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Short Communication

Novel Therapies in Hairy Cell Leukemia

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1. Editorial

Hairy Cell Leukemia (HCL) is a rare subtype of B-cell chronic lymphoid leukemia which was first described by Bertha Bouroncle in 1958 [1]. The annual incidence of HCL is approximately 0.3 cases per 100,000 and the disease comprises 2-3% of all leukaemia's in the Western world [2,3]. Its diagnosis is based on the identifying the distinctive morphology of hairy cells, and evaluating bone marrow histology and immunological profile (CD19+, CD20+, CD11c+, CD25+, CD103+, CD123+, CD200+, CD27-, and light chain restriction) [4,5]. HCL cells have strong positivity for tartrate-resistant acid phosphatase (TRAP) [5]. In addition, molecular studies have shown that almost all cases of HCL are associated with a point mutation in the signalling protein BRAF (V600E) [6]. The disease usually has an indolent course, and some patients with asymptomatic disease do not require therapy until progression. The first active agent for HCL was interferon-a (IFN-a), which can produce a Complete Response (CR) in approximately 10% of HCL patients and a Partial Response (PR) in the majority of the remainder [7]. Although its use in the treatment of HCL is currently limited, IFN-α may still have a place in treating HCL in patients who are pregnant or are highly neutropenic. Otherwise, Purine Nucleoside Analogs (PNA), cladribine (2-chlorodeoxyadenosine, 2-CdA) and pentostatin (deoxycoformycin, DCF) have become gold standards in the treatment of this disease [8]. Piro et al. [9] were the first to describe sustained CR in HCL patients who had undergone splenectomy and received a single continuous intravenous infusion of 2-CdA for seven days [9]. Further multiple studies on larger groups of patients have demonstrated that 2-CdA induces durable and unmaintained CR in about 80% of patients after a single course of therapy [10-12]. Cladribine is administered either as a continuous i.v. infusion at a dose of 0.09 mg/kg over a five- to seven-day period, once a week for six weeks. Similar results were achieved when the drug was given as subcutaneous injection. A 1984 study by Spiers et al. [13] first demonstrated that pentostatin is also a highly active agent in HCL [13], and since then, a randomized study found that pentostatin produced higher CR and PR rates than IFN-a with more durable responses in HCL [14]. Purine nucleoside analogs are well tolerated in HCL, especially when neutropenia is not severe or there is no history of life-threatening infections. Myelosuppression is the main toxicity and may require delays in planned chemotherapy schedule. Purine nucleoside analogs dramatically improved the outcome of HCL, achieving 10-year OS rates close to 90%. Cladribine and pentostatin seem to induce similar high response rates but only a large randomized trial with the two agents will be able to evaluate the CR rates, duration of response, recurrence rates and adverse events that have appeared to be comparable so far [15,16]. Nevertheless, cladribine affords the convenience of a single course of administration.

Although purine nucleoside analogs are still recommended as first line therapy for HCL, patients treated with PNAs do still relapse and the OS curves have not yet reached a plateau, suggesting that a cure remains elusive. Purine nucleoside analogs are also effective in re-induction therapy; however, novel therapies are needed for many patients who ultimately relapse or go on

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to develop refractory disease despite initial very high response rates. Rituximab, a chimeric mouse-human anti-CD20 Monoclonal Antibody (MAb), seems to be a promising agent for patients with HCL [17,18] which can be used as a single agent or in combination with PNA. Its use has been associated with an OR in up to 80% of relapsed or refractory patients, and occurrence and duration of response rates can be increased by combining rituximab with PNA. Ravandi et al. [19] demonstrated a 100% CR rate using a regimen consisting of cladribine followed by eight doses of rituximab [19]. Another anti-CD20 antibody, obinutuzumab, also has demonstrated potential in treating HCL, but further studies are needed [20,21]. Recent progress in the understanding of the molecular biology of HCL has stimulated the development of new active drugs, particularly immunotoxins, BRAF inhibitors and B-Cell Receptor (BCR) pathway inhibitors [22]. Immunotoxins may play a role in the treatment of HCL, especially in patients with limited responses or treatment failure after conventional therapy. Moxetumomab pasudotox (CAT-8015, HA22, Med Immune LLC /Cambridge Antibody Technology/Astra Zeneca) is a new generation of CD22-specific targeted immunotoxins composed of the Fv fragment of an anti-CD22 monoclonal antibody fused to a 38-kDa fragment of Pseudomonas exotoxin A, called PE38 [23,24].

