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New therapeutic options for hairy cell leukemia

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Abstract

Hairy cell leukemia (HCL) is a rare B-cell lymphoproliferative disorder characterized by pancytopenia, splenomegaly and increased susceptibility to infections. In 2011, *BRAF* gene mutation was identified in almost all the patients with the classical type of HCL. The purine analogs cladribine and pentostatin induce long-term remission in the majority of patients, and they remain the standard treatment for this type of leukemia.

However, more than half of patients in complete response relapse over the long term, with a quarter of them relapsing within the first five years.

Recently, new drugs have been developed and have demonstrated efficacy in refractory or relapsed HCL. The immunotoxin Moxetumomab pasudotox was registered for HCL in 2018. The BRAF kinase inhibitors vemurafenib and dabrafenib, as well as the Bruton kinase inhibitor ibrutinib, are also proven highly effective in clinical trials.

Key words: BRAF, dabrafenib, hairy cell leukemia, ibrutinib, moxetumomab pasudotox, purine analogs, rituximab, vemurafenib

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Introduction

Hairy cell leukemia (HCL) is a rare B-cell lymphoproliferative disorder [1, 2]. The classical type is characterized by pancytopenia, splenomegaly, general symptoms and increased susceptibility to infections. Rarer clinical presentations and manifestations include lymphadenopathy, skin lesions, osteolytic bone changes, and leukemic infiltrates in the gastrointestinal tract and liver [3–5]. HCL gets its name from the characteristic villous cytoplasmic projections. The classic phenotype of HCL consists of high expression of surface immunoglobulin, with high co-expression of CD20, CD22, CD11c, CD103 and CD25, CD123 and CD200. The *BRAF* V600E mutation is almost universally present in classical HCL [6]. HCL incidence is estimated to be 0.3 cases per 100,000 people per year [7, 8]. The median age at diagnosis is 58 years. HCL accounts for 2–3% of all adult leukemias [1, 2]. There is a strong male predominance, with a male-to-female ratio of 4 to 1.

In 2008, the World Health Organization (WHO) reclassified HCL and distinguished a variant of hairy cell leukemia (HCLv), which it then included as a provisional entity within the spectrum of 'splenic B-cell leukemia/lymphomas unclassifiable' [9–11]. HCLv is characterized by leucocytosis with lymphocytosis, cytopenias without monocytopenia, lymphoid cells of relatively large size with prominent nucleoli, atypical HCL immunophenotype, and resistance to conventional HCL therapy. BRAF mutation is not detected. Mutations of the immunoglobulin heavy chain (IGVH) are seen in two thirds of cases with a preferential VH4-34 family usage [9].

This article presents new therapeutic options for patients with hairy cell leukemia.

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Standard therapies

As with chronic lymphocytic leukemia (CLL) and indolent lymphomas, in asymptomatic HCL patients, the strategy applied is one of deferred treatment to progression (watch and wait) [1, 2]. The indications for treatment initiation are anemia [hemoglobin (Hb) <11 g/dL] not due to other causes, thrombocytopenia [platelets (PLT) <100,000/μL], neutropenia [absolute neutrophil count (ANC) <1,000 μL], symptomatic splenomegaly, recurrent infections, or systemic symptoms. Only 10% of patients with newly diagnosed HCL have no indication to start treatment [1]. Cladribine (2-CdA, 2-chlorodeoxyadenosine) and pentostatin (DCF, deoxycoformycin) are recommended for first-line treatment [1, 2]. Their introduction to HCL therapies in 1990 was a breakthrough in the treatment of this group of patients, and allowed for long-term remissions in over 90% of patients [12, 13]. Both drugs interfere with DNA synthesis in resting and proliferating cells, disrupting their metabolism and inducing apoptosis. Both drugs also show a strong myelosuppressive effect and cause long-term immunosuppression [14].

