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The first allogeneic stem cell transplantation in Poland in a patient with refractory hairy cell leukemia

Pierwsze w Polsce przeszczepienie allogenicznych krwiotwórczych komórek macierzystych u chorego na oporną białaczkę włochatokomórkową

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Abstract

Introduction. *Hairy cell leukemia (HCL) is an uncommon B-cell lymphoproliferative disorder characterized by the presence of lymphoid cells with cytoplasmic projections within the bone marrow, peripheral blood and spleen. Treatment of relapsed and/or refractory (R/R) HCL remains a therapeutic challenge.*

Case report. *We report on a 28-year-old male who was treated with cladribine ± rituximab for his newly diagnosed BRAF-V600E-mutated HCL. A year later leukemia relapsed and he received interferon alfa followed by vemurafenib for 5 months but both treatments failed. Then, bendamustine with rituximab was administered with no significant hematologic response. Finally, he was found eligible for allogeneic stem cell transplantation from a 9/10-matched unrelated donor. The conditioning consisted of total body irradiation and cyclophosphamide. Cyclosporine and methotrexate were used as graft-versus-host disease prophylaxis. He engrafted and achieved full donor chimerism. There were 0.4% of hairy cells in bone marrow sample by flow cytometry at discharge. 3 months after transplantation he developed neurological and psychiatric deficits which remained unexplained despite a detailed work-up. The symptoms partly resolved after steroids use. At the last contact, 14 months after transplantation he remains in complete remission and his neurological condition is improving.*

Conclusions. *Allogeneic stem cell transplantation seems to be a promising treatment option for R/R HCL*

Key words: hairy cell leukemia, allogenic hematopoietic stem cell transplantation, treatment, outcome

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Streszczenie

Wprowadzenie. *Białaczka włochatokomórkowa (HCL) jest rzadkim nowotworem limfoproliferacyjnym, który cechuje obecność komórek limfoidalnych z wypustkami cytoplazmatycznymi we krwi obwodowej, szpiku oraz śledzionie. Postępowanie w postaci nawrotowej i opornej (R/R) HCL jest wyzwaniem terapeutycznym.*

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Opis przypadku. *W pracy przedstawiono opis przypadku 28-letniego mężczyzny z rozpoznaniem HCL i obecną mutacją BRAF-V600E, u którego w pierwszej linii leczenia zastosowano kladrybinę z rytuksymabem. Rok później z powodu nawrotu choroby do leczenia włączono interferon alfa, a następnie wemurafenib, którego przyjmowanie chory kontynuował przez 5 miesięcy. Terapie te okazały się jednak nieskuteczne. Jako kolejną linię leczenia zastosowano bendamustynę z rytuksymabem, ponownie nie uzyskując znaczącej odpowiedzi hematologicznej. Ostatecznie u chorego wykonano przeszczepienie allogenicznych krwiotwórczych komórek macierzystych od dawcy niespokrewnionego zgodnego w 9/10 antygenów układu ludzkich antygenów leukocytarnych. W ramach kondycjonowania pacjenta poddano radioterapii całego ciała oraz leczeniu cyklofosfamidem. W profilaktyce choroby przeszczep przeciwko gospodarzowi podawano cyklosporynę i metotreksat. Zaobserwowano cechy wszczepu i chory uzyskał chimeryzm dawcy. Przy wypisaniu odsetek komórek włochatych w szpiku wynosił 0,4% w badaniu metodą cytometrii przepływowej. Trzy miesiące po przeszczepieniu u pacjenta wykazano objawy neurologiczne i psychiatryczne, których przyczyna pozostała niejasna mimo szerokiej diagnostyki. Dolegliwości częściowo ustąpiły w wyniku leczenia steroidami. Obecnie, 14 miesięcy po transplantacji, chory pozostaje w całkowitej remisji, a obserwowane objawy neurologiczne ustępują.*