Moxetumomab pasudotox is highly active in relapsed/refractory HCL. A Phase 1 trial in 28 patients with refractory/relapsed HCL [25] identified an OR rate of 86% and CR 46% among 26 evaluable patients. In one patient, CR lasted less than one year and the median disease-free survival time was not reached at 26 months. The long-term follow-up results of this study were recently published [26]. In total, 33 patients received 50 μg/kg every other day for three doses in four-week cycles. The combined 33-patient cohort achieved 64% CR and 88% OR rates, with a median CR duration of 42.4 months. Moxetumomab pasudotox can eliminate MRD in a significant percentage of HCL patients. An evaluation of MRD in 32 patients by bone marrow aspirate flow cytometry found median CR duration to be 13.5 months in nine MRD-positive patients and 42.1 months in 11 MRD-negative patients ($P < 0.001$). At the end of the study, 10 patients among MRD-negative CRs, had ongoing CR and nine of them without MRD. Repeated dosing, despite the early neutralization of antibodies, increased active drug levels without detectable toxicity associated with immunogenicity. Recently, the results were reported of a pivotal, multicenter, open-label study of moxetumomab pasudotox in 80 patients with relapsed/ refractory HCL who had undergone two or more prior systemic therapies [27]. Moxetumomab pasudotox was given at a dose 40 μg/kg intravenously on days 1, 3, and 5 every 28 days for six cycles, or less if not tolerated. The objective response rate was 75% and CR rate 41%. Immunohistochemistry identified MRD negativity in 85% of the patients with CR. Treatment was generally well tolerated. The most frequent adverse events (AEs) were peripheral edema (39%), nausea (35%), fatigue (34%) and headache (33%) [27]. It has been documented that inhibitors of BRAF V600E and/or mitogen-activated protein kinase (MEK), including vemurafenib, cause HCL cell death [28]. Vemurafenib (Zelboraf™, Roche) is an ATP-competitive BRAF V600 inhibitor that has been shown to have potent antitumor activity in HCL. Vemurafenib has shown remarkable activity in multiple relapsed and refractory disease [29-33]. Patients treated with vemurafenib experienced rapidly decreased splenomegaly, increased platelet counts, and normalization of hemoglobin and granulocyte counts. In some studies, patients achieved morphologic and molecular remissions as early as one month after starting the therapy.

Investigators from Italy and the United States designed a single-arm phase 2 studies in patients with HCL who were refractory to purine analogues [33]. Vemurafenib was administered at a dose of 960 mg twice daily for a median of 16 weeks in the Italian study and 18 weeks in the U.S. study. In the Italian study, the OR rates were 96% and CR rates 35% after a median of eight weeks. The median relapse-free survival was 19 months among patients with a CR and six months among patients with a PR, with median treatment-free survival being 25 months and 18 months, respectively. In the U.S. study, OR rates were found to be 100% and CR rates 42%, after a median treatment of 12 weeks. At one year, the PFS rate was 73% and the OS rate was 91%. The treatment was well tolerated. However, skin changes, arthralgia and pancreatitis were relatively frequent events, all of them being grade 1 or 2. Lower doses of vemurafenib are also effective in HCL. In the study by Dietrich et al, 21 patients were treated with vemurafenib at doses 240-1920 mg per day with a median treatment duration of 90 days [32]. All patients responded to vemurafenib, with platelet count, neutrophil count and hemoglobin level recovering within 28, 43 and 55 days (median), respectively. Complete remission was observed in 40% of 15 evaluable patients and median event-free survival was 17 months. No significant difference in CR rate was found between lower and higher doses of vemurafenib, and CR did not translate into longer Evidence-Free Survival (EFS). As the response duration after vemurafenib is relatively short, further studies are needed to determine the optimal dosing and treatment duration.

