained Complete Response (CR) in 76% to 98% of patients, and the relapse rates are about 30% to 40% after 5 to 10 years of follow-up. Moreover, purine analogs are effective in re-induction therapy. However, despite initial very high response rates following these drugs, many patients ultimately relapse or have refractory disease, particularly patients with HCL-V. For these patients, novel therapies are needed.

Rituximab is a chimeric mouse-human monoclonal antibody (mAb) consisting of murine variable region that recognizes human CD20 antigen and human constant region sequences [8]. Rituximab appears promising in the treatment of HCL. The drug can be given as a single agent or in combination with purine nucleoside analogs. Hagberg and Lundholm evaluated rituximab in a dose of 375 mg/m^2 once a week for 4 weeks in 11 patients with HCL including 8 relapsing and 3 newly diagnosed patients [9,10]. The response rate was seen in 7 out of 11 (64%) patients including 6 CR and 1 Partial Response (PR), lasting between 0 and 34 months (median 14 months). In another study Thomas et al. treated 15 patients with refractory to or relapsing disease after interferon and/or purine analog therapy [10]. Rituximab was given at a dose of 375 mg/m^2 weekly for a total of 8 planned doses. In addition, 4 further doses could be administered to responders who had not achieved CR. Overall response (OR) rate was observed in 12 (80%) of the patients, including CR in 8 (53%) patients. Among the responders a median remission duration of 32 months was reported. In other studies, rituximab had only modest single-agent activity in cladribine-failed HCL patients when compared with other agents. Nieva et al. performed a Phase 2 (Table 1) trial with rituximab at 375 mg/m^2 intravenously weekly for 4 weeks in 24 patients relapsing after cladribine [11]. Six (25%) patients responded including 3 CR and 3 PR. The median remission duration in this cohort was 73 months. Better results were observed when rituximab was combined with cladribine [12,13]. This form of immunochemotherapy is more effective than cladribine alone and is well tolerated. Ravandi et al. reported the results of treating 43 HCL patients with 5.6 mg/m^2 cladribine for 5 days and 28 days and 375 mg/m^2 rituximab every week for eight doses [12,13]. A CR was achieved in all patients and therapy was safe and feasible. With a median observation time of 26 months, relapse was observed only in one patient. However, a longer follow-up of the patients is needed to clearly determine the superiority of the combination therapy over cladribine alone. Whether rituximab should be administered concurrently with cladribine or sequentially to obtain the maximum benefit also remains unclear. Future studies further exploring these strategies are encouraged. Bendamustine and rituximab combination has also a significant activity in multiply relapsed/refractory HCL [14]. Burotto et al. [14] treated 12 patients with rituximab 375 mg/m^2 on days 1 and 15 combined with bendamustine 70 or 90 mg/m^2 on days 1 and 2, for six cycles at 4-week intervals. All patients responded and seven patients were in CR including six without Minimal Residual Disease (MRD) [15].

There is currently no effective treatment for HCL-V and the results of the therapy with cladribine are unsatisfactory. In contrast to classic HCL, HCL-V is not associated with the BRAF V600E mutation [16-18]. Recently, Kreitman et al. reported 10 patients with HCL-V treated simultaneously with cladribine and rituximab [19]. Patients previously treated with 0 to 1 courses of cladribine received this agent again at a dose of 0.15 mg/kg for 5 days, with 8 doses of rituximab 375 mg/m^2 beginning on day 1 and then administered weekly. Nine patients (90%) achieved a CR, compared with 3 (8%) of 39 cases reported in the literature who were treated with cladribine alone (P<0.0001). In addition, 8 patients remained free of MRD at 12 to 48 months of observation. Most patients received steroids to prevent and treat rituximab infusion reactions. These results indicate that patients with HCL-V should receive rituximab in addition to cladribine.

Immunotoxins may also play a role in the treatment of HCL especially in patients where conventional therapies produce limited responses or treatment failure [17]. LMB-2 is an anti-CD25 recombinant immunotoxin containing variable domains of mAb anti-Tac and truncated *Pseudomonas* exotoxin [18]. In a phase I trial, it was found that the Maximal Tolerated Dose (MTD) of LMB-2 was 40 microg/Kg IV given every other day for 3 doses (QOD x3) [19]. In this study 4 chemoresistant patients with HCL had major responses, including 1 CR and 3 PRs. Phase 2 trial of LMB-2 in HCL is ongoing (ClinicalTrials.gov Identifier: NCT00321555).

