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Development of cladribine treatment in multiple sclerosis

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Cladribine is a new type of drug with properties of selective lymphocyte suppression that appear to favorably alter the clinical course of progressive multiple sclerosis (MS). The history of the development of cladribine treatment in chronic progressive MS is discussed, and the application of cladribine treatment to progressive multiple sclerosis in a double-blind, placebo crossover study is reviewed. Cladribine selectively targets both resting and dividing lymphocytes and may be able to destroy the activated lymphocytes that induce CNS demyelination, thus producing stabilization or improvement in chronic MS. Although the role of cladribine has not yet been fully defined, additional studies are underway to evaluate the efficacy and safety of cladribine in both progressive MS and relapsing-remitting MS.

Keywords: *multiple sclerosis; cladribine; immunosuppression*

Introduction

Cladribine [2-chlorodeoxyadenosine (2-CdA), Leustatin™] is a relatively new type of selective immunosuppressive drug that was synthesized by Carson[11] to mimic the immunodeficiency state seen in hereditary adenosine deaminase deficiency. This compound is a purine nucleoside that contains substitution of a chlorine atom for hydrogen at the two position of the purine ring. This change in the structure of deoxyadenosine to 2-chlorodeoxyadenosine renders the molecule resistant to the effects of adenosine deaminase and produces a phenomenon of selective lymphocyte killing with relatively low toxicity toward other tissues.[12]

The history of the development of cladribine for use in clinical medicine begins with the discovery of hereditary adenosine deaminase (ADA) deficiency by Giblett in 1972[13] in patients with severe combined immunodeficiency syndrome. However, the cause of the severe lymphocyte depletion seen in ADA deficiency was not clearly understood until 1977, when Carson[7] showed that degradation of deoxynucleotides in lymphocytes is entirely dependent upon the activity of ADA. Carson proposed that the very high levels of lymphocyte deoxycytidine kinase specifically predisposes these cells to accumulate lethal levels of deoxyribonucleotides.[10] Indeed, extraordinarily high levels of deoxyribonucleotides were subsequently found in ADA-deficient lymphocytes.[6]

The mechanism of cell death in lymphocytes exposed to cladribine is as follows: nicks and standbreaks appear spontaneously in lymphocyte double-stranded DNA. Repair of these nicks is inhibited by high levels of deoxyribonucleotides and leads to excessive activation of the enzyme poly-ADPribose polymerase. This in turn exhausts cellular NAD and leads to lymphocyte death (apoptosis).[8]

With this insight into lymphocyte metabolism, Carson and colleagues synthesized some 25 compounds, and of these, 2-CdA (or cladribine) was found to have the most favorable therapeutic ratio. *In vitro* studies demonstrated that the selectivity of cladribine is related to the cellular level of deoxycytidine kinase and that T and non-T, non-B lymphocytes are the most susceptible to killing, with B lymphocytes being less susceptible and monolayer cell lines being the most resistant.[10]

Phase I and II clinical trials were begun in patients with advanced lymphoid neoplasms undergoing bone marrow transplantation, in chronic lymphocytic leukemia and in cutaneous T-cell lymphomas.[4,9,18–20] The most notable results were seen in patients with hairy cell leukemia.[16,17] By 1993 at Scripps Clinic, a total of 350 hairy cell leukemia patients had been treated with cladribine and 97% responded to treatment, 86% with a complete and durable remission. Cladribine is now licensed in the United States for treatment of hairy cell leukemia. Thus, cladribine was designed, synthesized, tested *in vitro* and *in vivo*, and introduced into clinical medicine at Scripps Clinic and Research Foundation. Even at this time the therapeutic range of cladribine is being expanded into other clinical disorders including neoplasms, autoimmune disorders, particularly autoimmune hemolytic anemia, rheumatoid arthritis, and inflammatory bowel disease.

We first proposed to test cladribine in MS with the background of 10 years experience in dose-escalation studies in treatment of lymphoid neoplasms and autoimmune disorders.[1,2,21] It was apparent that cladribine has a very favorable toxicity profile relative to other lymphotoxic drugs. Patients treated with cladribine had virutally no sensation of adverse effects since deviations from normal occurred only in the blood counts.

