Cladribine in aggressive forms of multiple sclerosis

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Cladribine (2-chlorodeoxyadenosine) is an immunosuppressant drug previously evaluated in multiple sclerosis (MS) with variable results. We report six patients with aggressive relapsing MS who despite a poor response to other therapies had a favourable clinical evolution after cladribine. Four women and two men with a rapid increase in the number and severity of relapses leading to increasing disability [mean Expanded Disability Status Scale (EDSS) 6.42, standard deviation ± 0.58, mean relapse rate per year in the 2 years prior to study entry 2.67 ± 0.75] were retrospectively evaluated. Brain magnetic resonance imaging (MRI) performed in five patients showed active disease with gadolinium-enhancing lesions. Cladribine was given at 0.07 mg/kg/day for five consecutive days once monthly with a total of 2- to 4-monthly courses. After 6 months, mean EDSS decreased to 3.75 ± 1.64 and MRIs showed a decrease or suppression in the number of gadolinium-enhancing lesions. After 1 year from first dose, cladribine dosage was repeated in four patients because of recurrence of relapses with subsequent similar positive clinical results. In the follow-up period (49.33 ± 39.66 months), the mean relapse rate decreased to 0.71 ± 0.55 and no unexpected or serious adverse events were observed.

Introduction

Aggressive or malignant forms of multiple sclerosis (MS) represent a small group of patients with a severe and rapid accumulation of disability with or without frequent relapses. When beta-interferons and glatiramer acetate fail to adequately control the disease, intense immunosuppression, plasmapheresis and autologous stem cell transplantation are often used to treat these patients, although with considerable risk of severe adverse events.

Cladribine (2-chlorodeoxyadenosine) is a relatively selective lymphocytotoxic drug used in the treatment of hairy cell leukaemia and other lymphoid and myeloid malignancies. Cladribine has been evaluated in MS with variable clinical results in reducing relapse rate or slowing disability progression, but achieving an effective reduction of magnetic resonance imaging (MRI) inflammatory lesions [1–5]. We report a small series of patients with aggressive MS who despite failure to respond to other therapies had a favourable clinical evolution after cladribine.

Patients and results

We retrospectively evaluated a series of six patients, four women and two men, who were treated with cladribine in the period from October 1996 to April 2006 for aggressive relapsing MS leading to rapid accumulation of disability in the prior 6–18 months (Table 1). The mean disease duration was 54.83, standard deviation ± 43.65 months (range, 15–133). Patients 1, 4 and 5 had an aggressive course which started in the first 2 years of their disease. Patient 1 was previously reported as a single case report [6]. Patient 6 presented with an aggressive form of MS 2 months post-delivery period. The mean calculated Expanded Disability Status Scale (EDSS) in the 1-year and 6-month periods prior to treatment were 3.2 ± 2.04 (range, 1.0–5.5) and 5.25 ± 0.61 (range, 4.5–5.5) respectively (Table 1). Severe gait disturbances in all patients, brainstem and cerebellar involvement in three patients, and cognitive dysfunction in two patients characterized the main clinical disability. MRI showed active disease with gadolinium-enhancing lesions in all patients except patient 4 who had no available MRI (Fig. 1a–d).

At the time of cladribine initiation, the mean age was 28.2 ± 8.45 years (range, 15–38), the mean EDSS was 6.42 ± 0.58 (range, 5.5–7.0) and the mean relapse rate per year in the prior 2 years was 2.67 ± 0.75 (Table 1).
Previous treatment with steroids (all patients), beta-interferon (five patients), glatiramer acetate (three patients), intravenous immunoglobulins (four patients), methotrexate (one patient) or plasmapheresis (one patient) did not appreciably modify the disease course (Table 1). Cladribine was given at 0.07 mg/kg/day for five consecutive days once monthly a total of 2- to 4-monthly courses. Intravenous immunoglobulin was given concomitantly with the first cladribine course in two patients.

All patients demonstrated a slow but sustained recovery in clinical disability following cladribine therapy. After 6 months from first dose, mean EDSS was reduced from 6.42 ± 0.58 to 3.75 ± 1.64 (P < 0.01) (Table 1). Mean absolute lymphocyte counts fell from 1358 ± 557/μl prior to first dose of cladribine to 452 ± 248/μl after the last course of cladribine (P < 0.01). MRIs post-cladribine showed a decrease or suppression in the number of gadolinium enhancement lesions (Fig. 1e–h).

Four patients had repeated courses of cladribine ranging from 0.7 to 1.4 mg/kg because of new relapses 10–24 months after last drug administration. This strategy again resulted in clinical improvement and maintaining the same degree of disability reached in the 6 months after the first dose regimen (Table 1). In the mean follow-up period (49.33 ± 39.66 months; range, 6–102), the mean relapse rate per year was reduced to 0.71 ± 0.55 (P < 0.001) (Table 1). No unexpected or major adverse events were found following treatment.

