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Letter to the Editor

Cladribine in Relapsed Hairy Cell Leukemia After One or More Prior Purine Nucleoside Analog Treatments

Marlies E.H.M. Van Hoef*

Lipomed AG, Switzerland

***Corresponding author:** Marlies E.H.M. Van Hoef, Lipomed AG, Switzerland. Tel: +41798944764; Email: vanhoef@vanhoefconsulting.com

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In a recent publication Kreitman et al. [1] reported a complete response rate of 41%, with 30% of patients still in complete remission at 16.7 months follow-up, and an overall response rate of 75% in 80 patients who received moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Patient had received two or more systemic therapies including one or more purine nucleoside analogs. Moxetumomab pasudotox is an intravenous treatment to be administered on days 1, 3 and 5 for up to 6 cycles every four weeks.

Cladribine is a purine nucleoside analog. High complete and overall response rates have been reported after a single five to seven days cycle of intravenous (i.v.) or five days Subcutaneous (s.c.) administration in relapsed hairy cell leukemia after among others one or more prior purine nucleoside analog therapies (Table 1).

Table 1. Prior systemic, first, second and third line purine nucleoside analog therapy in hairy cell leukemia.

Author	Therapy	Prior treatment	(n) 1st line CR/ORR	Duration	(n) 2nd line CR/ORR	Duration	(n) 3rd line CR/ORR	Duration
Saven A	Cladiribine 7d continuous i.v.	0 to 2 prior treatments	CR 319/349 (91%) ORR 98%	At 4 year TTF 19%, 16% for CR and 54% for PR	CR 33/53 (62%) ORR 88%	At median DOR of 23 months 19 (36%) relapsed	CR 2/7 (29%) ORR 6/7 (86%)	
Robak T	Cladribine 5d over 2hr i.v.	0 to 2 prior treatments	CR 75/103 (77%)[1] ORR 96%	Mean time CR 32 months (range 3-72); 20 pat with CR relapsed[2]	CR 7/10 (70%) ORR 100%	CR duration 19+ (range 8-47) months		
Jehn U	Cladribine 7d continuous i.v.,	0 to 3 prior treatments	CR 41/42 (98) ORR 96%	At 6 years 75% DFS; 6 relapses.	CR 3/3 (100%) for +1, +2, +13 months			
Else M	Pentostatin or Cladribine 7d continuous i.v. no significant difference in outcome	unclear	CR of 80% in 223 patients	Median Relapse free survival 16 years	CR of 69% in 84 patients ORR 97%	Median relapse free survival 11 years	CR in 50% of 23 patients	Median relapse free survival 6.5 years

Somasundaram V	Cladribine 7d continuous i.v.,	Newly diagnosed	CR 25/27 (93%), 2 pat 2nd cycle-> both CR ORR 100%	At median 26 months, 5 (18%) patients relapsed	CR 5/5 (100%)	Median DOR 18 (3-50) months		
Hacioglu S	Cladiribine 5 or 7d continuous i.v.	Newly diagnosed	CR of 80.7% in 78 patients ORR 97%	Relapse rate of 16.6% at median 24 months	CR 13/19 (68.4%) ORR 100%	6 pat relapsed, median time to relapse 60 months	CR 2/3 (66.6%) ORR 100%	

Table 1: In the 75 patients CR was achieved, in 53 after a single cycle, in 16 after 2 cycles and in 6 after 3 cycles; [2]Of 20 patients who relapsed, 17 relapsed after one cycle of cladribine and 3 after 2 or 3 cycles. ORR=overall response rate (complete (CR) + partial remission); DOR=duration of response;d=days.

Saven et al. [2] reported 90 patients who relapsed after prior cladribine therapy (n=319) at a median of 29 months. In first line cladribine therapy 91% complete and 98% overall response rates had been obtained. Of 53 evaluable patient treated with a second cycle of cladribine at relapse after first line cladribine, 33 (62%) achieved complete response and 14 (26%) partial response for an overall response rate of 88%. Seven patients received third line cladribine therapy with a third cycle of cladribine and 2 (29%) achieved complete and 4 (57%) partial response for an overall response rate of 86%.

Robak et al. [3] reported 20 patients who relapsed after first line cladribine therapy (n=75) at a median of 37.4 months. In first line 53 patients had received one, 16 two and 6 three cycles of cladribine to obtain complete remission for a complete response rate of 100%. Ten of the 20 relapsed patients were retreated with one cycle of cladribine. Seven patients entered a second complete remission lasting 19+ (range 8-47) months and 3 experienced partial responses for an overall response rate of 100%. The 10 remaining patients did not require retreatment at the time of analysis.

Jehn et al [4] reported six patients who relapsed after prior cladribine therapy (n=42) at a median follow-up of 32 (range 2 to 72) months. In first line treatment complete and overall response rates had been 98% and 100% respectively. Three of the relapsed six patients were retreated with one cycle of cladribine. All three patients received another complete remission for 1+, 2+ and 13+ months. The overall response rate in second line was 100%.

Else et al [5] reported 79 patients who relapsed and five patients who did not have an initial response after first line pentostatin or cladribine therapy (n=233), in which line of treatment complete and overall response rates had been 80% and 97% respectively. In second line treatment, 26 patients received one cycle of pentostatin and 59 one cycle of cladribine. The complete and overall response rates were 69% and 97% respectively, and the median relapse free survival was 11 years. After third line therapy with one cycle of purine nucleoside analogue therapy in 23 patients, 50% achieve complete remission and the median relapse free survival was 6.5 years. The authors reported equally durable complete remissions after first, second and third line purine nucleoside analog therapy.

Somasandram et al [6] reported five patients who relapsed after first line cladribine therapy (n=27) at a median follow-up of 26 months, that induced 93% and 100% complete and overall response rates respectively. All five relapsed patients went into a second remission with one cycle of cladribine with a duration of response of median 18 months.

Hacioglu et al [7] reported a relapse rate of 16.6% in 78 patients initially treated with one cycle cladribine. In first line, complete and overall response rates had been 80.7% and 97% respectively. Nineteen of twenty relapsed patients were again treated with one cycle of cladribine therapy in second line and three of six relapsed patients with another cycle cladribine in third line. Complete remission rates in second and third line were 68.4% and 66.6% respectively, whereas overall response in both lines of treatment was 100%.

All authors reported high rates of complete responses after first, second and third line cladribine therapy, and despite the fact that patients in some of the publications were pre-treated complete response rates of at least 77% and overall response rates of at least 96% were obtained in first line purine nucleoside analog therapy; complete response rates of at least 62% and overall response rates of at least 88% were obtained in second line purine nucleoside analog therapy, and 29% to 66.6% complete and at least 86% overall response rates were obtained after third line purine nucleoside analogs. This compares favourably with the results obtained by moxetumomab pasudotox and reported by Kreitman et al. [1].

Cladribine is administered either i.v. over twenty-four hours or over two hours for five or seven days at a dose of 0.09 to 0.12 mg/kg or as s.c. injection for five days at a dose of 0.14 mg/kg/d (2-8). Subcutaneous administration is at least as effective as the i.v. route [8,9]. Subcutaneous administration is preferred as it eliminates the need for hospitalization or long stay in the outpatient unit and is therewith highly cost-efficient. Noteworthy are the results reported by Robak et al. with first line cladribine therapy, in which the complete response rate increased with the number of cycles of

cladribine from one (71%), via two (92%) to three (100%) [3]. In view of efficacy, easiness of administration and cost-efficacy use of more than one cycle of cladribine s.c. in first, second or later relapse warrants investigation, to evaluate whether such regimen could induce durable responses or eliminate the disease.

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