Wnioski. *Przeszczepienie allogenicznych krwiotwórczych komórek macierzystych wydaje się obiecującą opcją terapeutyczną u chorych na R/R HCL.*

Słowa kluczowe: białaczka włochatokomórkowa, przeszczepienie allogenicznych krwiotwórczych komórek macierzystych, leczenie, przebieg

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Introduction

Hairy cell leukemia (HCL) is an indolent B-cell chronic lymphoproliferative disorder characterized by distinctive cells present in blood, bone marrow and spleen (so called hairy cells). Median age at diagnosis is 52 years and disease occurs 4 times more frequently in male than in female. Splenomegaly, lymphadenopathy and pancytopenia are the common clinical manifestations [1]. The incidence is estimated to be 0.3 per 100,000 per annum [2].

Neutropenia and monocytopenia are frequently seen in peripheral blood. Bone marrow aspiration is often unsuccessful due to prominent fibrosis. Trephine biopsy usually presents hypercellularity with dense infiltration of small lymphocytes with oval nuclei and abundant cytoplasm with "hairy" projections. These cells show the expression of pan B-cells markers (CD19, CD20 and CD22) and other markers which are characteristic of HCL: CD11c, CD25, CD103, CD123, tartrate-resistant acid phosphatase (TRAP) and annexin A_1. The final diagnosis of HCL is based on unique immunophenotype of lymphoid cells and the presence of V600E mutation within *BRAF* gene [3, 4].

HCL responses well to front-line treatment including purine analogs *e.g.* cladribine (2-CdA), with 70% of patients achieving long-term complete response (CR). Approximately 10% of patients show primary resistance [1, 3, 4]. Relapse may occur in up to 40% of those with initial CR [5–7].

Treatment of relapsed and/or refractory (R/R) HCL is challenging. There are multiple options, including various chemotherapy regimens combined with rituximab, anti-CD22 immunotoxins, BRAF and BCR inhibitors. The most promising agents seem to be BRAF inhibitor — vemurafenib and anti-CD22 immunotoxin — moxetomumab pasudotox. Studies involving bendamustine + rituximab showed satisfactory results as well [8–11].

Herein, we present a young male who had HCL resistant to multiple treatments including vemurafenib and who was then successfully treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT). To date, only single allografts for resistant HCL have been reported in the literature [12, 13].

Case report

A 28-year-old male was admitted to Internal Medicine Unit due to progressive weakness and unexplained fever. Splenomegaly was demonstrated on physical examination (2 cm below costal margin). Complete blood count (CBC) showed severe pancytopenia with hemoglobin level of

6.7 g/dL, leukocyte count of 3.4×10^9/L and platelet count of 17 10^9/L. Blood film was dominated by lymphocytes with cytoplasm projections (62%). Monocytes and neutrophils accounted for 10% and 18% respectively. Biochemistry was normal. Abdominal ultrasound demonstrated splenomegaly (18 cm). Chest X-ray showed no abnormalities.

Bone marrow aspiration was unsuccessful and patients were referred to Hematology Unit. The trephine biopsy was hypercellular with 98% infiltration by small lymphocytes, with immunophenotype being in line with the diagnosis of HCL. He started chemotherapy with intravenous cladribine (2-CdA) at 0.12 mg/kg for 5 consecutive days. Rituximab was added to 2-CdA for the subsequent 5 cycles. As a result he achieved complete remission (CR).

A year later he relapsed and received interferon alfa at 3 million units every second day for 6 weeks. This treatment failed and, as the *BRAF-V600E* mutation was detectable, he was given vemurafenib 960 mg twice daily for 20 weeks. His CBC returned to normal; however, the proportion of hairy cells was 50% on trephine biopsy.

Due to disease refractoriness, the patient was found to be eligible for allo-HSCT. He had no siblings; therefore, the searching for unrelated donor was initiated. In meantime, he received 4 cycles of RB (rituximab, bendamustine) regimen. A trephine biopsy performed before transplantation showed the presence of 20% of hairy cells. A focal and diffused reticulin fibrosis was also demonstrated.