### Discussion

Cladribine has been previously evaluated in MS with variable clinical efficacy. Whereas most studies note a marked improvement of radiological activity in patients treated with cladribine (up to 90% reduction in enhanced lesions) [5], this change has not been always correlated with a clinical benefit. Some studies showed a reduction in the clinical deterioration in patients with chronic progressive forms [1,2] and a favourable course in the frequency and severity of relapses in relapsing–remitting forms when compared with placebo [7,8]. In a larger phase III study of progressive MS no significant effect on the degree of disability [5] or in preventing brain atrophy [3] was noted. However, patients with both secondary and primary progressive MS having high baseline EDSSs were included in this study, and

### Table 1 Clinical characteristics of six patients with aggressive MS treated with cladribine (2CdA)

| Patient | Sex     | Age of MS onset | Disease duration before 2CdA (months) | Time from start of worsening to 2CdA (months) | Age at 2CdA onset (years) | EDSS 12 months pre-2CdA | EDSS 6 months pre-2CdA | EDSS at 2CdA | EDSS 6 months post-2CdA | Last EDSS (months of follow-up) | Annual relapse rate 2 years prior to 2CdA | Annual relapse rate post-2CdA | Previous treatments (date) | 2CdA courses (date) |
|---------|---------|----------------|--------------------------------------|---------------------------------------------|---------------------------|-------------------------|------------------------|----------------|--------------------------|---------------------------------|-------------------------------|-----------------------------|---------------------------------|--------------------------|----------------|------------------|
| 1       | Male    | 13             | 27                                   | 12–18                                       | 15                         | 5.5                      | 6.0                    | 7.0          | 2.0                      | 1.5 (27)                          | 3                                           | 0.44                        | DMD (5/02 → ) DMD (02/94-09/95)  | 4 (02-05/04) 2 (06-07/05) |
| 2       | Female  | 27             | 73                                   | 12                                          | 34                         | 4.0                      | 6.0                    | 6.5          | 4.5                      | 4.0 (102)                          | 2.5                                          |                            | IVIG (02/04) IVIG (03-09/96)    | 4 (08-11/04) 2 (09-12/05) |
| 3       | Female  | 34             | 53                                   | 6–12                                        | 38                         | 2.0                      | 4.5                    | 5.5          | 5.5                      | 4.5 (21)                          | 2.0                                          |                            | DMD (08/01 → ) IVIG (07/04)    | 2 (03-02/99) 2 (04-00) |
| 4       | Male    | 29             | 28                                   | 12                                          | 32                         | 3.5                      | 4.5                    | 5.5          | 5.5                      | 4.5 (93)                          | 2.5                                          |                            | DMD (10/97 → ) DMD (06/05 → ) | 2 (08-09/98) 2 (04-05/00) |
| 5       | Female  | 21             | 15                                   | 6                                           | 32                         | 1.0                      | 4.5                    | 6.0          | 6.0                      | 2.5 (6)                           | 4.0                                          |                            | IVIG (06/05-04/06) DMD (9/00 → ) | 1.52                        | 0                             | DMD (08-11/05) 2 (09-12/05) 4 (08-11/05) |
| 6       | Female  | 16             | 133                                  | 6                                           | 22                         | NA                       | 5.5                    | 7.0          | 5.0                      | 5.0 (47)                          | 2.5                                          |                            | Plasmapheresis (10/00) IVIG (01-03/01) | 2 (04-05/01) 4 (12-05/04) |

DMD, disease-modifying drugs; EDSS, Expanded Disability Status Scale; IVIG, intravenous immunoglobulins; MTX, methotrexate; MS, multiple sclerosis; NA, not available.
patients on placebo did not deteriorate rapidly. The study lasted only 1 year and there were only 52, 53 and 54 patients respectively in each of the three groups (cladribine 2.1 mg/kg, cladribine 0.7 mg/kg and placebo). Therefore, both patient selection and experimental design might have limited the ability to detect a beneficial response to cladribine [4].

Irreversible disability in MS may be due to two possible mechanisms: (i) clinical impairment resulting from a deficient recovery after a relapse or repetitive relapses and (ii) progression of the disease independent of relapses. These mechanisms are probably the consequence of some combination of two biological phenomena: inflammation and neurodegeneration. Once sufficient neural tissue has been lost, disability may be irreversible. However, recovery of function may be possible if the patient is treated early during the course of the disease, mainly when the EDSS is <4 [9]. The clinical course of our patients prior to cladribine treatment was characterized by an increase in disability associated with relapses. The clinical improvement was usually manifested in the first 6 months after treatment. In one patient treated with multiple courses of cladribine, the clinical change was even greater for the following 3 years (patient 4). Prior treatments with other drugs did not appear to have induced the improvement as these therapies had been used for long periods prior to the initiation of cladribine therapy. On the other hand, intravenous monthly immunoglobulin was given to two patients at the same time as cladribine was administered, so an additive effect of both treatments could not be excluded. However, subsequent relapses in these patients responded favourably to repeated isolated administration of cladribine. The recurrence of the disease after 10–24 months indicates that the biological effect of cladribine wanes after this time in the doses administered.

In summary, our preliminary small uncontrolled retrospective case report suggests that cladribine may be an effective treatment in relapsing MS patients with intense active inflammatory disease. This type of report has obvious limitations and results must be interpreted cautiously. Nevertheless, cladribine, because of its short-term safety profile in the above dosages, might be used in carefully selected patients as an alternative to potentially more toxic immunosuppressive regimens. It should be emphasized that we are not suggesting that cladribine is more effective than other aggressive immunosuppressant drugs nor advocating the routine use of cladribine for MS at the present time, pending definitive studies on the efficacy and safety of this drug in relapsing forms of MS.

Figure 1 T1 W brain magnetic resonance images with contrast of patients 1 (a and b) and 6 (c and d) showing multiple enhancing lesions prior to cladribine. New MRIs post-cladribine (5 months after the first dose in patient 1 (e and f); and after 4 months in patient 6 (g and h) showing a dramatic reduction of contrast enhancing lesions.
Conflict of interest

Dr Cook serves on the Steering Committee and Advisory Board for the CLARITY study of cladribine in relapsing remitting multiple sclerosis and is an investigator in these studies. Drs Martinez-Rodriguez, Cadavid, Wolansky and Pliner have nothing to disclose.

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References