So far, no randomized study directly comparing the efficacy of 2-CdA and DCF therapy has been conducted. However, both drugs seem to be similarly effective [14]. In addition, 2-CdA can be given as second-line treatment in patients with primary DCF resistance. In practice, 2-CdA is used more often, mainly due to easier dosing and lower drug toxicity, especially nephrotoxicity [15]. Purine analogs induce long-term complete response (CR) in over 70% of patients with classic HCL, with a median response duration of 8–10 years [16, 17]. Patients who achieve a CR without minimal residual disease (MRD) have a longer disease-free survival (DFS). Purine analogs can be used in second-line treatment, but the response rate is lower and response duration shorter. The median duration of the second response to purine analogs is 2–9 years [18–23].

Rituximab monotherapy is not very effective [24]. In patients with early relapse (within 12–18 months), it is recommended to combine 2-CdA with rituximab [25, 26]. Such treatment allows CR to be obtained in 89–100% of patients with a 5-year progression-free survival (PFS) reaching 100%, and a 3-year risk of recurrence of about 7% [25].

Another treatment option for relapsed patients is fludarabine (administered orally at 40 mg/m^2 for 5 days) or bendamustine (70–90 mg/m^2 on days 1 and 2) in combination with rituximab (375 mg/m^2) on the first day of the cycle, every 28 days, for up to four cycles [27, 28]. Splenectomy is considered in patients with refractory, massive splenomegaly (>10 cm below the costal arch) with minor bone marrow involvement, or in pregnant women who have not responded to treatment with alpha interferon (IFN-α) [29].

New drugs

In recent years, the effectiveness of several new drugs has been demonstrated in patients with the classic form of HCL. These include the immunotoxin moxetumomab pasudotox (Moxe, Lumoxiti™), targeting the CD22 antigen, BRAF kinase inhibitors (vemurafenib and dabrafenib), as well as the Bruton kinase (BTK) inhibitor ibrutinib [14]. These drugs have been studied mainly in patients who are refractory to purine analogs. Table I presents the characteristics of the new drugs showing clinical activity in HCL patients [30–36].

Moxetumomab pasudotox

Moxetumomab pasudotox (Moxe) is a recombinant immunotoxin that consists of an anti-CD22 monoclonal antibody and *Pseudomonas* PE38 exotoxin [37]. The CD22 antigen is a transmembrane protein present only on B lymphocytes. This antigen is seen in increased numbers on HCL leukemic cells. Moxetumomab pasudotox binds to CD22-expressing cells followed by internalization of the drug-CD22 complex. The active form of PE38 exotoxin is released, which inactivates elongation factor 2 (EF-2). This in turn results in protein synthesis inhibition and, consequently, cell apoptosis. The amount of both normal lymphocytes and leukemic cells decreases over a short period of time. About six months after the end of therapy, the amount of normal B lymphocytes returns to baseline values. The efficacy of Moxe was assessed in phase I and phase III trials in patients with refractory and recurrent HCL [30–33].

In the phase I study, Moxe was used in 26 patients at increasing doses of 5, 10, 20, 30 μg/kg, 40 μg/kg, and 50 μg/kg administered on days 1, 3, and 5 of each 28-day treatment cycle [30]. The treatment was well tolerated, and no dose-limiting toxicity was observed. Two patients developed moderate hemolytic uremic syndrome (HUS). In 10 patients (38%), the development of drug-neutralizing antibodies was observed during the use of Moxe. A response was achieved in 86% of patients, including 13 (46%) CR. Lesser efficacy was observed in patients who had undergone splenectomy and with massive splenomegaly. In the next analysis, the study group was increased by 21 patients who received a dose of 50 μg/kg [31]. A total of 33 patients received this dose. As in the previous analysis, 88% of patients responded to the treatment, and 64% achieved a CR of a mean duration of 42.4 months. The duration of CR was significantly longer in 11 patients without minimal residual disease (MRD) (42.1 months) than in MRD-positive patients (13.5 months) (p <0.001). The most common adverse drug reactions observed were: peripheral edema (52.5%), nausea (35.0%), infusion-related reactions (25.0%), hypoalbuminemia (21.3%), and increased transaminases (21.3%).