The conditioning consisted of total body irradiation (TBI) at 12 Grey (Gy) and cyclophosphamide (CTX) at a dose of 120 mg/kg of body weight (bw). Anti-thymocyte globulin (ATG, thymoglobulin) at a total dose of 2500 mg was also given. Graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporine and methotrexate. He received a graft from 9/10 human leukocyte antigen (HLA)-matched unrelated donor. A total number of transplanted CD34+ cells was 3.2×10^6/kg and $12.4 \times \times 10^7$/kg of CD3+ cells were provided. Engraftment was observed on day +26. Granulocyte colony-stimulating factor was not required. Bone marrow aspirate at day +30 revealed 0.4% of cells with HCL immunophenotype.

On day +31 the patient developed symptoms of cutaneous acute GvHD (grade 2) which remained resistant to topical steroids and he received a pulse of methylprednisolone with good response. On day +103, he was urgently admitted to the hospital due to neurological deficits. He suffered from progressive weakness, sensory disturbances and movement impairment. Lumbar puncture showed an elevated protein level and the predominance of T and natural killers (NK) lymphocytes. The presence of hairy cells was ruled out. Cytomegalovirus study was negative. He was treated with intravenous acyclovir with a significant improvement. Bone marrow biopsy was free of disease and that was confirmed by flow cytometry.

A month later the patient manifested a neurological deterioration with a significant peripheral neuropathy and behavioral disturbances. Pregabalin (75 mg twice daily) was implemented leading to partial improvement. He was diagnosed in Neurological Unit for several weeks but the cause of deficits remained unexplained. In T2 and fluid-attenuated inversion recovery (FLAIR) sequences of magnetic resonance imaging (MRI) increased periventricular, symmetrical signals were present; however. there was no pathological enhancement. An increased signal was also demonstrated in hippocampus area. In summary, this description was inconclusive and may suggest both toxic damage of the white matter and inflammation. John Cunningham (JC) virus by polymerase chain reaction (PCR) was excluded. He received steroids, after which slow motoric and sensory improvement was observed. On the last visit, 14 months after the transplant procedure, the patient's CBC was normal as well as the results of bone marrow biopsy. His neurological condition is getting better.

Discussion

Although HCL generally responds well to front-line treatment, especially to purine analogs, therapy for R/R disease remains a challenge. The several therapeutic approaches have been tested in R/R setting; however, none of them provided satisfactory results [8, 9, 14]. Most common treatments recommended for R/R HCL include RB and fludarabine with rituximab (FR). The efficacy of these regimens has been found to be promising. RB treatment resulted in 100% CR rate and slightly less effectiveness was demonstrated for those treated with FR [9, 14]. For patients who are resistant to RB and/or FR, vemurafenib (*Zelboraf*®, Roche) remains an option. However, it should be noted that this agent is approved for the *BRAF-V600E*-mutated advanced melanoma only. The results of vemurafenib treatment for R/R HCL were demonstrated by Dietrich et al. [8]. Sixteen patients received two or more prior therapies for HCL and 15 of them responded to vemurafenib; however, only 4 CRs were confirmed. The large group of R/R HCL patients was included

Table 1. Differential diagnosis: classical hairy cell leukemia vs hairy cell leukemia-variant [17]

Parameter	Classical hairy cell leukemia	Hairy cell leukemia-variant
Blood results	Pancytopenia, monocytopenia, neutropenia, circulating "hairy cells"	Leukocytosis, usually normal neutrophil and monocyte count
Bone marrow aspirate	Dry tap due to fibrosis	Easy aspiration
Immunophenotyping by flow cytometry	CD19, CD20, CD22, CD11c, CD25, CD103, CD123, CD200, FMC-7-positive	CD200-negative, CD25, CD123 usually negative
Immunohistochemistry; immunocytochemistry	DBA.44, annexin, BRAF V600E-positive, TRAP-positive	BRAF V600E, TRAP-negative
Soluble IL-2 receptor in plasma	Elevated	Normal