Because there is no satisfactory treatment for progressive multiple sclerosis and there is considerable evidence that CNS demyelination in MS is mediated by immunopathologic mechanisms, the use of cladribine was considered in view of the long-lasting lymphopenia it produces, and its relatively low

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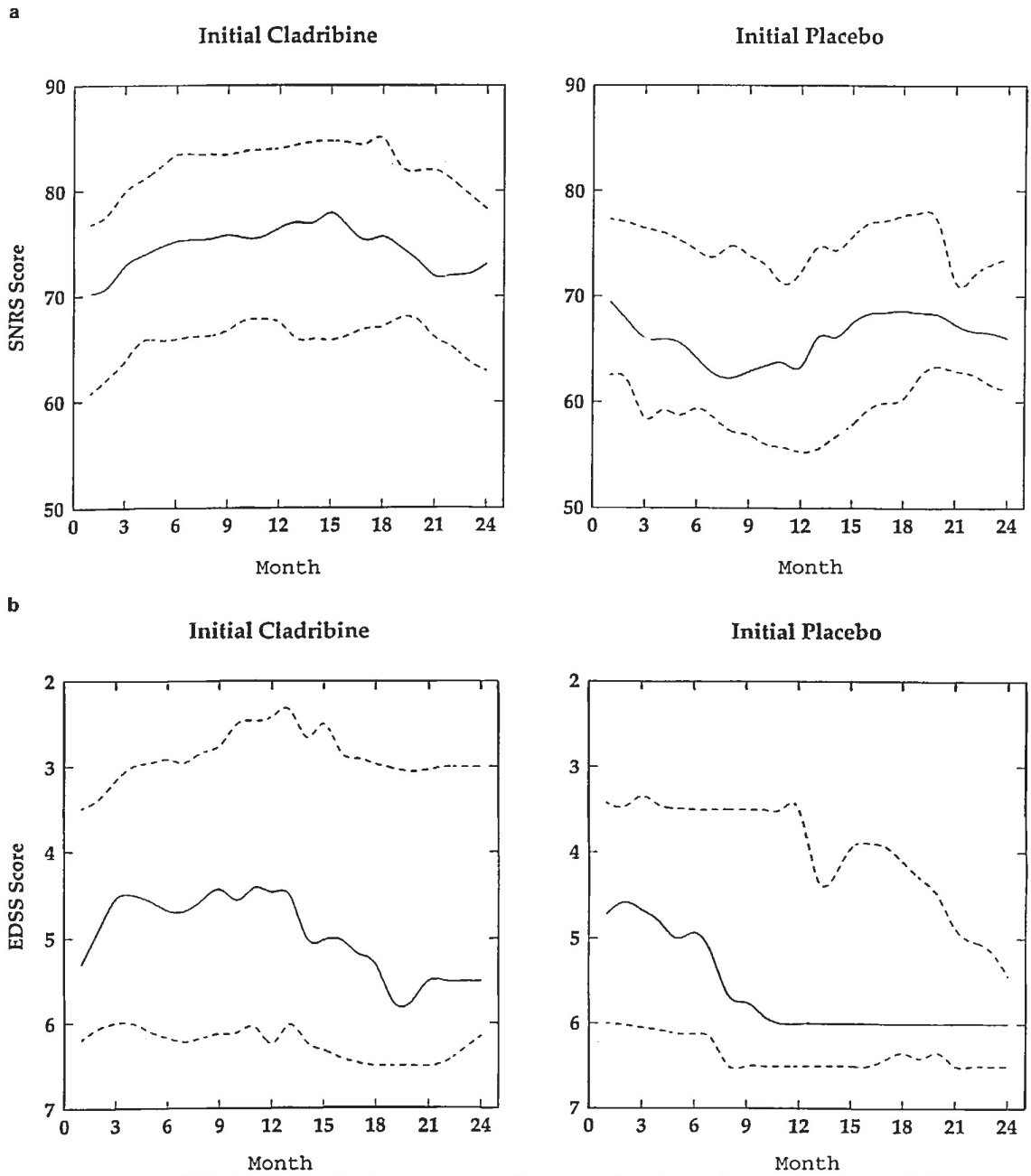

Figure 1 *Twenty-fifth, fiftieth (median), and seventy-fifth percentiles of neurologic scores, separately by treatment group, over the course of clinical trial. (a) SNRS. (b) EDSS. In the initial cladribine group, scores tend to improve during the first 12 months, then stabilize over the second year. In the initial placebo group, scores decline during the first 12 months, then tend to stabilize or improve*

toxicity. An open-label feasibility study was begun in 1990 with a small number of patients. The results were favorable in terms of apparent improvement in neurologic function and lack of toxicity. We were encouraged to proceed with a double-blind, placebo-controlled crossover study of cladribine in progressive MS. The first year results demonstrated improvement in the clinical course of progressive MS and have been published.[22] We now have data on the complete 2-year study with an additional 6 months of unblinded data.[5]