Table I. New drugs active in hairy cell leukemia (acc. to [30–36])

Drug	Drug's mechanism of action	Drug dosage	Drug effectiveness	Side effects	Literature
Moxetumomab pasudotox (Lumoxiti™)	After association with cell, drug-CD22 complex is internalized and active form of exotoxin is released	0.04 mg/kg on days 1, 3 and 5 of each 28-day cycle, up to 6 cycles, disease progression or drug-induced toxicity	Follow-up* 24.6 months ORR 75% CR 41% CR MRD(–) 34% PR 34% PFS 71.7 months	Edema, peripheral nausea, infusion reactions, hypoalbuminemia, increase in transaminases, hemolytic uremic syndrome, capillary leak syndrome	[30–33]
Vemurafenib (Zelboraf®)	BRAF serine-threonine kinase inhibitor caused mutations in *BRAF* gene in codon 600	240–960 mg twice a day orally for 16/18 weeks	Follow-up* 23 months ORR 96% CR 35% PR 62% PFS 9 months	Skin rash, skin sensitivity to light, joint pain and inflammation, fever, increase in transaminases and creatinine, QT prolongation, ocular reactions, skin tumors	[34]
Dabrafenib (Tafinlar®)	BRAF serine-threonine kinase inhibitor caused mutations in *BRAF* gene in codon 600	150 mg twice a day orally for 12 weeks	Follow-up* 64 months ORR 80% CR 30% CR MRD(–) 10% PR 50% PFS 14 months	Skin rash, skin sensitivity to light, joint pain and inflammation, fever, increase in transaminases and creatinine, QT prolongation, ocular reactions, skin tumors	[35]
Ibrutinib (Imbruvica®)	Bruton's kinase inhibitor	420, 840 mg 1 pc, orally until disease progression or unacceptable toxicity	Follow-up* 3.5 years ORR 36% after 48 weeks of treatment	Diarrhea, weakness, muscle and joint pain, nausea, hemorrhagic diathesis, cytopenia, hypertension, atrial fibrillation	[36]

*Follow-up — observation time; ORR — overall response rate; CR — complete remission; MRD — minimal residual disease; PR — partial response; PFS — progression-free survival

The results obtained in the phase I study were confirmed by a phase III study in 80 patients with refractory and recurrent HCL [37]. Moxe was administered at a dose of 40 µg/kg on days 1, 3, and 5 every 28 days for up to 6 cycles. Patients who had previously received at least two lines of treatment, including one with a purine analog, were included in the study. The mean follow-up was 16.7 months. Hematological remission was achieved by 80% of patients, and CR in 41%. In the group of patients with CR, 85% of patients did not show MRD in immunohistochemical tests. The most common adverse events were peripheral edema (39%), nausea (35%), fatigue (34%), and headache (33%). Hemolytic uremic syndrome occurred in 7.5%, and capillary leak syndrome in 8.8% of patients. These symptoms resolved after discontinuation of therapy. The long-term results of this study with a median follow-up of 24.6 months were recently presented [33]. The median for prior lines of treatment was three lines, and 49% of patients were refractory to purine analogs. The CR rate was 41%. Long-term CR (>180 days) was achieved by 36% of patients and of over 360 days by 33%. In 27 patients with CR (82%) no minimal residual disease was found. The median PFS was 71.7 months, and 61% of patients with CR had no relapse by 60 months. No treatment-related death was observed.

In 2018, Moxe was approved by the Food and Drug Administration (FDA) for the treatment of patients with refractory and relapsed HCL who have received at least two systemic therapies, including one with a purine analog [37]. The recommended dose is 0.04 mg/kg. The drug should be administered as a 30-minute intravenous infusion on days 1, 3 and 5 of each 28-day cycle, after the patient has been hydrated and supplied with antiallergic drugs. Patients should continue treatment for a maximum of six cycles or until disease progression or signs of unacceptable drug toxicity. In special circumstances, treatment may be discontinued earlier if the patient has achieved CR. FDA also

allows repeated treatment with Moxe within 3–12 years after completing the first treatment. Yurkiewicz et al. [38] analyzed the cases of three patients who achieved at least PR after the first Moxe therapy. In two of the three patients treated with Moxe a hematological response was achieved, and in one CR was confirmed by bone marrow examination. One patient did not respond to treatment. No serious side effects were observed during the second treatment with Moxe. The combined treatment of Moxe with rituximab remains in the first phase of clinical trials [39].