TRAP — tartrate resistant acid phosphatase; IL — interleukin

in vemurafenib study by Tiacci et al. [15]. In total, 54 patients received vemurafenib and overall response rate was close to 100% with CR rate of 40%. Relapse-free survival was 9 months. Our patient purchased vemurafenib commercially and this treatment resulted in a transient response. Unfortunately, 50% of hairy cells was seen on repeated bone marrow biopsy. Another hope for patients with R/R HCL is associated with the use of anti-CD22 antibody, moxetomumab pasudotox. A study carried by Kreitman et al. [10] showed an overall response rate of 75% with 41% CR. 85% of patients with CR achieved minimal residual disease (MRD) negativity.

Allo-HSCT seems to be a salvage therapeutic approach for those who were found to be refractory to prior treatments. However, the data on allo-HSCT for R/R HCL are scarce and only single case reports have been published so far [12, 13, 16]. Although, the results may look encouraging, several issues have to be elucidated. Zinzani et al. [12] noted a slow clearance of hairy cells in bone marrow after transplantation and the patients required donor lymphocyte infusion to achieve remission. Similar findings were demonstrated by Kiyasu et al. [13]. In contrast, our patient achieved fast response and completely eradicated hairy cells at day +100 post transplantation. Differential diagnosis and recommended therapeutic approaches for HCL patients were presented in Table 1 [17] and 2 [3, 4, 17].

Another issue is related to graft-versus-leukemia (GvL) effect. All transplanted patients with R/R HCL reported in the literature developed GvHD which according to the authors, was responsible for successful outcome of the procedure [12–16]. On the other hand, our patient had only transient cutaneous GvHD which disappeared promptly after steroid pulse.

The reason of neurological complications remains unresolved. In differential diagnosis we took under consideration the toxicity of conditioning (especially cyclophosphamide), viral or bacterial infections and GvHD. An improvement of his neurological condition was observed after prolonged use of steroids so one can suspect the immunological cause (GvHD?). However, our patient did not meet the criteria of central nervous system (CNS) manifestations of GvHD [18]. Possible manifestations of CNS-GvHD include immune-mediated neuropathies, especially Guillain-Barré syndrome; however, this diagnosis was not confirmed during a detailed neurological work-up. The efficacy of

Table 2. Recommended therapeutic approach to classical hairy cell leukemia (authors' modification according to [3, 4, 17])

Indication for treatment
Systemic symptoms Massive splenomegaly Recurrent infection Progressive lymphocytosis or lymphadenopathy Cytopenia (hemoglobin < 11 g/dL and/or platelets < 100 × 10^9/L and/or neutropenia < × 10^9/L)
Initial therapy
Purine analogs: • cladribine • pentostatin
Incomplete response to purine analogs or early relapse < 2 years
1. Clinical trial 2. Alternative purine analog with rituximab 3. Vemurafenib 4. Interferon alfa 5. Rituximab (when purine analog contraindicated)
Late relapse > 2 years 1. Re-treat with initial purine analog with rituximab 2. Re-treat with alternative purine analog with rituximab
Progressive and refractory disease
1. Clinical trial 2. Moxetumumab pasudotox 3. Vemurafenib ± rituximab 4. Ibrutinib 5. Allogeneic stem cell transplantation for young and fit patients

prolonged use of steroids may indicate an unexplained immunological cause.

Conclusions

Allo-HSCT remains a promising therapeutic option especially for those with HCL who remained refractory to previous treatment including vemurafenib.

Conflict of interest

The authors have no competing interest.

Statement of informed consent

Informed consent was obtained from the patient being included in the study. The patient provided an informed consent in accordance with the Declaration of Helsinki.

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