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Original Article / Özgün Araştırma

Comparison of Mitoxantrone versus Cyclophosphamide Treatment in Patients with Secondary Progressive Multiple Sclerosis

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Abstract

Objective: Mitoxantrone (Mtx) and cyclophosphamide (Cyc) have successfully been used in highly aggressive multiple sclerosis (MS) patients. This study aims to compare the efficacy of these drugs in patients with secondary progressive MS (pwSPMS).

Method: Clinical data of pwSPMS treated with either Mtx or Cyc were collected retrospectively. The EDSS scores before, during, and after the drug was determined. The efficacy of the drug was evaluated according to the EDSS change after the completion of therapy. The variations in clinical benefit between the two groups were investigated, as well as the factors that influenced them.

Results: Fifty-nine SPMS patients (29 Mtx, 30 Cyc) were included in our study. Mean treatment periods were 19.5±9.9 months for Mtx and 9.1±4.1 months for the Cyc group. Mean EDSS in Mtx and Cyc groups at the first dose were 6.2±0.7 and 6.3±0.8, respectively (p=0.42). The percentage of patients who benefited from treatment was 41.6% in the Mtx group and 43.0% in the Cyc group (p=0.54). However, Mtx was more effective in patients with younger age of disease onset (p=0.01).

Conclusion: Immunosuppression with intravenous Mtx and Cyc may equally prevent progression in patients with SPMS. Additionally, Mtx may be more beneficial in MS patients with earlier disease onset.

Keywords: Mitoxantrone; Cyclophosphamide; Multiple Sclerosis, Chronic Progressive; Alkylating Agents; Topoisomerase II Inhibitors

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Sekonder Progresif Multipl Skleroz Hastalarında Mitoksantron ve Siklofosfamid Tedavilerinin Etkinliğinin Karşılaştırılması

Öz

Amaç: Mitoksantron (Mtx) ve siklofosfamid (Cyc)agresif gidişli multipl skleroz hastalarında başarıyla kullanılmıştır. Bu çalışma, sekonder progresif multipl sklerozlu (SPMS) hastalarında bu ilaçların etkinliklerini karşılaştırmayı amaçlamaktadır.

Yöntemler: Mtx veya Cyc ile tedavi edilen SPMS hastalarının klinik verileri geriye dönük olarak toplandı. İlaç öncesinde, ilacı kullanırken ve kesildikten sonrasındaki EDSS skorları belirlendi. İlacın etkinliği, tedavi tamamlandıktan sonraki EDSS değişikliğine göre değerlendirildi. İki grup arasındaki klinik faydada farklılıklar ve bunları etkileyen faktörler araştırıldı.

Bulgular: Çalışmaya elli dokuz SPMS hastası (29 Mtx, 30 Cyc) dahil edildi. Ortalama tedavi süreleri Mtx için 19.5±9.9 ay ve Cyc grubu için 9.1±4.1 ay idi. İlk doz öncesi ortalama EDSS skorları Mtx grubunda 6.2±0.7 ve Cyc grubunda 6.3±0.8 idi (p=0.42). Tedaviden fayda gören hastaların oranı Mtx grubunda %41.6 ve Cyc grubunda %43.0 idi (p=0.54). Ancak Mtx, MS başlangıç yaşı daha küçük olan hastalarda daha etkiliydi (p=0.01).

Sonuç: İntravenöz Mtx ve Cyc ile immünosupresyon, SPMS'li hastalarda progresyonu eşit derecede önleyebilir. Ek olarak, Mtx daha erken hastalık başlangıcı olan MS hastalarında daha faydalı olabilir.

Anahtar kelimeler: mitoksantron, siklofosfamid, Multipl Skleroz, Kronik Progresif,Alkilleyici ajanlar,Topoizomeraz II İnhibitörleri.

INTRODUCTION

Multiple sclerosis (MS), an autoimmune disease of the central nervous system, most commonly begins with relapse and remission episodes (relapsing-remitting MS; RRMS), except for a group of 10-15% of patients with progressive onset. Acute neurological complaints caused by acute localized inflammation usually resolve with the cessation of inflammation and remyelination[1]. A significant portion of the patients enter the secondary progressive phase (SPMS), in which neurodegeneration mechanisms predominate over the years, and neurologic disability accumulates[2]. New relapses and MRI lesions may also develop in some patients. Early initiation of treatment is recommended to prevent progression into this phase. Indeed, early started disease-modifying treatments reduce the risk of developing disability[3], while most of the approved MS treatments were found to be ineffective in patients entering the SPMS phase because they can prevent inflammation rather than neurodegeneration. However, some studies found that inflammation and relapses are still effective in disability accumulation. Therefore they suggested that active SPMS patients should be treated with disease-modifying treatments as well[4].

