Cladribine (2-chlorodeoxyadenosine) therapy in hairy cell leukemia variant. A report of three cases

Hairy cell leukemia-variant (HCL-V) is a distinct clinicopathological entity which seems to be resistant to several avalaible treatments. We report on three patients with B-prolymphocytic HCL-V who were treated with cladribine at a daily dosage of 0.1 mg/Kg by continous intravenous infusion for 7 days. Two partial remissions and 1 complete remission were achieved.

Hairy cell leukemia-variant (HCL-V) is an extremely rare variant of classic hairy cell leukemia (HCL) and described by Cawley *et al*.[1] in 1980. It differs from classic hairy cell leukemia in its morphologic, immunologic and clinical features. The clinical course of HCL-V is variable, but usually aggressive and associated with a short survival.[2] Treatments such as splenectomy, α-interferon and deoxycoformicin, which are effective in HCL, are ineffective in HCL-V. More recently, 2-chlorodeoxyadenosine (2CdA) has been introduced in the treatment of HCL, achieving about 90% of complete responses.[3,4] Due to the fact that HCL-V is so rare, there is little information about the effect of 2CdA in its treatment. This is why we consider it useful to report our experience with its use in three cases of HCL-V, diagnosed in over a 10-year period. These 3 cases of HCL-V were diagnosed between 1990 and 2000. The diagnosis was based on morphologic, cytochemical and immunologic criteria using a range of monoclonal antibodies which included T, B and HCL markers. All patients showed prolymphocytic type.[5] The clinical characteristics and the analytical values of the patients are described in Table 1. The three patients were given 2CdA (cladribine) at a dose of 0.1 mg/kg/day by continuous intravenous infusion for 7 days. Patient #1, after undergoing splenectomy and treatment with α-interferon on two occasions, each of them resulting in partial remission (PR), began treatment with 2CdA for hyperleukocytosis in 1999, being given two cycles at an interval of 3 months. For the other two patients (#2 and #3), the 2CdA was the first-line treatment. Patient #2 was given 3 cycles every six months, for massive splenomegaly, hyperleukocytosis and anemia and patient #3 was given only one cycle, for B-symptoms and left costal pain. Response criteria were those reported by Spiers *et al*.[6] The cladribine was well tolerated. Prophylaxis of tumor lysis-syndrome consisted of hyperhydratation, alkalinization and allopurinol. Treatment was continued in patients #1 and #2 because of progression of the disease. The responses to treatment are shown in Table 2. All three patients responded (2 PR and 1 CR).

The three patients described fulfil the diagnostic criteria for HCL-V.[2] This lymphoproliferative syndrome is extremely rare - according to the largest series published, its occurrence is only 1.1% compared to classic HCL- so there is not much therapeutic experience.[7] Give the generally massive splenomegaly, splenectomy is a reasonable option, but one which most frequently achieves only partial response according to the available results.[2] α-interferon, effective in cases of HCL, has a low level of activity in HCL-V,[6] apparently because of loss of α-interferon receptors in the leukemic cells.[2] Purine analog compounds such as deoxycoformycin[2,6] and fludarabine,[8] which have been used in isolated cases show fairly poor results, with PR in approximately 50% of cases. More recently, in view of the great efficacy demonstrated by 2CdA in HCL,[3,4] this drug has been used in HCL-V; reports on a total of 19 patients have been published.[5,7,9,10] As occurs with the other analogs, the response rate is 55%, but there was one CR . Logically, these results cannot be superimposed on the spectacular CR rates in HCL treated with 2CdA, in which remission rates of over 90% are obtained with a single cycle.[4] In this respect, we should note that the lack of expression of CD-25 in HCL, as occurs in HCL-V, is a negative predictive factor of the response to 2CdA.[7,9] Our patients, like those previously published, required more than one cycle[7] to maintain PR, except for case #3, in whom CR was obtained with only one cycle. In conclusion, our study shows that 2CdA has a

Table 1. Clinical and hematologic characteristics.

