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Long-Term Remissions With Use of High Dose Cyclophosphamide in Multiple Sclerosis

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Abstract

Background: In this study, the results of high dose intravenous monthly pulse CYC on patients with worsening relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) were evaluated.

Methods: Fifty-six patients who presented with worsening RRMS (30) or SPMS (26) were to be treated with intravenous (IV) monthly pulse of 800 mg/m² CYC in the first year and bimonthly in the second year. We evaluated the results before treatment and after 12 and 24 months.

Results: In the RRMS patients, after 2 years baseline EDSS had improved in 18, was unchanged in 5 and worse in 3. In RRMS group annual relapse rate was 0.92 at the beginning. it decreased to 0.23 in first year and to 0.23 in second year. The SPMS patients after 2 years baseline EDSS had improved in 5, was unchanged in 15 and worse in 3. In SPMS group annual relapse rate was 0.26 at the beggining. It decreased 0.13 in the first year and 0.04 in the second year.

Conclusion: This study showed that high dose CYC treatment for two years was well tolerated and seemed effective for both RRMS and SPMS.

Keywords: Cyclophosphamide; Multiple sclerosis; Memission; Treatment

Introduction

Multiple sclerosis (MS) is an inflammatory cell-mediated, autoimmune disease affecting the central nervous system. Over the last decades, there has been a considerable increase in the number of parenteral agents available for the treatment of MS. Such agents for relapsing or progressive MS have included corticosteroids, cyclophosphamide (CYC), beta-interferons, glatiramer acetate and mitoxantrone. Patients with MS usually respond to these therapies to some extent, but progression is not prevented with these modalities. After this study was completed, several new oral agents have been approved for RRMS [1,2].

Cylophosphamide, a cytotoxic alkylating agent exhibiting immunosuppressive effects has been used for more than 40 years in the treatment of neoplastic and autoimmune disorders. Cyclophosphamide, although rejected as immunosuppressive therapy for MS by Cochrane analysis [3] based on the pivotal studies on progressive MS [4,5], was shown to arrest clinical deterioration in RRMS patients unresponsive to immunomodulatory agents and in those rapidly evolving secondary progressive phase of the disesase [6]. In a study [7] that compared mitoxantrone and cyclophosphamide, the response to treatment with both drugs was similar in secondary progressive MS.

This study was carried out in Dr. Lütfi Kirdar Kartal Training and Research Hospital on worsening RRMS and SPMS patients. CYC treatment was given as mointhly IV pulse monotheraphy and the results were evaluated.

Patients and Methods

We prospectively evaluated the patients to be treated with CYC for two years in Dr. Lütfi Kırdar Kartal training and research hospital between 2000 and 2009.

Diagnosis of MS was based on Poser et al. criteria [8] and all patients were followed by a neurologist experienced in the treatment of MS. The inclusion criteria for worsening RRMS was having had more than 2 attacks in the last year or lack of response to other parenteral immunomodulatory therapy. That for secondary progressive MS was a 1.0 point worsening in EDSS in the last year.

Patients had undergone biological screening and chest X-ray before CYC treatment in order to detect any contraindications to this immunosuppressive drug. Patients were excluded if they had clinical evidence of liver, kidney, lung or heart disease; infections; hematologic disease; other neurologic and psychiatric diseases; or pregnancy. Patients were included if they also had not taken any immunomodulatory treatment in the last 6 months before starting CYC treatment. The patients who had attacks during the two-year treatment period were managed with 1000 mg IV pulse methylprednisolone daily for 7 to 10 days.

Each patient gave written informed consent before treatment. The local ethics committee of Dr. Lütfi Kırdar Kartal Training and Research Hospital approved the study.

Relapse was defined as new or worsening symptoms of neurologic dysfunction with objective confirmation lasting at least 48 h, following a period of symptomatic stability of at least 30 days, occurring in the absence of febrile illness or steroid withdrawal, and within 15 days of onset showing an increase of at least 1.0 point on EDSS.

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Before each treatment, patients were hospitalized in neurology clinics. We performed complete neurologic examination and biochemical blood and urine tests. Impairment and disability were assessed using the Expanded Disability Status Scale (EDSS) [9] at baseline and every month after the beginning of treatment. Patients were treated monthly with intravenous (IV) pulse of CYC (800 mg/m^2) in the first year and bimonthly in the second year.