Currently, ocrelizumab and siponimod are the drugs of choice, with multiple randomized controlled clinical trials demonstrating their efficacy in progressive MS patients. In the last 20 years, DNA-binding alkylating cyclophosphamide (Cyc) and topoisomerase-2 inhibitor mitoxantrone (Mtx) have been shown to be effective in highly active and progressive MS patients[5-8]. Both agents have shown promising success in preventing relapses, new MRI lesions, and disability. One open-label study found Cyc and Mtx equally effective in reducing clinical and radiological disease activity in RRMS and SPMS patients[9]. Despite the proven efficacy of these agents, they have gradually been replaced by other treatments due to their potentially serious side effects.

In the past, these two chemotherapeutic agents have been used in progressive MS patients

frequently in our center. We hypothesize that both drugs prevented disability progression equally in patients with secondary progressive multiple sclerosis (pwSPMS). This study aimed to compare the potency of Mtx and Cyc on preventing disability progression in pwSPMS.

METHOD

In this study, we included pwSPMS treated either with Mtx or Cyc. The SPMS was defined as neurological disability accumulation independent of acute relapses for at least one year. The onset of progressive phase data is updated for every progressive MS patient in our database on a regular basis. Other inclusion criteria were; using Mtx or Cyc at least for six months and having relapses in addition to progression. Exclusion criteria were inadequate EDSS and other clinical data, a follow-up period of less than one year, and chemotherapeutic use of fewer than six months. Demographic and clinical data included age at disease onset, first MS symptom, previous MS treatments, time to the onset of progressive phase, cumulative chemotherapeutic drug doses, body mass index, EDSS scores before and after the chemotherapeutic treatment, and EDSS score at the last visit. Consequently,EDSS change after the treatment was calculated for each patient. An objective clinical benefit from the treatment was considered when the EDSS at the last visit was either not changed or decreased compared to pre-treatment EDSS scores.

We used SPSS 21.0 (IBM©) software for statistical analysis. We performed independent samples T-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, chi-square test for variables with percent value. We also created a logistic regression model to investigate the effect of various demographic and clinical parameters on the likelihood of objective clinical benefit from chemotherapeutics.

The study was approved by the local ethical committee of our institution (approval number: 2020/1833).

RESULTS

Among the pwSPMS, 129 patients have taken Mtx at least one dose. Among all, 24 patients used the drug for less than six months, and 13 patients had a follow-up period of fewer than six months. Treatment duration data in 42 patients and EDSS data in 12 patients were missing. A total of 207 patients have taken Cyc at least one dose. Among all, 45 patients used the drug for less than six months, 53 patients had a follow-up period of fewer than six months, and nine patients used both chemotherapeutics. Treatment duration data in 39 patients and EDSS data in 31 patients were missing. Nine patients used both Cyc and Mtx at different periods.

After the analysis, 30 Cyc and 29 Mtx patients treated between 2002 and 2016 were found to meet the inclusion criteria (Table 1). Mtx was administered to each patient once every three months with a dose of 12 mg/m2 (usually 20 mg). Cyc was administered 1000 mg/day once a month for a maximum duration of two years. Gender ratio and body surface area were the same among the groups (65% vs 50% female, p=0.34; 1,76±0.22 m2 vs 1.79±0.20, p=0,67). Previous disease-modifying treatments were interferon-β, glatiramer acetate, azathioprine, and natalizumab which were distributed similarly among the groups (p=0.74). Mean age at MS disease onset was slightly lower in the Mtx group than Cyc group (28.0±10.1 vs. 33.1±9.2, p=0.047). The time to the second attack, time to progression, and chemotherapeutic treatment onset were similar in both groups (p=0.29, p=0.27, and p=0.69, respectively). Mean chemotherapeutic treatment periods were 19.5±9.9 months for Mtx and 9.1±4.1 months for the Cyc group. Regarding the neurological disability status,

mean EDSS in Mtx and Cyc groups at the first dose were 6.2±0.7 and 6.3±0.8, respectively (p=0.42). Mean follow-up durations were 4.5±3.3 years in

the Mtx group and 2.4±2.2 in the Cyc group (p=0.005).