Methods

The study subjects were 51 patients with clinically definite MS (mostly secondary progressive). Three patients dropped from the study in the first year, and four patients dropped from the study in the second year, but the data of all patients has been retained on an intent-to-treat basis. Patients were paired by age, sex, duration and severity of MS, and each gave informed consent to participate in the study. Study

subjects were randomized to cladribine treatment or placebo by the statistician using a random number table. At baseline, both groups were equivalent in terms of neurologic rating scale scores, disability and MRI lesion activity. In the first year of the study, patients on the cladribine arm were given 4 monthly, 7-day infusions of cladribine 0.1 mg/kg/day (0.7 mg cladribine per course), for a total of four courses (total dose=2.8 mg/kg). During the second year, blinding was maintained but patients who had received placebo were given active drug at one-half the total dose given during the first year (total dose=1.4 mg/kg). Patients who had received cladribine in the first year were given 4 monthly saline infusions from the start of the second year. Throughout the study, patients, neurologists, nurses and neuroradiologists had no knowledge of the treatment protocol or laboratory studies. Monthly examinations were carried out to monitor adverse events and to determine the patients' Extended Disability Status Scale (EDSS) and Scripps Neurologic Rating Scale (SNRS). Laboratory blood studies were carried out at least montly and MRI brain scans with and without contrast enhancement were completed at 0, 6, 12, 18 and 24 months of the study. All patients had a portacath central venous access device implanted for drug or placebo administration. MRI scans and statistical analyses were performed using methods previously described.[16]

The results of clinical performance (SNRS) and disability (EDSS) score during the first and second years of the cladribine study have been previously reported.[5,22] In the first year of the study, average EDSS and SNRS scores of patients on full dose cladribine improved modestly while patients on placebo continued to deteriorate. Differences at 1 year were highly significant in both scoring systems (Figure 1A and B): P=0.001 for SNRS, P=0.02 for EDSS. Improvement in SNRS scores appeared to peak at about 18 months and was maintained for 24 months of follow-up, even though the first year treatment group had received no therapy after the first 4 months of the study (Figure 1A). SNRS scores of patients initially on placebo and then treated with half-dose cladribine (1.4 mg/kg) seemed also to stabilize or improve but for a shorter period of time with peak at approximately 8 months. After 2 years, unblinded observations revealed a decline in the average scores. These findings suggest a dose-response effect with cladribine and a wearing off of improvement and resumption of progressive MS symptoms in some patients after 2 years. Analysis of variance based on the two-period crossover design with primary endpoints, the absolute EDSS and SNRS revealed no significant carryover effects between subjects or period effects within subjects. Highly significant treatment effects using F-statistics were found.

Kaplan–Meier time-to-failure analyses also indicated positive treatment effects with cladribine. Whether time-to-failure is defined as a gain of 0.5, 1.0 or 1.5 points on the EDSS scale, or a reduction of 5, 10 or 15 points on the SNRS scale, patients receiving cladribine fared much better than placebo. Time-to-improvement plots also showed a statistically significant advantage for patients on cladribine.

Analysis of MRI data showed a highly significant difference in the number of enhancing lesions, a measure of current disease activity (Figure 2). In this analysis, enhancing lesions were differentiated by designating the complete disappearance or continued absence of enhancement as 'absent', and the emergence or continued presence of enhancement as 'present'. As noted in Figure 2, there is no significant difference in the proportion of individuals in the initial placebo group with enhancing lesions over the first year. In contrast, there was a dramatic fall in the proportion of individuals with enhancing lesions