Two other BRAF inhibitors which may be potentially useful in the treatment of HCL are Dabrafenib (Tafinlar®, GlaxoSmith-Kline) and encorafenib (LGX818, Novartis). These compounds have entered clinical trials and shown promising results [34-36]. Further prospective studies are needed to optimize the

doses of BRAF inhibitors and treatment duration against HCL. Ibrutinib (PCI-32765, IMBRUVICA®, Pharmacyclics, Janssen) is an inhibitor of Bruton's Tyrosine Kinase (BTK), which also demonstrates antitumor activity in HCL. Sivina et al. report that ibrutinib reduces the survival and proliferation of HCL cells in vitro [37]. Other encouraging results are presented by Jones et al., who report the preliminary data obtained by a study of 13 patients undergoing a median of four (range: 1-11) prior therapies: eleven relapsed, one untreated and one with HCL-variant [38]. The presented data concerning the initial dose 420mg/day cohort found an overall response rate of 46% including one MRD-negative CR and five partial responses. Four additional patients have since experienced clinical benefit and continue on treatment. At a median follow-up of 14.5 months, nine patients (69%) remained progression-free on treatment with ibrutinib, and responses have improved with continued treatment. Grade 3/4 adverse effects included hypophosphatemia (30%), neutropenia (23%) and infections (23%). In conclusion, in the coming years, new agents will probably replace standard therapy of HCL, especially for patients who have suboptimal results after treatment with PNAs. For these patients, novel therapies, especially those based around immunotoxins and BRAF inhibitors, show promising results.

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3. Declaration of interest

The author has no conflicts of interest that are directly relevant to the content of this article.

References

1. Bouroncle BA, Wiseman BK, Doan CA: Leukemic reticuloendotheliosis. Blood 1958;13(7):609-30.

2. Bernstein L, Newton P, Ross RK. Epidemiology of hairy cell leukemia: an update. Curr Opin Hematol. 2003;10:258-66.

3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.

4. Robak T, Matutes E, Catovsky D, Zinzani PL, Buske C, ESMO Guidelines Committee. Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 (Suppl 5):v100-7.

5. Grever MR, Abdel-Wahab O, Andritsos LA, Banerji V, Barrientos J, Blachly JS, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. Blood. 2017;129:553-60.

6. Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med. 2011;364(24):2305-15.

7. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an Intergroup study. J Clin Oncol. 1995;13:974-82.

8. Robak T. Current treatment options in hairy cell leukemia and hairy cell leukemia variant. Cancer Treat Rev. 2006;32(5):365-76.

9. Piro LD, Miller WE, Carrera CJ, Carson DA, Beutler E. Hairy cell leukemia. N Engl J Med. 1987;317:901 (letter).

10. Robak T, Jamroziak K, Góra-Tybor J, Blonski JZ, Kasznicki M, Dwilewicz-Trojaczek J, et al. Cladribine weekly versus daily schedule for untreated hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective , randomized multicenter trial. Blood. 2007;109:3672-5.

11. Flinn IW, Kopecky KJ, Foucar MK, Head D, Bennett JM, Hutchison R, et al. Long-term follow-up of remission duration, mortality and second malignancies in hairy cell leukemia patients treated with pentostatin. Blood. 2000;96(9):2981-6.

12. Robak T, Błasińska-Morawiec M, Błoński J, Hellmann A, Hałaburda K, Konopka L, et al. 2-chlorodeoxyadenosine (cladribine) in the treatment of hairy cell leukemia and hairy cell leukemia variant: 7-year experience in Poland. Eur J Haematol. 1999;62(1):49-56.

13. Spiers AS, Parekh SJ, Bishop MB. Hairy cell leukemia : induction of complete remission with pentostatin (2'-deoxycoformycin). J Clin Oncol. 1984;2:1336-42.

14. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an Intergroup study. J Clin Oncol. 1995;13:974-82.

15. Else M, Dearden CE, Matutes E, Garcia-Talavera J, Rohatiner AZ, Johnson SA, et al. Long-term follow-up of 233 patients with hairy cell leukaemia treated initially with pentostatin or cladribine at a median of 16 years. Br J Haematol. 2009;145(6):733-40.

16. Dearden CE, Else M, Catovsky D. Long term results for pentostatin and cladribine treatment of hairy cell leukemia. Leuk Lymphoma. 2011;52(Suppl 2):21-4.