Table I: Data of the patients. Note that there is no difference in terms of demographic features between the groups except age at onset and follow-up duration after the treatments. Calculated by a:Chi-square, b:independent samples T test, c:Mann-Whitney U, N/A: Not applicable.

	Mitoxantrone (n=29)	**Cyclophosphamide (n=30)**	**p**
Gender	19 F (65%) 10 M (35%)	15 F (50%) 15 M (50%)	0.34[a]
Mean disease onset age (years ±SD)	28±10.1	33.1±9.2	0.047[b]
Time to the second relapse	33.2±32.4	24.8±26.6	0.29[b]
Time to transition to progressive phase (years ±SD)	9.0±6.4	7.3±5.4	0.272[c]
Duration of disease before chemotherapeutic treatment (years ±SD)	12.0±7.3	11.3±5.8	0.696[c]
Duration of chemotherapeutic treatment (months ±SD)	19.5±9.9	9.1±4.1	N/A
EDSS at first dose	6.2±0.7	6.3±0.8	0.424[c]
Mean difference between final EDSS and last dose EDSS	0.5±0.9	0.3±0.6	0.495[c]
Last visit EDSS	6.7±1.6	6.9±0.9	0.533[c]
Cumulative dose per body surface area (mg/m^2)	81±26.3	4815±1965.7	N/A
Follow up period after treatment (years)	4.5±3.3	2.4±2.2	0.005[c]
Percentage of patients benefited from treatment	41.6%	43%	0.544[a]

EDSS scores of the patients at the last visit were 6.7±1.6 for Mtx and 6.9±0.9 for the Cyc group. The mean difference between the last visit EDSS and pre-treatment EDSS were 0.5±0.9 in the Mtx group and 0.3±0.6 in the Cyc group (p=0.49) (Figure 1). The percentage of patients who benefited from treatment was 41.6% in the Mtx group and 43.0% in the Cyc group (p=0.54). However, Mtx was more effective in patients with younger age of disease onset (p=0.01) (Figure 2).

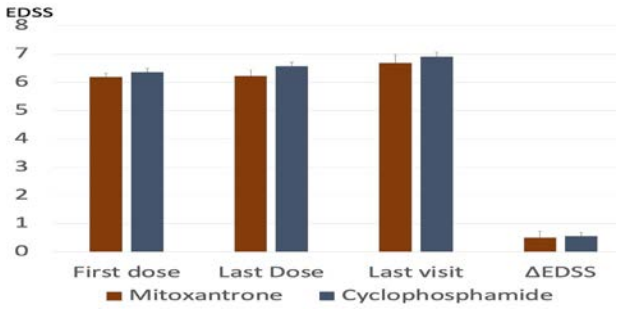

Figure 1: Comparison of mean EDSS values at last visit, first and last doses. ΔEDSS: Difference of EDSS values between two time points at the last visit and first dose. Note that there is no difference between any of the bar graphs.

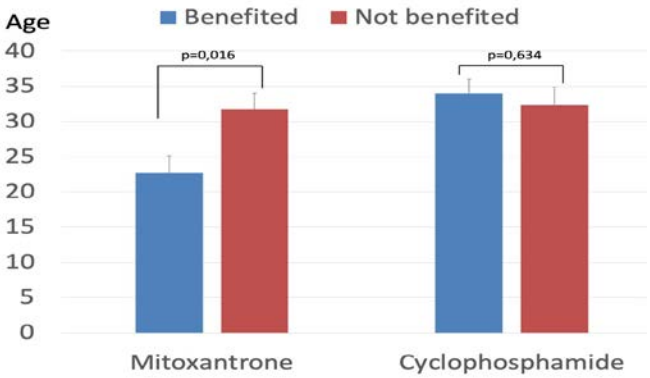

Figure 2: Comparison of treatment efficacy according to age at disease onset. Note that mitoxantrone was more effective in patients with younger disease onset. There was no difference in cyclophosphamide group.

In the logistic regression model, which included the variables of gender, time to the second attack, time to the progressive phase, and follow-up duration for both groups, variables did not predict the treatment benefit from chemotherapeutics (p>0.05).

DISCUSSION

The purpose of this study was to determine if Mtx and Cyc therapies were effective in pwSPMS. The efficacy of the treatments was determined by the difference in EDSS scores before and after treatment. Patients with SPMS usually have EDSS scores of 5.0 or above at diagnosis. Within a few years, these patients will enter into the progressive phase, ongoing inflammation will diminish, and neurodegeneration will increase[10,11]. The EDSS 3 and EDSS 6 scores have long been regarded as indicators of disease progression. According to the previous studies, the time between EDSS 3 and 6 is consistent despite considerable variations in time to EDSS 3 among patients[12]. Therefore, starting early treatment is recommended[13].

