ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LV, 34 SECTIO D 2000

Katedra i Klinika Neurologii Akademii Medycznej w Lublinie
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The effect of cladribine on some parameters of blood and cerebrospinal fluid in patients with relapsing-remitting multiple sclerosis (RR-MS)

Wpływ kladrybiny na wybrane parametry krwi i płynu mózgowo-rdzeniowego u chorych z zaostrzająco-zwalniającą postacią stwardnienia rozsianego

Lymphocytes T have been assumed to play a key role in the etiopathogenesis of multiple sclerosis. Therefore drugs which selectively suppress those cells arouse particular interest. And cladribine is one of them. It is a synthetic derivative of purine which contains an atom of chlorine instead of hydrogen in position 2 of the purine ring (2-chlorodeoxyadenosine, 2-CdA). Its selectivity is connected with the cellular level of deoxycytidine kinase. That enzyme is particularly active in lymphocytes, whereas in other cells or tissues its amount is much lower. This causes a selective accumulation of cladribine in lymphocytes, inside which its concentration is several hundred times higher than in blood sera. The drug accumulates both in rest lymphocytes and in the divisive ones and may lead to the destruction of the activated lymphocytes (3, 5, 8). They in turn induce demyelinization of the central nervous system. Attempts to use cladribine in the treatment of patients with various forms of multiple sclerosis have been conducted in several centres (1, 2). Despite that the significance of that drug in multiple sclerosis therapy has not yet been explained. The positive effects both in the assessment of the clinical status and in the biochemical parameters encourage further tests.

OBJECTIVE

The aim of the study is to monitor parameters of peripheral blood, cerebrospinal fluid, biochemical factors of the liver and kidneys function

in patients treated with cladribine due to relapsing-remitting multiple sclerosis.

MATERIAL AND METHOD

38 patients have been examined, 26 women and 12 men, with mean age 35.7±6.1 years. According to Poser's criteria (7), all the patients have been clinically diagnosed with relapsing-remitting multiple sclerosis. The duration of the disease equalled from 2 to 22 years, the mean value 7.37±4.67 years, the number of attacks during the disease was 2 to 8, with the mean 4.5 ± 1.88 per person. EDSS before treatment was started equalled 2 to 5 points, with the mean 3.0 ± 1.22 points. The study included those patients during remission who had had at least one attack of the disease during the last year and who had not received steroid therapy for the last 8 weeks. All the patients received Cladribine (Biodribin, made by Bioton). The drug was given subcutaneously at the dose of 0.07 mg/kg body weight through 5 successive days. The patients had received six courses of treatment in 5-week intervals. Before the treatment started, after each successive course, 3 and 6 months after the last course the morphology of peripheral blood was assessed. Before and after treatment bilirubin level was examined, as well as that of thymol, total protein, transaminase (ASPAT, ALAT), urea, creatinine, urine acid, cholesterol and cerebrospinal fluid. The analysis of urine was also made. In all the periods the patients under study were neurologically examined and assessed according to EDSS scale (11). The findings were then submitted to statistical analysis with the use of Wilcoxon's rank sum test.

RESULTS

The use of cladribine in multiple sclerosis patients considerably lowers the number of leukocytes, mainly the lymphocytes of peripheral blood. The decrease of lymphocyte is statistically significant starting from the first month of therapy and for leucocyte starting from the second month of terapy. That drop is still retained 6 months after treatment. At the same time, the number of granulocytes essentially increases. An essential decrease in the number of thrombocytes has also been reported. The decrease was statistically significant from the sixth month of therapy. That decrease was also retained 6 months after treatment. No essential change of red blood cells was reported, as regards the parameters of the liver and the kidneys function. The decrease in cytosis and protein in CSF was statistically significant. EDSS scoring before treatment 3.0 ± 1.22, after 6 months 2.9 ± 1.42 and after 12 months 2.6 ± 1.46 – its change was not statistically significant. The table depicts our results.