17. Hagberg H. Lundholm L. Rituximab, a chimeric anti-CD20 monoclonal antibody in the treatment of hairy cell leukaemia. Br J Haematol. 2001;115;609-11.

18. Leclerc M, Suarez F, Noel MP, Vekhoff A, Troussard X, Claisse JF, et al. Rituximab therapy for hairy cell leukemia:A retrospective study of 41 cases. Ann Hematol. 2015;94:89-95.

19. Ravandi F, O'Brien S, Jorgensen J, Pierce S, Faderl S, Ferrajoli A, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. Blood. 2011;118(14):3818-23.

20. Sadeghi N, Li HC. MRD-negative complete remission in relapsed refractory hairy cell leukemia with bendamustine and obinutuzumab. Ann Hematol. 2018;97:723-4.

21. Sadeghi N, Li HC. MRD-negative complete remission in relapsed refractory hairy cell leukemia with bendamustine and obinutuzumab. Ann Hematol. 2018;97(4):723-4

22. Bohn JP, Willenbacher E, Steurer M. Obinutuzumab in multidrug-resistant hairy cell leukemia. Ann Hematol. 2016;95(2):351-2.

23. Robak T, Wolska A, Robak P. Potential breakthroughs with investigational drugs for hairy cell leukemia. Expert Opin Investig Drugs. 2015;24(11):1419-31.

24. Wolska-Washer A, Robak P, Smolewski P, Robak T. Emerging antibody-drug conjugates for treating lymphoid malignancies. Expert Opin Emerg Drugs. 2017;22(3):259-73.

25. Kreitman RJ, Tallman MS, Robak T, Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015 or HA22) in patients with hairy cell leukemia. J Clin Oncol. 2012;28(4):1822-8.

26. Kreitman RJ, Tallman MS, Robak T et al. Minimal residual hairy cell leukemia eradication with moxetumomab pasudotox: phase 1 results and long-term follow-up. Blood. 2018;131(21):2331-4.

27. Kreitman RJ, Dearden C, Zinzani PL, Delgado J, Karlin L, Robak T, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Leukemia. 2018;32(8):1768-77.

28. Pettirossi V, Santi A, Imperi E, Russo G, Pucciarini A, Bigerna B, et al. BRAF inhibitors reverse the unique molecular signature and phenotype of hairy cell leukemia and exert potent antileukemic activity. Blood. 2015;125(8):1207-16.

29. Samuel J, Macip S, Dyer MJ. Efficacy of vemurafenib in hairy-cell leukemia. N Engl J Med. 2014;370(3): 286-8.

30. Dietrich S, Glimm H, Andrulis M, von Kalle C, Ho AD, Zenz T. BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med. 2012; 366(21):2038-40

31. Follows GA, Sims H, Bloxham DM, Zenz T, Hopper MA, Liu H, Bench A, et al. Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol. 2013;161(1):150-3.

32. Dietrich S, Pircher A, Endris V, et al.: BRAF inhibition in hairy cell leukemia with low-dose vemurafenib. Blood. 2016;127:2847-55.

33. Tiacci E, Park JH, de Carolis L, et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med. 2015;373:1733-47.

34. Vergote V, Dierickx D, Janssens A, Verhoef G, Tousseyn T, Vandenberghe P, et al. Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib. Ann Hematol. 2014;93(12):2087-9.

35. Blachly JS, Lozanski G, Lucas DM, Grever MR, Kendra K, Andritsos LA. Cotreatment of hairy cell leukemia and melanoma with the BRAF inhibitor. J Natl Compr Canc Netw. 2015;13(1):9-13.

36. Vergote V, Dierickx D, Janssens A, Verhoef G, Tousseyn T, Vandenberghe P, et al. Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib Ann Hematol. 2014 ;93(12):2087-9.

37. Sivina M, Kreitman RJ, Arons E, Ravandi F, Burger JA. The bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) blocks hairy cell leukaemia survival, proliferation and B cell receptor signalling: a new therapeutic approach. Br J Haematol. 2014;166(2):177-88.

38. Jones A, Andritsos L, Ravandi F, et al. Safety and efficacy of the Bruton tyrosine kinase inhibitor ibrutinib in patients with hairy cell leukemia: interim results of a phase 2 study. Haematologica. 2015.