Currently, effective treatments for progressive patients are limited. Ocrelizumab and siponimod are the only approved drugs in progressive MS patients with varying degrees of efficacy[14,15]. A pivotal study published in 2017 demonstrated that ocrelizumab treatment reduced disability progression in a subset of patients with primary progressive MS[16]. Subsequently, ocrelizumab was approved to treat RRMS, SPMS, and PPMS patients in Turkey. Since the approval, ocrelizumab has been widely used in individuals with progressive MS due to its low side effect profile. No comparison between Cyc/Mtx and ocrelizumab could be conducted because ocrelizumab was not used during the treatment period of the patients in our study.

Mtx, a DNA binding topoisomerase-2 enzyme inhibitor, affects proliferating immune cells and has immunosuppressive and immunomodulatory properties[17]. It acts by inhibiting the proliferation of macrophages, B, and T lymphocytes and by reducing various proinflammatory cytokines. In the first randomized controlled pivotal study evaluating Mtx combined with methylprednisolone, Mtx increased the percentage of patients without new gadolinium-enhancing MRI lesions (31% vs. 90%, p=0.001), a higher mean EDSS decrease (-1.1 vs. 0.3, p=0.001), and a higher number of patients without relapse (66% vs. 33%, p=0.001)[18]. Likewise, Mtx reduced the EDSS score, the change in the ambulation index, and the number of relapses in another progressive MS trial and reduced the annualized relapse rate (ARR)[19]. Short-term induction with Mtx before starting interferon beta 1-b and glatiramer acetate reduces the development of new MRI lesions and disability[20-22].

Cyclophosphamide, an alkylating agent that suppresses replication by binding to DNA, was first used in an MS patient in 1966[23]. Cyc treatment combined with interferon-beta significantly decreases the mean number of relapses (ARR=0.2, p=0.0001) and the EDSS (mean 2.2, p=0.0001) in a group of 10 patients[24] and slows disease activity in 50-60% of patients[17]. In younger patients with active disease, the decrease in the MRI activity and ARR following the Cyc treatment is more substantial[25]. Despite having a higher rate of drug discontinuation due to adverse effects in a randomized controlled study comparing Cyc with methylprednisolone in SPMS patients, the Cyc reduced the risk of developing disability by 67% in the ad-hoc analysis[26].

In our study, Mtx and Cyc both slowed disability accumulation in SPMS patients. In a prospective comparative study including 50 SPMS patients, both Mtx and Cyc reduced disability (56% for Mtx and 68% for Cyc) and ARR[27]. However, we found no significant reduction in the mean EDSS scores in our cohort following treatment. The higher baseline EDSS scores of the patients in our study could be one explanation for this disparity (6.2 and 6.3 vs. 5.4 and 5.7). We also found that earlier-disease onset MS patients benefited more from Mtx therapy.

Mitoxantrone and Cyc are proposed to be potent induction treatments[28,29]. One retrospective

study evaluated MS patients treated with glatiramer acetate after induction treatment with Cyc[30]. They found that 75% of patients did not relapse and that the likelihood of being free of disability progression at two years was 0.77 (95% CI 0.43–0.92). Their use has declined dramatically due to cardiomyopathy, leukemia, and infusion-related adverse effects. However, because of the potential for significant adverse events, they are suggested to be used in patients with an aggressive course. Additionally, compared to the escalation approach, induction therapies significantly reduce the risk of disability[31]. This observation could justify the use of induction treatments such as alemtuzumab or cladribine, which have a lower risk of adverse events compared to Mtx and Cyc[28].

Our study has several limitations. Retrospective study design prevented the exact demographic and clinical matching of the two groups. We did not include a control group treated with a different agent. We could not investigate disease relapse and MRI progression parameters inour study due to lack of data. The follow-up duration difference between the treatment arms also might have affected the results.

In conclusion, immunosuppression with intravenous Mtx and Cyc may equally prevent progression in patients with SPMS. Additionally, Mtx may be more beneficial in MS patients with earlier disease onset. In progressive MS patients, these drugs may be considered as treatment alternatives when other agents are ineffective.

Ethics Committee Approval: The study was approved by the local ethical committee of our institution (approval number: 2020/1833).

Conflict of Interest: The authors declared no conflicts of interest.

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