

Disease-modifying therapies in Chinese children with multiple sclerosis

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Limited data are available about the use of disease-modifying therapies (DMTs) in children with multiple sclerosis (MS). This study aimed to present our experience using DMTs in Chinese children with MS and provide additional evidence to consider treating these patients with cyclophosphamide. A retrospective chart review was conducted and data were obtained from 25 children with MS. Only three (12%) of these patients received and responded well to first-line interferon β -1b therapy, while 10 (40%) chose cyclophosphamide and 12 (48%) refused to use DMTs. For the 10 patients being treated with cyclophosphamide, the median annualized relapse rate decreased from 3.0 to 1.0, and the median score on the Expanded Disability Status Scale decreased from 3.5 to 2.0. After 12 months of treatment, no gadolinium-enhancing lesions were reported in seven of the 10 patients. The use of DMTs plays an important role in the treatment of children with MS. If first-line therapies fail, cyclophosphamide may be a good option.

Key words: children, multiple sclerosis, disease-modifying therapies, cyclophosphamide.

Childhood-onset multiple sclerosis (MS) accounts for approximately 3–10% of all cases of MS¹. Compared to adults, children with MS experience more frequent relapses and reach a state of irreversible disability at a younger age². At the age at which one might expect to enter the workforce and have a family, patients with childhood-onset MS may have to face disease-induced disability.

Disease-modifying therapies (DMTs) play an important role in reducing the number of relapses and preventing disability. First-line therapies such as interferon β and glatiramer acetate, which have been approved for use in adults, should be used as the initial DMT in childhood-onset MS. However, these two therapies are expensive and must be given by injection at daily to weekly frequencies. Moreover, not all children with MS respond well to the first-line therapies, so second-line therapies may be necessary. To our knowledge, only one study to date has reported that cyclophosphamide reduces the relapse rate in children with MS³. Limited data are available

regarding treatment services for Chinese children with MS. The aim of this study was to present our experience with DMTs in Chinese children with MS and provide additional evidence to consider treating these patients with cyclophosphamide.

Material and Methods

A retrospective chart review was conducted on 25 children <14 years of age with MS who were cared for at the Chinese People's Liberation Army General Hospital between July 2007 and July 2012. All patients met the 2012 International Pediatric Multiple Sclerosis Group (IPMSSG) criteria for the diagnosis of pediatric MS⁴. The parents of all patients who received DMTs provided written informed consent. This study protocol was approved by the Research and Ethics Committee of the Chinese People's Liberation Army General Hospital.

Information included gender, age at MS diagnosis, disease duration, DMT type, Expanded Disability Status Scale (EDSS) scores and annual relapse rates (ARR). Disease activity was detected by magnetic resonance

imaging (MRI) before and after 12 months of treatment. In the MRI studies, gadolinium-enhancing (Gd+) lesions were reviewed by two neurologists. DMT efficacy was measured by changes in EDSS scores and ARRs.

The use of interferon β -1b was recommended at the start of DMT; however, it was refused by most patients because of the high expense, so cyclophosphamide was offered as an alternative. Treatment data, including drug, dosage and side effects, were recorded.

Results

This study included 16 girls and 9 boys with ages at MS diagnosis of 2–14 years (mean, 9.6 years). The female to male ratio was 1.78:1. Disease duration was 1.5–6 years (mean, 3 years). All patients had relapsing–remitting disease. As the first-line therapy, interferon β -1b was used in three patients, while cyclophosphamide was administered to 10 patients. Twelve patients who did not respond to DMT and experienced relapses (<1–2 per year) were given methylprednisolone or intravenous immune globulin at the time of an acute attack. Disease characteristics are summarized in Table I.

Interferon β -1b was started at 25% of the adult dose. The total dose reached 80% of the adult dose in every patient, with careful monitoring for side effects. Three patients who received interferon β -1b had no relapses and showed reduced ARRs and decreased EDSS scores. Side effects included transient flu-like symptoms of fever in two patients and headache in one (Table II).