DISCUSSION

The data analysis from this study has shown that cladribine lowers the number of leucocytes and especially of the lymphocytes of the peripheral blood. The lymphocytopenia was marked and existed still 6 months after treatment but in most patients the leucocyte count was above 3 G/l. In our study only in one patient the total count of leucocytes fell below 3 G/l and lymphocyte belove The reduction of lymphocyte counts depends on dosing and schedule of treatment. In the Scripps study (2) patients received higher dosing of cladribine and the reduction of lymphocyte counts was more marked than that observed in our study. However, more often observed adverse events (trombocytopenia, infections). In some of our patients granulocyte counts increased markedly. This can be caused by the reaction of the leucocyte system to infections present during treatment (mainly infections of the urine tracts, where were succesfully treated with standard antibiotic therapy). It indicates that cladribine is toxic against lymphocytes but is toxic neither

Table 1. Parameters of blood patients treated with 2-DCA

	Parameters of blood							
	Leukocytes (G/l)		Granulocytes (%)		Lymphocytes (%)		Trombocytes (G/l)	
	M	SD	M	SD	M	SD	M	SD
Before therapy	6.8	2.01	66.1	12.34	23.2	6.49	223	38.61
After 1 month	7.4	1.88	73.9**	6.92	17.9*	6.01	237	54.44
After 2 months	6.2	1.55	70.0	16.55	18.7*	6.47	220	62.78
After 3 months	5.6**	1.64	74.5**	7.8	20.0	11.60	208	60.34
After 4 months	5.3**	1.48	74.1**	7.66	18.4*	6.74	210	51.84
After 5 months	5.1**	1.84	74.6**	7.59	18.4*	7.25	206	52.81
After 6 months	5.6**	4.28	73.6**	15.31	18.0*	8.04	191*	55.20
After 9 months	4.1**	1.19	69.8	7.78	22.6	6.69	190*	66.98
After 12 months	5.1**	1.43	71.5*	13.29	18.1*	4.68	197*	41.60

Statistically significant *$p<0.05$ **$p<0.001$

to granulocytes nor to granulocyte progenitors. The decrease of cytosis and protein in CSF has shown that the treatment leads to a decrease in inflammatory reaction in CSF. An analysis of the neurologic performance and disability rating scale showed stabilisation. The treatment was well tolerated. Cladribine may be useful in the therapy of RR-MS patients.

Table 2. Parameters of cerebrospinal fluid patients treated by 2-DCA

	Parameters of cerebrospinal fluid					
	Protein (mg%)		Glucose (mg%)		Cytosis	
	M	SD	M	SD	M	SD
Before therapy	34	14.22	59.14	12.97	16.5	19.20
After 6 months	30.1*	8.04	53.32	6.04	5.3**	6.21

Statistically significant *$p<0.05$ **$p<0.001$

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Otrz.: 2000.07.26

STRESZCZENIE

Kladrybina (2-chlorodeoxyadenozyna) jest syntetyczną pochodną purynową o selektywnym działaniu w stosunku do limfocytów i monocytów. Celem pracy była ocena chorych z klinicznie pewnym RR-MS leczonych kladrybiną podawaną podskórnie w dawce 0,07 mg/kg przez 5 kolejnych dni w powtarzanych co 5 tygodni 6 cyklach. Badania wykonano u 38 chorych. Przed leczeniem, przed każdym kolejnym cyklem oraz w 3 i 6 miesięcy po zakończeniu leczenia badano u nich morfologię krwi obwodowej. Przed i po zakończeniu leczenia analizowano biochemiczne parametry funkcji wątroby i nerek oraz płyn mózgowo-rdzeniowy. Po leczeniu stwierdzono istotny statystycznie spadek liczby leukocytów, limfocytów i trombocytów. W obrazie czerwonokrwinkowym i w zakresie parametrów funkcji wątroby i nerek nie było istotnych zmian. W płynie mózgowo-rdzeniowym wykazano istotne obniżenie cytozy i białka . Kladrybina zmniejsza liczbę limfocytów krwi obwodowej oraz prowadzi do spadku wykładników odczynu zapalnego w PMR. Może mieć korzystne znaczenie w terapii chorych z RR-SM.