BRAF kinase inhibitors

The identification of the *BRAF* V600E kinase mutation in 2011 as the pathogenetic cause of classical HCL allowed for the introduction of new drugs for HCL therapy [6, 40–42]. The mutation causes constitutive activation of the MAP kinase pathway and determines the survival of the leukemic cells. In 2014, the BRAF kinase inhibitors, vemurafenib and dabrafenib, began to be used in patients with refractory and recurrent HCL [40]. Another reason for choosing BRAF inhibitors are patients with contraindications to purine analogs, agranulocytosis and active infection [2]. BRAF kinase inhibitors have turned out to be effective in the treatment of classic HCL, but CR is achieved only in some patients, and median time to relapse after cessation of vemurafenib is just 14 months [34, 42].

Vemurafenib

Vemurafenib (Zelboraf®) was originally approved for the treatment of malignant melanoma. In 2015, Tiacci et al. [34] published the results of a phase II clinical trial involving 54 patients with relapsed or refractory BRAF positive HCL. The study was conducted in Italy (28 patients) and in the USA (26 patients). The drug was administered at a dose of 960 mg twice daily for 16–18 weeks. The overall response rates (ORR) were 96% and 100% after 8 and 12 weeks, in the Italian and in the American study, respectively. The CR rates were 35% and 42% in the two trials. After a median follow-up of 23 months, the Italian median relapse-free survival was 19 months for patients who achieved CR, and 6 months for those with partial response (PR). Patients who required dose reduction due to toxicity obtained similar results (CR 60%, PR 40%). Splenectomy or the number of prior treatments did not correlate with the quality of response. However, splenectomy was associated with shorter progression-free survival (PFS) and time to treatment (6 vs. 11 months).

In 2020, Libers et al. [42] presented retrospective data of 27 patients treated with different doses of BRAF inhibitors (vemurafenib, dabrafenib) outside clinical trials, in seven different European centers. The analysis of variable doses (range: vemurafenib: 240–1,920 mg per day; dabrafenib: 150–300 mg per day) and treatment durations (median 3.8 months, range: 1.7–19.9) addressed the question of whether individual approach had an impact on time to next treatment (TTT). All patients obtained complete hematological response. Based on the available 18 samples of bone marrow biopsies, six patients achieved CR and 12 achieved PR. The analysis also showed that neither the dose nor duration of treatment, or the number of previous lines, had any effect on the final response. Similarly to other studies, patients who achieved CR had a significantly longer PFS than those who achieved PR (19.8 vs. 11.4 months respectively). In addition, it has been shown that vemurafenib increases platelet count >100 G/L after two weeks, the number of neutrophils >1.5 G/L after four weeks, and an improvement in red blood cell parameters hemoglobin (Hg) >11 g/dL after eight weeks [42]. The best results were obtained during the first two relapses, with PFS 10.9 and 12.1 months. The duration of remission after successive cycles of vemurafenib was significantly shorter (median 3.4 months) [42]. An early, retrospective analysis indicated that lower doses of the drug (2 × 240 mg per day) are as effective as higher doses (2 × 960 mg per day) [41]. However, patients who received higher doses of BRAF inhibitors (vemurafenib >480 mg and dabrafenib >150 mg) had a significantly longer treatment-free survival (14.6 months vs. 9.4 months) than patients receiving lower doses.

In summary, it seems that the highest, well-tolerated doses of BRAF inhibitors should be used in order to obtain the best response.

Vemurafenib is well-tolerated. The most common drug-related adverse events are grade 1/2 and include skin rash, photosensitivity, arthritis, fever, elevated liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGTP)] and renal function tests. A temporary dose reduction and symptomatic treatment relieve the symptoms [34, 42]. Vemurafenib may also accelerate the growth of secondary skin cancers. The risk of developing a new tumor may be dose-related [34, 42–44].