Cyclophosphamide therapy lasted <1 year. The

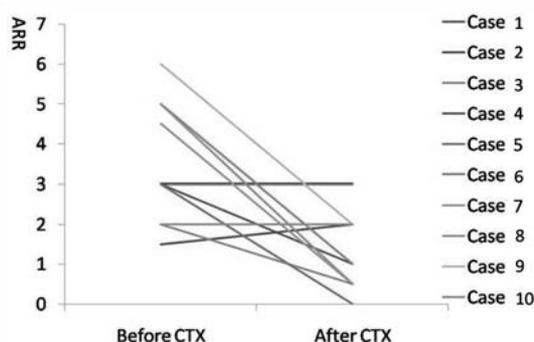


Fig. 1. Annual relapse rate before and after cyclophosphamide treatment

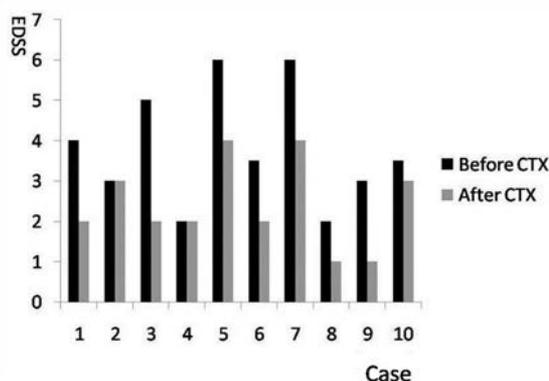


Fig. 2. Expanded Disability Status Scale (EDSS) scores before and after cyclophosphamide treatment (CTX)

patients received monthly pulsed therapy at doses of 600–1000 mg/m² and were carefully monitored for side effects. The total dose was 5.6–10 g. Side effects included nausea and vomiting in five patients, leukopenia in three, elevated liver enzymes in one and hematuria in one patient (Table III). The median annualized relapse rate decreased from 3.0 to 1.0, and the median EDSS score decreased from 3.5 to 2.0

Table I. Baseline Data of Children with Childhood-Onset Multiple Sclerosis

| Variables | n=25 |
|------------------------|------------------|
| Ratio (female:male) | 1.78:1 |
| Age at diagnosis of MS | 9.6 years (2-14) |
| Disease duration | 3 years (1.5-6) |
| Type of DMT | |
| First-line DMT | 3 (12%) |
| Interferon β -1b | |
| Second-line DMT | 10 (40%) |
| Cyclophosphamide | |
| No DMT* | 12 (48%) |

MS= Multiple sclerosis; DMT= Disease-modifying therapy.

*Corticosteroid or immunoglobulin therapy was administrated in acute relapse

Table II. Interferon β -1b Treatment Data for Three Children with Multiple Sclerosis

| Case | Age | Disease duration (years) | Side effects | ARR | | EDSS | | Gd+ Lesions | |
|------|-----|--------------------------|--------------|--------|-------|--------|-------|-------------|-------|
| | | | | Before | After | Before | After | Before | After |
| 1 | 6 | 1.5 | fever | 5.0 | 1 | 3 | 1 | 7 | 0 |
| 2 | 6 | 3 | fever | 4.5 | 1 | 6 | 2 | 4 | 0 |
| 3 | 8 | 5 | headache | 6.0 | 0.5 | 4 | 1 | 6 | 0 |

Age=Age on diagnosis of multiple sclerosis; ARR= annualized relapse rate; EDSS= Expanded Disability Status Scale; Gd+=gadolinium-enhancing

(Figs. 1, 2). After 12 months' treatment, no Gd+ lesions were reported in seven patients, cyclophosphamide treatment was discontinued in the remaining three patients due to lack of efficacy, and three patients resumed interferon β -1b treatment.

Discussion

With the low overall incidence of MS in China, it is difficult to conduct a large-scale study to evaluate the use of DMTs in children with MS. Here we present our experience using DMTs in 25 children with MS. Glatiramer acetate was not available in China when the study was conducted, and the high expense of interferon β -1b had to be borne by the patient. In this study, approximately half of the patients (48%) refused to use DMTs at all, and only three (12%) accepted the first-line therapy. This phenomenon can be explained by the high expense and poor compliance rate. The alternative strategy was to administer second-

line therapies to children with MS.

Natalizumab, mitoxantrone, rituximab and some other new treatments have been approved for use in adult patients with MS. The IPMSSG recommends the initiation of DMT for children with relapsing–remitting disease⁵. However, the use of DMTs in the treatment of childhood-onset MS lacks a clear standard. No large-scale randomized controlled studies in children with MS have been published. DMT selection mainly follows the practice used in adults with MS⁶. We expect more studies will be performed in such patients and more effective and inexpensive drugs will emerge in the future, so that Chinese children with MS will receive adapted DMTs when the diagnosis of MS is established.