As symptomatic treatment, the anti-nausea agent ondansetron was administered at a dose of 8 mg immediately before CYC administration. Large volumes of fluids (3 L) were administered IV on the day of CYC treatment to prevent bladder toxicity. Patients were encouraged to drink large quantities of water in the three days following CYC administration.

Other than the findings on neurologic exmination, including Functional System Scores [9], the following clinical data were recorded: age, sex, EDSS score, disease duration, disease modifying treatment and relapse rates before and during CYC treatment. Side effects were considered when they were reported by the patients or detected on physical examination. Biological abnormalities were also noted. We assessed the EDSS score after 12 and 24 months of treatment.

Improvement or worsening was defined as a change of at least 1.0 steps on the EDSS. For any given patient, EDSS score was calculated by the same observer before and during treatment. When relapse occurred during treatment, the EDSS measured here was that scored at least 3 months after the relapse.

In both RRMS and SPMS patients, age of onset and duration of disease were compared. Annual relapse rate before and during treatment were compared at 0, 12 and 24 months in RRMS and SPMS groups. The baseline EDSS was compared with 12 and 24 month EDSS.

Statistical analysis

Independent samples Chi-Square test, Mann-Whitney U test and Pearson parametric correlation analysis were performed where necessary using SPSS 11.5 software.

Results

Fifty-six patients began treatment with CYC and 49 (21 male, 28 female) completed the 2 year period. Age at entry of the 49 was age 20 to 55 with a mean of 41.1 ± 8.8. Twenty-six patients (13 female) comprised the RRMS group and 23 (15 female) the SPMS group. There were statistically significant differences at entry between the groups for age at entry (p=0.000), EDSS scores (p=0.000) and mean duration of disease (p=0.003), with higher ages, scores, and durations in the SPMS group.

Results of relapsing remitting MS group

Of 26 RRMS patients, 13 were female. At study entry mean age was 39.1 ± 8.1 years, with mean duration of disease 5.7 ± 3.9 years and mean EDSS 3.3 ± 1.0. Eleven had used disease modifying treatment (DMT) before the study as noted in Table 1, where all demographic and clinical characteristics of the group are presented.

Patient	Sex	Age at onset	Age at start CP treatment	DMT before CYP			EDSS M0	EDSS M12	EDSS M24	Relapse during treatment at month
				Drug (DMT)	*Duration of use (mo)*	*Interval Between DMT-CYC*				
1.	M	30	33	-		.	2.5	1	1	
2.	F	28	30	-		.	2	2	1	17
3.	M	24	26	GA	12	14	3.5	2	2.5	13
4.	F	18	31	GA	24	32	3.5	3.5	2.5	03-07-2023
5.	F	22	45	GA	18	23	3.5	3.5	3.5	
6.	M	29	32	IF	36	6	3.5	2	2	
7.	M	36	38	-		.	2	1.5	1	02-Jul
8.	F	28	44	-		.	5	4.5	5	
9.	M	31	34	-		.	3	1	1	
10.	M	28	33	IF	36	34	3.5	4.5	6	03-Dec
11.	F	23	25	IF	18	7	2.5	1	1	02-07-2014
12.	F	17	21	IF	27	6	4.5	1	1	
13.	M	18	35	-		.	3.5	2	2	01-Jun
14.	M	20	23	IF	12	17	2	3.5	4	02-07-2023
15.	F	23	32	-		.	3.5	3.5	3	
16.	F	13	21	-		.	4	3	3	Jan-14
17.	F	25	28	-		.	3	2	2	
18.	F	35	48	IF	36	29	3.5	3.5	3.5	02-Dec
19.	M	28	33	-		.	2.5	3	4	
20.	M	40	43	IF	36	12	2	2.5	2	
21.	F	25	39	-		.	4.5	3.5	3.5	
22.	F	36	39	-		.	3.5	2.5	1.5	
23.	M	44	46	IF	28	15	6	4	2	
24.	M	34	42	-		.	3.5	2	2	
25.	F	29	31			.	2	1.5	1	04-07-2022
26.	M	28	34	-		.	2.5	1.5	1.5	
GA=Glatiremar Acetate, IF=Interferon										

Table 1: Demographic and clinical characteristic of RRMS patients.

The relations between age of onset and duration of disease with improvement in EDSS at 12 and 24 months were not statistically significant (p>0.05).