The effectiveness of BRAF inhibitors is higher when combined with rituximab [45]. Tiacci et al. recently published the results of a study with vemurafenib at a dose of 960 mg, given twice daily for eight weeks combined with eight doses of rituximab 375 mg/m^2 over 18 weeks [45]. Thirty patients with refractory or recurrent HCL were enrolled to the study, including 10 patients resistant to chemotherapy, five patients resistant to rituximab, and seven patients resistant to BRAF inhibitors. 26 patients achieved CR (87%), with 17 of them (65%) having an MRD negative response. Median PFS was 78% (median follow-up was 37 months). Lack of MRD and no prior use of BRAF inhibitors correlated with a longer PFS.

In another study, the utility of targeted therapy for nine patients (three treatment-naive patients with severe neutropenia and active infection) was reported. Vemurafenib was administered at 240–480 mg twice daily and

combined with rituximab in seven patients. Vemurafenib was given for 38–140 days. In spite of lower doses of vemurafenib than those in previous studies, therapy with the BRAF inhibitor was successful in achieving a remission in all patients. Our observations are compatible with these results [46, 47]. Recently, we reported the cases of four relapsed patients with classical HCL who were treated with vemurafenib combined with rituximab after the failure of at least three lines of therapy including 2-CdA and Moxe [46]. Two patients achieved MRD negative CR, and a third achieved a hematologic response. The fourth patient died due to severe infection.

To overcome resistance to the BRAF inhibitor, vemurafenib was also administered together with the MEK inhibitor, cobimetinib [48]. Caesar et al. [48] presented a case report of a patient resistant to purine analogs who was treated with cobimetinib, initially at a dose of 20 mg/ /day, in combination with vemurafenib 240 mg twice a day. After four months, the cobimetinib dose was increased to 60 mg daily for 21 days. The cycles were repeated every four weeks. At 12 months, the patient remains well and asymptomatic with continued combination therapy.

It should be emphasized that retreatment with vemurafenib may also be effective in relapsed patients [34]. However, the duration of response after retreatment is shorter than after the first treatment. Liebers et al. [42] observed rapid hematological improvement after repeated drug use in most patients. Our observations indicate that vemurafenib in combination with rituximab shows therapeutic efficacy, and this includes patients previously treated with Moxe [46].

Dabrafenib

Dabrafenib (Tafinlar®) is another oral BRAF inhibitor used in patients with relapsed classic HCL. Tiacci et al. [35] presented the results of 10 patients with relapsed HCL treated with dabrafenib, including two previously treated with vemurafenib. The drug was administered at a dose of 150 mg twice a day for 12 weeks. 60% of patients required a dose reduction to 50–100 mg twice a day due to adverse drug events. Most of them returned to the initial dose of 150 mg twice daily after appropriate symptomatic treatment. Response was obtained in 80% of patients, including CR in 30% and PR in 50%. The increase in platelet count was the fastest (after c. 15 days), then in neutrophils (after an average of 35 days), and finally in hemoglobin (after 51 days). After a follow-up period of 14–79 months (median 64) from the start of treatment, survival in this group was 90%. One patient still remains in CR 60 months after the end of treatment, and two relapsed at 14 and 15 months. As with vemurafenib, the most common adverse events were grade 1–2. These included joint pain, facial flushing, skin changes, asymptomatic QT prolongation, and increased levels of transaminases and pancreatic enzymes.

Kreitman et al. [49] assessed the effectiveness of treatment with dabrafenib at a dose of 150 mg twice a day in combination with the MEK inhibitor trametinib 2 mg once a day. The drug was used in 43 patients with relapsed and refractory HCL. Response to treatment was achieved in 78% of patients, including 49% of patients achieving CR. MRD negative CR was found in 15% of patients, and MRD positive CR in 34%. PFS and OS at 12 months were 97.6%.