In our study, three patients were administered interferon β -1b. The IPMSSG suggested that the titration of interferon β -1b should follow adult protocols or gradual titration to 250 mg; caution

Table III. Cyclophosphamide Treatment Data for 10 Children with Multiple Sclerosis

| Case | Age | Disease duration (years) | Side effects | ARR | | EDSS | | Gd+ lesions | |
|------|-----|--------------------------|-------------------------|--------|-------|--------|-------|-------------|-------|
| | | | | Before | After | Before | After | Before | After |
| 1 | 11 | 5 | Nausea/vomiting | 3.0 | 1.0 | 4 | 2 | 7 | 0 |
| 2 | 8 | 6 | Leukopenia | 1.5 | 2.0 | 3 | 3 | 4 | 6 |
| 3 | 10 | 5 | Nausea/vomiting | 2.0 | 0.5 | 5 | 2 | 6 | 0 |
| 4 | 12 | 4 | Nausea/vomiting | 3.0 | 3.0 | 2 | 2 | 4 | 3 |
| 5 | 8 | 5 | Leukopenia | 3.0 | 0 | 6 | 4 | 3 | 0 |
| 6 | 8 | 3 | Liver enzyme elevations | 5.0 | 1.0 | 3.5 | 2 | 9 | 0 |
| 7 | 7 | 4.5 | Leukopenia | 4.5 | 0.5 | 6 | 4 | 2 | 0 |
| 8 | 14 | 2 | Nausea/vomiting | 5.0 | 0.5 | 2 | 1 | 5 | 0 |
| 9 | 7 | 2 | Nausea/vomiting | 6.0 | 2.0 | 3 | 1 | 7 | 0 |
| 10 | 8 | 3 | Hematuria | 2.0 | 2.0 | 3.5 | 3 | 6 | 9 |

Age=Age on diagnosis of multiple sclerosis; ARR=annualized relapse rate; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing

should be advised in younger children⁷. Because our patients had a young average age at the time of MS diagnosis, the initial administered dose was 25% of the adult dose, and the total dose reached 80% of the adult dose as the titration endpoint. We found that interferon β -1b could reduce the ARR and the EDSS score. Some retrospective case series have reported the use of interferon β -1b in children with MS. Ghezzi et al.⁸ followed 52 patients with childhood-onset MS and found a reduction in the ARR from 1.9 before treatment to 0.4 after treatment. Mikaeloff et al.⁹ reported a similar result in 197 children with MS on interferon β -1b treatment. The use of interferon β -1b in children also appears to be safe. In our patients, side effects were flu-like symptoms, which were those most commonly seen elsewhere as well. Other reported side effects have included leukopenia, transient elevation in transaminases, thrombocytopenia, anemia and injection-site reactions^{10, 11}. Although interferon β -1b has demonstrated efficacy and safety, discontinuation rates are 30–58%¹⁰⁻¹³. Some children may not respond well to first-line DMTs, requiring regimen adjustment¹². In such cases, second-line DMTs may be considered.

Cyclophosphamide, an alkylating agent, has been shown effective in clinical and MRI suppression in adult patients with MS¹⁴. Monthly pulse cyclophosphamide 800 mg/m² has been widely used. Dose adjustments are made based on the peripheral white blood cell nadir. Treatment duration ranges from a few months to 3 years^{15, 16}. Data on the use of cyclophosphamide in childhood-onset MS are limited. Makhani et al.³ reported that 17 children with MS were administered cyclophosphamide, a therapy that resulted in a reduction in relapse rate from 3.8 to 1.1, and seven of these patients were relapse-free 1 year after therapy. In our series, seven patients who received cyclophosphamide had similar outcomes. Three patients were unresponsive to cyclophosphamide and had to resume interferon β -1b treatment. Children receiving cyclophosphamide showed mild side effects, including nausea, vomiting, leukopenia, elevated liver enzymes, and hematuria. However, Makhani et al. found that one patient who received a total of 72.7 g of cyclophosphamide developed transitional cell carcinoma of the bladder³. The risk of bladder carcinoma may

be associated with cumulative exposures >100 g as well as exposure duration (>2.7 years)¹⁷. Fluid loading before and after treatment can reduce such risks.

With regard to DMTs, age must be considered. In our study, the mean age at onset was 9.6 years. However, onset of MS before 10 years old is rare². Chinese children with MS appear to be characterized by a younger onset age. Among our patients who received DMTs, those in the cyclophosphamide group were older and had a longer treatment duration compared with those in the interferon β -1b group. This finding indicates that cyclophosphamide may be a good option for refractory childhood-onset MS. In accordance with other studies, our study found interferon β -1b to be safe and well tolerated¹⁸.

In conclusion, although the present study has some limitations, imposed by its retrospective design and the small number of patients included, our experience demonstrates that DMTs play an important role in the treatment of children with MS. If first-line therapies fail in children with MS, cyclophosphamide may be a good alternative option.

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