The annual relapse rate before CYC treatment was 0.92. It decreased to 0.23 after 1 year and to 0.23 in the second. The decrease in relapse rate versus baseline was statistically significant for the first and second years (p=0.000 and p=0.000, respectively).

a) Change month 0 to month 12		
Change	male	female
İmproved >1 step	7	2
İmproved 1 step	2	4
Unchanged (± 0,5 step)	3	7
Worse 1 step	-	-
Worse >1 step	1	-
b) Change month 12 to month 24		
Change	male	female
İmproved >1 step	1	-
İmproved 1 step	-	3
Unchanged (± 0,5 step)	10	10
Worse 1 step	1	-
Worse >1 step	1	-
c) Change month 0 to month 24		
Change	male	female
İmproved >1 step	6	3
İmproved 1 step	3	6
Unchanged (± 0,5 step)	1	4
Worse 1 step	-	-
Worse >1 step	3	-

Table 2: Change in EDSS in 26 RRMS cases.

After the first year of treatment 14/26 showed improvement by 1.0 or more steps in EDSS, no change by 1.0 step in 10 and worsening by 1.0 or more steps in 2. After the second year there had been further improvement in 4 and worsening in 2. Overall after two years baseline EDSS had improved in 18 was unchanged in 5 and worse in 3 (Table 2). The difference between baseline EDSS and EDSS at 24 months in the "improved group" was significant (p=0.000); but that in the "worsening group" was not (p=0.109).

Results of secondary progressive MS group

Of 23 SPMS patients, 15 were female for a F:M sex ratio of 1.9. Mean age at entry was 43.3 ± 9.2 years, mean duration of disease 11.7 ± 7.2 years, and mean EDSS 5.6 ± 1.7. Seven had used DMT before the study, as shown in Table 3 where the demographic and clinical characteristics of the group are presented.

The relations between age of onset and improvement of EDSS at 12 and 24 months were not statistically significant (p>0.05). Relation between duration of disease and improvement of EDSS was not significant at 12 months and at 24 months (p>0.05).

Annual relapse rate preceding CYC treatment was 0.26. It was 0.13 at 12 months and decreased to 0.04 in the second year. The decrease in relapse rate versus baseline was not statistically significant for the first year (p=0.35) but was significant for the second year (p=0.04).

The 23 SPMS patients after one year had improvement in EDSS in 5 and no change in 18. In the second year 1 had worsened and the rest were unchanged. After two years, the baseline EDSS had shown improvement in 5, no change in 15 and worsening in 3 (Table 4). The changes from baseline EDSS overall were not statistically significant (p>0.05) for improvement (22%) or worsening (13%).

Patient	Sex	Age at onset	Age at start CYC treatment	Progression time (yr)	DMT before CYC		İnterval Between DMT-CYC	EDSS M0	EDSS M12	EDSS M24	Relapse during treatment at month
					Drug (DMT)	Duration of use (mo)					
1	F	44	59	13	-	-	-	7.5	7	8.5	19
2	F	15	37	18	-	-	-	9	8.5	9	-
3	F	24	42	11	-	-	-	6	5	5	-
4	F	25	38	7	-	-	-	5.5	5	5	-
5	F	20	55	6	-	-	-	3.5	3	3.5	-
6	F	34	40	3	-	-	-	4.5	4.5	4.5	-
7	F	15	36	11	-	-	-	3.5	4	4.5	-
8	M	29	33	1	-	-	-	8	6	6	-
9	M	26	33	3	GA	12	13	6	6.5	6	-
10	M	21	35	9	GA	24	9	4	4.5	5	2/10
11	F	23	32	6	-	-	-	7.5	7.5	7.5	-
12	F	19	25	4	-	-	-	7.5	7.5	7.5	-
13	F	28	33	1	-	-	-	4.5	3.5	3.5	-
14	M	37	40	1	-	-	-	3	3	3	-
15	M	34	37	2	-	-	-	3.5	3	3	1/5
16	F	40	45	3	-	-	-	4.5	3.5	3.5	-
17	M	33	50	9	-	-	-	7.5	7.5	7.5	-
18	F	19	33	7	IF	60	27	6.5	6.5	6.5	-
19	F	26	32	3	IF	40	-	6	5.5	5.5	-
20	F	27	35	5	IF	42	-	6	6	6	1/6
21	M	22	24	1	-	-	10	3.5	1.5	1	-
22	M	36	47	8	IF	60	33	6	6	6.5	-
23	F	25	35	6	IF	62	6	6	6	6	-
GA=Glatiremar Acetate, IF=İnterferon											