Ibrutinib

Ibrutinib (Imbruvica®) is a BTK inhibitor widely used in CLL and other B-cell lymphomas [50]. Ibrutinib works by modulating the signaling pathway from the B-cell receptor (BCR). In a multicenter phase II study, ibrutinib was used in 28 patients with newly diagnosed and relapsing classic HCL and in nine patients with HCLv [48]. The *BRAF* V600E mutation was found in 20 patients. Ibrutinib at a dose of 420 mg/day was used in 24 patients, and in 13 patients at 840 mg/day. After an initial assessment of the response to treatment and analysis of drug-related complications after 32 weeks, the original dose of 840 mg/day was reduced to 420 mg/day. The median follow-up time was 3.5 years for all patients. Fifteen patients are still receiving ibrutinib, and 22 patients have had the therapy discontinued. The response rate at 32 weeks was 24% and was 36% at 48 weeks. At week 32, one patient had achieved CR, eight PR, 21 stable disease (SD), and three patients had progressed. Treatment was discontinued in four patients, three due to non-response and one due to death. During a longer follow-up, seven patients achieved CR including three CR MRD negative, and 13 achieved PR, and 10 SD. The median PFS was not reached, and the PFS over 36 months was estimated to be 73%. The median OS was 69 months. There were no differences in PFS and OS between the histological subtypes or the dose of ibrutinib. A better response was seen in younger patients. However, no differences were found in ORR, PFS and OS in patients with classic HCL and HCLv. Hematological complications included anemia (43%), thrombocytopenia (41%), and neutropenia (32%). Of the 13 neutropenic patients, only four developed fever. Among the non-hematological adverse events, diarrhea, weakness, myalgia, nausea, and infection of the upper respiratory tract were observed. Hypertension, atrial fibrillation, palpitations, sinus bradycardia, and heart failure have also been reported as in other lymphoproliferative malignancies. Treatment was discontinued in seven patients due to cardiac complications (decreased ejection fraction, arrhythmias), hypersensitivity to ibrutinib, thrombocytopenia and neutropenia, as well as a diagnosis of colorectal cancer. Five patients died, three from pneumonia and two from disease progression.

The obtained results indicate that ibrutinib is an effective drug in patients with HCL after multiple treatment lines. The study also showed that, as with treatments for

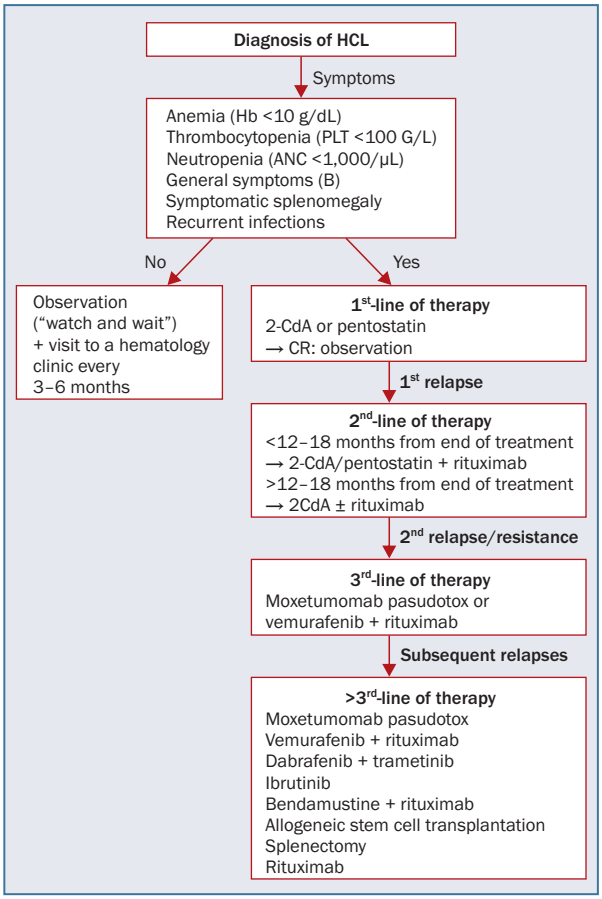

Figure 1. Proposed treatment regimen of hairy cell leukemia (HCL) in different stages of disease (acc. to [14]); Hb — hemoglobin; PLT — platelets; ANC — absolute neutrophil count; 2-CdA — (2-chlorodeoxyadenosine) cladribine; CR — complete response

other B-cell cancers, longer treatment duration may be required to obtain an optimal response. Drug-induced complications were similar to those in patients treated for other hematological malignancies. Dose-related drug toxicity has not been reported.