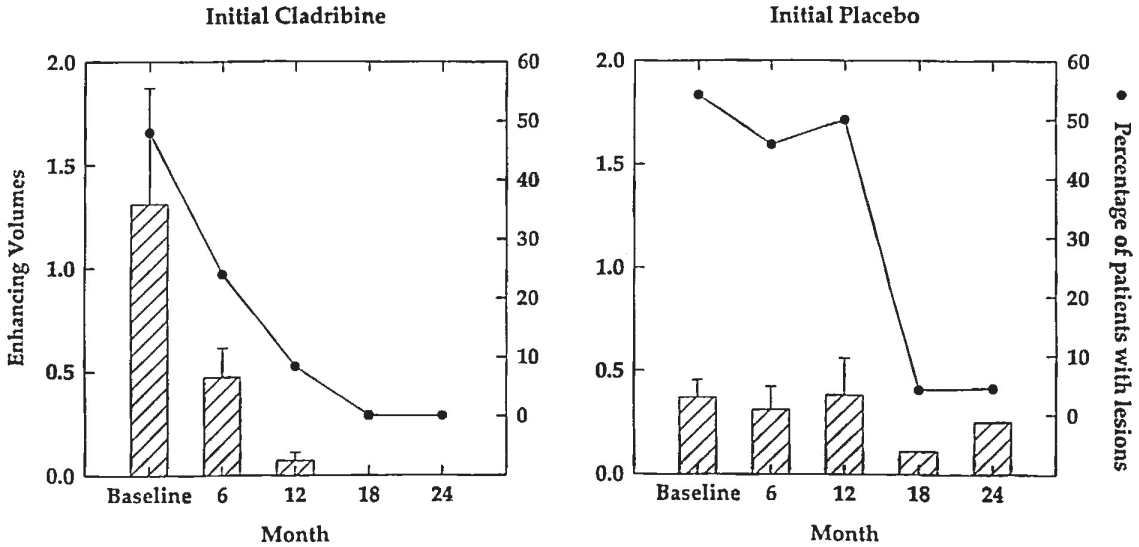

Figure 2 *Percentages of patients with enhancing lesions over the course of the clinical trial; and, mean volumes (±s.e.) of the enhancing lesions, in cubic millimeters. Means are taken solely over those patients with enhancing lesions, at each of the specific time points*

present in the cladribine group during the same time interval (P=0.001). Analysis after the crossover at 1 year showed complete absence of enhancing lesions at 2 years in the group first treated with cladribine and near-complete absence in the group treated with placebo first and cladribine second.

Toxicity and adverse events

Analysis of the laboratory studies during the first study year have previously been reported.[3] There were no side effects or adverse events that could have systematically affected the double-blind protocol status. However, a few problems were encountered in the study. More thrombocytopenia than expected was seen with the higher dose of cladribine. Two of 24 patients on the full dose developed platelet counts of under 50 000 μl. One patient who was receiving high doses of Dilantin® and Tegretol® developed marrow suppression but completely recovered in 6 months. In this study, there were five cases of mild dermatomal herpes zoster; four after full dose cladribine and one after half-dose. One patient developed acute fatal newly acquired hepatitis B shortly after the second dose of cladribine. As previously discussed,[22] experts in hepatitis B immunopathogenesis who completely reviewed the post-mortem data from this patient consider it unlikely that cladribine played a role in the patient's illness. Some additional patients who were treated in an open-label protocol and were not part of this study also developed adverse events that have been discussed in detail elsewhere.[17]

Discussion

The data analysis from this study has shown that cladribine favorably alters the clinical course of progressive MS. There was proloned suppression of CD4 cells but no associated opportunistic infections except for mild segmental herpes zoster in about 10% of MS patients treated with cladribine. Analysis of the neurologic performance and disability rating scales showed highly significant stabilization or improvement with cladribine compared to placebo in average EDSS and SNRS scores, and in the time-to-failure and improvement plots. Enhancing lesions on brain MRI scans showed significant improvement in cladribine-treated patients. We conclude that cladribine is an effective agent for retarding the clinical progression of chronic MS. The beneficial effect is durable but not permanent since worsening has been observed to eventually recur in most patients.

Since our first study of cladribine in MS was completed, it has been recognized that subcutaneous cladribine is entirely equivalent in terms of pharmacokinetic[15] results compared to the intravenous route of administration. We are therefore continuing our studies of cladribine with subcutaneously administered drug. Studies presently underway at Scripps Clinic include blinded, placebo-controlled evaluations of cladribine in relapsing-remitting MS and in the retreatment of the chronic progressive patients with a recurrence of worsening, usually 2 or more years after initial treatment. A multicenter US and Canadian study of subcutaneously administered cladribine in chronic progressive MS is also now underway. It is notable that subcutaneous cladribine has been used in relapsing-remitting MS patients by Grieb *et al*.[14] who report preliminary evidence of benefit. Although the role of cladribine has not been fully delineated, it is our hope that this new drug will prove to be a useful therapeutic option for patients with all forms of active MS.

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