Table 3: Demographic and clinical characteristic of SPMS patients

Side Effects

During the first six months of CYC treatment, 7 (13%) of the original 56 patients accepted in the study dropped out. Four of them (7%) could not tolerate the side effects, one became pregnant, one refused treatment after 3 months and one gave no reason for leaving the study (Tables 5a and 5b). The main intolerable side effects were severe nausea, vomiting, definitive amenhorrea and serious fatigue. During treatment, 12/49 (24%) of the patients experienced tolerable side effects (Table 6). Moderate nausea and vomiting, headache, mild fatigue, mild upper respiratory infections, bacterial cystitis, mild leukopenia were among these. In two women amenorrhea occurred in the second year; they were older than 35 and continued in the study.

Discussion

This study showed that monthly high dose IV pulse CYC treatment seemed effective in both RRMS and SPMS patients. There was no relation found between age at onset or duration of disease with improvement on EDSS. CYC treatment significantly decreased the annual relapse rate in both groups. After two years improvement of 1.0 or more steps on EDSS was found for 69% of the RRMS patients. The SPMS patients showed no significant changes from baseline EDSS, suggesting that their disease had not progressed, at least on this measure of impairment. It was also demonstrated that high dose IV pulse CYC treatment for two years was safe and well tolerated with the total regimen employed.

Monotherapy use of CYC or Mitoxantrone [7,10] or either used in combination with immunomodulatory agents [11] has considerably increased over the last two decades. The first studies on CYC treatment in MS evaluated its efficacy in relapsing-remitting and progressive forms of MS with different regimens. Many of these reports claimed that CYC was efficacious in MS, but not all were positive [12,13].

CYC was first used in MS in 1966 by Aimard et al. [14] in a case of progressive MS, and was then studied by other investigators in open label trial [15-17]. Then Gonsette and Hommes reported positive effects in both RRMS and SPMS treated with CYC. Hommes et al. [18-20] treated 86 patients with short course CYC 400 mg/day plus prednisolone 100 mg/day given to induce leukopenia below 2000/mm^3 for a total dose of 8 g of cyclophosphamide. They reported stabilization of disease in 69% of patients. Theys et al. [21] found no benefit of 6-8 g of CYC given over 3-4 weeks in patients with moderately advanced MS. Gonsette et al. treated RRMS with CYC. They reported 110 patients with follow-up for 2-3 years [22] and 134 patients with follow-up of 2-10 years [23]. Patients were given CYC over a 1 to 2 week period and received 1-2 g to maintain a leukopenia of 2000. They showed 75% decrease in annual relapse rate in 70% of patients. Gonsette and Hommes identfied two major themes regarding treatment in MS with an anti-inflammatory chemotheraphy drugs such as CYC. First, earlier stage disease responds best to treatment; inflammation is then more prominent in earlier stage of the disease whereas degenerative proccess occurs later. Second, although a two week treatment with CYC may be efficacious in inflammatory stage of MS, longer term use may be preferable. Analysis of Canadian study also demonstrated that in later stages of progressive MS or in MS that is not inflammatory or not rapidly progressive, CYC was not effective. [12]

Another randomized controlled study of CYC was reported by Hauser et al. [24] Patients with progressive MS were treated with a 2-3 weeks course of intravenous CYC 400-500 mg/day to achieve leukopenia of 2000/mm^3 plus ACTH, compare to a group given ACTH alone. They showed that 80% of CYC treated patients were improved or stable at 1 year compared to only 20% in the ACTH treated group.

CYC has also been used for DMT treatment failures. Weinstock-Guttman et al. [25] reported 75% of such patients showed improvement or stabilized at 12 months following IV CYC for 5 days followed by maintenance therapy. Khan et al. [26,27] reported

a) Change month 0 to month 12		
Change	male	female
İmproved >1 step	2	-
İmproved 1 step	-	3
Unchanged (± 0,5 step)	6	12
Worse 1 step	-	-
Worse >1 step	-	-
b) Change month 12 to month 24		
Change	male	female
İmproved >1 step	-	-
İmproved 1 step	-	-
Unchanged (± 0,5 step)	8	14
Worse 1 step	-	-
Worse >1 step	-	1
c) Change month 0 to month 24		
Change	male	female
İmproved >1 step	2	-
İmproved 1 step	-	3
Unchanged (± 0,5 step)	5	10
Worse 1 step	1	2
Worse >1 step	-	-

Table 4: Change in EDSS in 23 SPMS cases.