BL-22 (CAT-3888, RFB4 (dsFv)-PE38, GCR-3888; Genencor/Cambridge Antibody Technology) is a 63-kDa recombinant immunotoxin containing truncated *Pseudomonas* exotoxin A called PE38 and variable domains from anti-CD22 antibody. In a Phase

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Drug	Characteristics	Current status in therapy	Clinical trials in HCL
Rituximab (Mabthera, Roche)	Anti-CD20 mAb	Approved for CLL, B-cell NHL and rheumatoid arthritis	Several Phase 2 clinical trials of rituximab alone or in combination with purine analogs completed
BL22 (CAT-3888 , National Cancer Institute)	Anti- CD22 immunotoxin (anti-CD22 mAb conjugated to PE38)	Not approved yet	No clinical trials ongoing
Moxetumomab pasudotox (CAT-8015, HA22, Medimmune)	High-CD22 affinity version of BL22	Not approved yet	Phase 1 clinical trial in refractory/relapsed HCL completed; Phase 3 clinical trial for advanced HCL ongoing
LMB-2 (National Cancer Institute)	Single-chain anti-CD25 Fv-portion of antibody fused to PE38	Not approved yet	Phase 2 clinical trial for HCL ongoing
Ibrutinib (Imbruvica, Pharmacyclics, Inc.)	Btk inhibitor	Approved for mantle cell lymphoma	Phase 2 trials evaluating the role of ibrutinib in patients with relapsed HCL ongoing
Vemurafenib (Zelboraf™, Roche)	BRAF inhibitor	Approved for melanoma	Phase 2 study in patients with relapsed or refractory HCL ongoing

Abbreviations: mAb-monoclonal antibody; Btk - Bruton's tyrosine kinase; HCL- hairy cell leukemia; PE38 - *Pseudomonas* exotoxin A.

Table 1: Candidate drugs for therapy of hairy cell leukemia.

1 dose-escalation trial performed by Kreitman et al., BL22 was administered at doses between 0.2-4.0 mg to HCL patients who were resistant to cladribine [20]. Eleven of 16 (69%) patients obtained a CR and 2 had a PR. Three relapsed patients were retreated with BL22 and all of them had a second CR during a median follow-up of 16 months. No dose limited toxicity has been established so far and MTD has not been reached. Nineteen patients (73.1%) responded with a CR rate of 34.6% and a PR rate of 38.5%.

Moxetumomab pasudotox (CAT-8015, HA22, MedImmune LLC / Cambridge Antibody Technology) is a new generation of CD22-specific targeted immunotoxin composed of the Fv fragment of an anti-CD22 monoclonal antibody fused to a 38-kDa fragment of *Pseudomonas* exotoxin A, called PE38 [21,22]. Moxetumomab pasudotox is an improved form of BL22 with a 14-fold increase in affinity and a significant increase in cell-killing activity with up to 50-times more activity on leukemic cells from patients with CLL and HCL. This drug is internalized upon binding to CD22, inhibiting protein translation and promoting apoptosis. The drug was investigated in a Phase 1 trial in 26 patients with refractory/relapsed HCL and the results have been recently reported [23]. Dose limited toxicity has been established so far and MTD has not been reached. Nineteen patients (73.1%) responded with a CR rate of 34.6% and a PR rate of 38.5%.

Vemurafenib (Zelboraf™, Roche), which inhibits the V600E mutant of BRAF, has been approved by the Food and Drug Administration (FDA) for the therapy of BRAFV600E mutant metastatic melanoma [24]. Vemurafenib, also exhibited remarkable activity in multiply relapsed and refractory HCL patients with rapidly decreased splenomegaly, increased platelets, and normalization of hemoglobin and granulocyte counts [25-30]. In addition, in some patients nearly complete clearing of MRD was observed. Chung et al. have designed a phase 2 trial to determine the clinical efficacy of vemurafenib in patients with relapsed or refractory HCL [31]. Eight patients who were resistant to or intolerant of purine analogs received vemurafenib 960 mg bid or 480 mg bid due to side effects, continuously in cycles of 4 weeks for 3 cycles. Five patients were evaluable for toxicity and disease response. The most common adverse events were rash, photosensitivity, arthralgia, hand-foot syndrome and febrile neutropenia. All evaluated patients achieved complete hematologic recovery. Two patients achieved marrow CR and 3 patients achieved marrow PR with very minimal disease. Further studies and longer follow-up are needed to confirm efficiency of this drug and the durability of the response. In particular, the adverse event profile of vemurafenib in HCL and the optimal drug dose and treatment duration should be established. Phase 2 study of vemurafenib, in patients with relapsed or refractory HCL is ongoing (ClinicalTrials.gov Identifier: NCT01711632).

The B-cell antigen receptor (BCR) signal transduction inhibitors, ibrutinib (PCI-32765, Imbruvica, Pharmacyclics, Inc.) and idelalisib (GS-1101, CAL-101), represent a promising new strategy for treatment of B-cell lymphoid neoplasms [31,32]. Recently, considerable interest in the role of BCR signal transduction inhibitors in HCL has arisen. Sivina et al. reported that ibrutinib inhibits BCR signalling in primary HCL cell and HCL cell lines, and significantly diminishes HCL survival and proliferation. These data provide rationale for investigation of the clinical activity of BCR inhibitors in patients with HCL. Consequently, a multicenter Phase 2 trials evaluating the role of ibrutinib in patients with relapsed HCL have been initiated (NCT01981512, NCT01841723).

In the coming years, new agents will assist and perhaps replace standard therapy for patients with HCL who now have a suboptimal results after treatment with purine nucleoside analogs. Future research should focus on the novel therapeutic strategies based on the molecular pathogenic mechanisms and the development of new targeted therapies.

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