HCL variant

The HCL variant (HCLv) is a rare B-cell neoplasm with different immunophenotypic and molecular characteristics compared to classic HCL [9, 36, 51, 52]. HCLv is less common than the classical form of HCL. The incidence is 0.2 cases per 100,000 people and 2% of all leukemias [7]. As in the classical form, patients with HCLv present with splenomegaly, but the marrow is cell-rich and easily aspirated, in contrast to classical HCL. Moreover, there is no BRAF mutation [9]. So far, there are no widely recognized recommendations for the treatment of HCLv patients. Choosing the optimal treatment for this group of patients is still a major challenge due to the unsatisfactory results of treatment with purine analogs. Less than half of patients achieve a response, which is most often a short-term partial remission [9, 51]. It is also rare to achieve a CR. Possible therapeutic options include primarily immunochemotherapy, but also splenectomy or radiotherapy. Due to the low effectiveness of purine analogs, they should not be used as monotherapy [9, 51]. Rituximab can be used as monotherapy or in combination with 2-CdA or bendamustine, especially in patients in a fairly good general condition without significant internal diseases. Rituximab monotherapy may reduce cytopenia and tumor size before the administration of immunochemotherapy. The combination of 2-CdA or bendamustine with rituximab caused a marked improvement in treatment outcomes, including the possibility of achieving CR and MRD negativity [53, 54]. This antibody can also be used as a consolidation treatment after splenectomy.

Splenectomy is another therapeutic option in patients with HCLv [2]. Among 19 patients who underwent splenectomy, 13 (74%) achieved a hematological response, and the median response duration was 4 years [9]. In the elderly, and in those who do not qualify for more intensive treatment, radiotherapy of the spleen may be considered as symptomatic treatment of hypersplenism [55]. Rituximab used after splenectomy may also be an effective treatment method [56]. Another treatment option is Moxe. In the studies published so far, only a few patients have received treatment [30, 32]. None achieved CR, but several achieved PR. Promising results were also obtained in patients treated with ibrutinib [36, 52].

Summary

Hairy cell leukemia (HCL) is a rare B-cell lymphoproliferative disorder characterized by pancytopenia, splenomegaly, general symptoms and increased susceptibility to infections. Until now, the standard treatment has been based on purine analogs, often in combination with rituximab. In recent years, new drugs have been developed that are effective in purine analog-resistant and relapsed patients, often after multiple lines of treatment. In addition to the previously available interferon-α and rituximab, the immunotoxin Moxetumomab pasudotox has recently been registered for HCL. BRAF kinase inhibitors (vemurafenib and dabrafenib) as well as the BTK inhibitor ibrutinib are also highly effective in clinical trials. Although these drugs are less effective than 2-CdA and pentostatin, they play an important role in the treatment of relapsed/refractory patients and patients unsuitable for purine nucleoside analogs (PNA).

BRAF inhibitors induce a high response rate in classical HCL. They are also well tolerated and can be used in patients with neutropenia and co-infection. Their therapeutic activity increases when used in combination with rituximab or a MEK inhibitor. Moxe and ibrutinib are clinically active in both HCL and HCLv, but their use is associated with the risk of serious complications such as hemolytic uremic syndrome and capillary leak syndrome. Moxe

induces deep remission, including a significant percentage of complete remissions with negative MRD. Unlike BRAF inhibitors, the responses in patients treated with ibrutinib are longer. However, this drug should be used protractedly until progression or unacceptable toxicity. It should be emphasized that, except for Moxe, other drugs active in HCL patients have not yet been approved for treatment of this disease and are used 'off-label'.

Despite the high effectiveness of the new targeted drugs, it is important to remember other therapeutic options that will cancel the activity effective in previously treated patients, such as the combination of bendamustine with rituximab or pegylated IFN-α [25]. The optimal sequence in which to use these drugs in patients with HCL requires further research. Figure 1 presents the current recommendations for the treatment of HCL at different stages of the disease.

Authors' contributions

All authors participated equally in the design, editing and approval of this work.

Conflict of interest

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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