Patient	*#1*	*#2*	*#3*
Date of diagnosis	31-10-1990	4-11-1998	10-3-2000
Age/sex	59/M	79/F	70/M
B-symptoms	no	yes	no
Lymph nodes	no	no	no
Spleen (cm below left CM)	12	20	13
Liver (cm below right CM)	4	2	not enlarged
Pretreatment analysis			
Hb (g/L)	126	9.9	13.4
WBC ($\times 10^9$/L)	219	70	21.1
Platelets ($\times 10^9$/L)	116	53	154
Hairy cells ($\times 10^9$/L)	215	56	24
Neutrophils ($\times 10^9$/L)	2.1	7.1	3.2
Monocytes ($\times 10^9$/L)	0.5	6.5	1.5
TRAP	negative	negative	negative
Bone marrow	easily aspirable hypercellular	easily aspirable hypercellular	easily aspirable hypercellular
% of hairy cells in BM	70	40	52
Immunophenotype	$CD19^+$,$CD23^-$, $CD11c^+$,$CD3^-$,$CD5^-$, $CD25^-CD103^+$	$CD19^+$,$CD23^-$,$CD11c^+$ $CD3^-$,$CD5^-$,$CD25^-$ $SmIgM^+$,$CD4^-$,$CD8^-$, $CD103^+$	$CD19^+$,CD23, CD11c, $CD3^-$, $CD5^-$,$CD25^-$, CD103 $weakly^+$
Spleen pathology	red and white pulp expansion	not applicable	not applicable

CM: costal margin; BM: bone marrow.

Table 2. Response to treatment with 2-CdA.

Patient	*1*	*2*	*3*
Previous therapy	splenectomy Interferon-alpha	none	none
Time from diagnosis to 2-CdA	9 years	1 month	10 months
Number of 2-CdA cycles	2	3	1
Response to 2-CdA	partial remission (PR)	partial remission (PR)	complete remission (CR)
Clinical follow-up	alive (PR)	alive (PR)	alive (CR)
Survival from diagnosis	127+months	31+months	15+ months

moderate level of activity in HCL-V, although much lower than that observed in classic HCL and similar to the other analogs as far as PR is concerned. Nevertheless, it is the only drug which, both in previous experiences[7] and in ours, has achieved CR. For this reason, we consider that this drug combined with other types of therapy, such as early splenectomy and anti-CD20 antibodies (rituximab), could be future directions to be explored in order to achieve better, longer-lasting remissions.

Luis Palomera, José M[a] Domingo, Carlos Sola, Gemma Azaceta, María Teresa Calvo, Martin Gutierrez*

Departments of Hematology and Hemotherapy of the University Clinical Hospital, Zaragoza and the "Reina Sofia" Hospital, Tudela, Spain

Key words: hairy cell leukemia-variant, 2-chlorodeoxyadenosine, cladribine.

Correspondence: Luis Palomera, Department of Hematology, C/ San Juan Bosco, 15 50009 Zaragoza, Spain.
Phone: international +34.9.76556400. Fax: international +34. 9.76351661. E-mail: hemh@hcu-lblesa.es

References

1. Cawley JC, Burns GF, Hayhoe FG. A chronic lymphoproliferative disorder with distinctive features: a distinct variant of hairy-cell leukemia. Leuk Res 1980; 4:547-59.
2. Sainati L, Matutes E, Mulligan S, de Oliveira MP, Rani S, Lampert IA, et al. A variant form of hairy cell leukemia resistant to α-interferon: clinical and phenotypic characteristics of 17 patients. Blood 1990; 76:157-62.
3. Cheson BD, Sorensen JM, Vena DA, Montello MJ, Barrett JA, Damasio E, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine via the Group C Protocol mechanism of the National Cancer Institute: a report of 979 patients. J Clin Oncol 1998; 16:3007-15.
4. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia following cladribine treatment. Blood 1998; 92:1918-26.
5. Robak T, Blasinska-Morawiec M, Blonski J, Hellmann A, Halaburda 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; 62:49-56.
6. Spiers AS, Moore D, Cassileth PA, Harrington DP, Cummings FJ, Neiman RS, et al. Remissions in hairy-cell leukemia with pentostatin (2'-deoxycoformycin). N Engl J Med 1987; 316:825-30.
7. Tetreault SA, Robbins BA, Saven A. Treatment of hairy cell leukemia-variant with cladribine. Leuk Lymphoma 1999; 35:347-54.
8. Kantarjian HM, Schachner J, Keating MJ. Fludarabine therapy in hairy cell leukemia. Cancer 1991; 67:1291-3.
9. Copeland AR, Bueso-Ramos C, Liu FJ, Kornblau SM, Huh YO, Albitar M. Molecular study of hairy cell leukemia variant with biclonal paraproteinemia. Arch Pathol Lab Med 1997; 121:150-4.
10. Matutes E, Wotherspoon A, Brito-Babapulle V , Catovsky D. The natural history and clinico-pathological features of the variant form of hairy cell leukemia. Leukemia 2001;15:184-6.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Francesco Lauria, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Lauria and the Editors. Manuscript received October 1, 2001; accepted November 19, 2001.