Patient	Age	Sex	EDSS M0	Treatment Start (Month, Year)	Treatment End (Month, Year)	Cause	Relapse During Treatment (mo)
1	27	F	4,5	3, 2001	7, 2001	Pregnancy	-
2	35	F	5,5	7, 2006	9, 2006	Amenorrhea	-
3	23	M	3,5	5, 2000	6, 2000	No reason	-

Table 5a: SPMS patients who dropped out of the study by duration of treatment and cause.

Patient	Age	Sex	EDSS M0	Treatment Start (Month, Year)	Treatment End (Month, Year)	Cause	Relapse During Treatment (mo)
1	38	F	2,0	5, 2004	10, 2004	Chronic UTI	-
2	24	F	1,5	1, 2006	6, 2006	Fatigue, nausea, vomiting	3
3	32	M	2,5	4, 2003	7, 2003	Therapy refusal	-
4	30	M	1,0	4, 2001	11, 2001	Hypertension, nausea,vomiting	-

Table 5b: RRMS patients who dropped out of the study by duration of treatment and cause.

Side effects	# Patients (%)
Nausea	12 (24)
Vomiting	10 (20)
Fatigue	9 (20)
Upper respiratory infections (mild)	4 (8)
Headache	4 (8)
Urinary tract infections (bacterial)	3 (6)
Leukopenia	3 (6)
Definitive amenorrhea	2 (4)
Total	12 (24)

Table 6: Frequency of tolerable side effects and laboratory abnormalities.

clinical improvement or stability in 14 such patients given CYC monthly at 1000 mg/m^2.

Perini et al. [28] and Perini and Gallo [29] reported significant reduction of T2 lesion and gadolinium enhancement lesion on MRI in 26 patients with secondary progressive course. The patients received monthly IV CYC at 800-1200 mg/m^2 for one year then every two weeks in the second year. They showed significant clinical improvement and the treatment was well tolerated and safe.

In a multicenter study conducted by Zephir at al. [30] 490 primary or secondary progressive patients were treated for at least one year with monthly CYC plus methylprenisolone (MP). After 12 months, 78.6% of SPMS and 73.5% of PPMS patients ha stabilized or improved. Gladstone et al. [31] treated 13 SPMS patients with 200 mg/kg CYC over 4 days. Their results indicated that high dose CYC treatment in severe refractory MS could result in disease stabilisation with improved functionality and quality of life.

Ford and Waubant [32] have just now published their update on progressive forms of multiple sclerosis, including review of all treatment trials to date, published or in progress, as well as the presentation by Brochet et al. [33] at the ECTRIMS Congress held in Copenhagen in October 2013 of the results of their comparison of cyclophosphamide with methylprednisone, called CPM and MP by Ford and Waubant: "Subjects receiving CPM were 2.4 times less likely to have disability progression than those receiving MP, but were also 2.6 times more likely to stop treatment. Discontinuations due to adverse effects limited the power of this trial in both agents (45% for CPM, 36% for MP). Because of the high rate of adverse events, use of CPM is usually reserved for highly selected patients with very active disease.

Ford and Waubant in the same paper decry the use of the EDSS in treatment trials, citing principally the objections raised in 1988 by Willoughby and Paty [34] not considering their refutation the next year in a full review of the origin and development of the (E)DSS [35].

The result of our study suggest efficacy of long term, high dose CYC in both RRMS and SPMS, which is similar to the result of some other studies. The principal limitation of CYC therapy has been treatment withdrawal due to intolerable side effects. Aggressive hydration during administration can minimize cystitis, and bladder cancer screening should be considered with long-term use. İn this study, side effects were mostly well tolerated and seldom so severe as to interrupt CYC treatment.

In conclusion, this study shows that the 2 year IV pulse treatment of CYC is safe and and appears effective in worsening relapsing-remitting and secondary progressive MS patients. In secondary progressive patient, treatment should be started early in the progressive phase of the disease. These results will need to be confirmed by a much larger controlled study testing the benefical effects of treatment on both clinical and MRI parameters in both short and long term.

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