Chemotherapy Plays a Major Role in the Inhibition of Catch-up Growth During Maintenance Therapy for Childhood Acute Lymphoblastic Leukemia

J. J. Groot-Loonen, MD*; B. J. Otten, MD, PhD†; M. A. van't Hof, PhD§; R. J. J. Lippens, MD, PhD*; and G. B. A. Stoelinga, MD, PhD‡

ABSTRACT. Objective. In children treated for acute lymphoblastic leukemia (ALL), catch-up growth occurs after cessation of therapy and not during maintenance therapy. In this study we investigated whether this inhibition of catch-up growth during maintenance treatment is attributable to the influence of chemotherapy or to the influence of corticosteroids.

Patients. Forty-six children treated for ALL were included in the study. Twenty-seven patients received chemotherapy comprised vincristine (VCR), prednisone (Pred), or dexamethasone (Dexa) alternated with 6-mercaptopurine (6-MP) and methotrexate (MTX) and 19 patients received maintenance therapy with 6-MP and MTX only. Treatment did not include cranial irradiation.

Results. Statural growth during maintenance treatment was comparable in both groups over the study period of 1.5 years.

Conclusion. Chemotherapy with 6-MP and MTX, and not corticosteroids, is the main factor that prevents catch-up growth from occurring during maintenance therapy for ALL. Pediatrics 1995;96:693-695; acute lymphoblastic leukemia, corticosteroids, growth, maintenance chemotherapy.

From the Departments of *Pediatric Oncology, †Pediatric Endocrinology, and ‡Medical Statistics, University of Nijmegen, The Netherlands. Received for publication Apr 8, 1994; accepted Nov 28, 1994.

Address correspondence to (J.J.G-L.) Department of Pediatric Oncology, University of Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. PEDIATRICS (ISSN 0031-4005). Copyright © 1995 by the American Academy of Pediatrics.
Measurements and Statistical Analysis

Patients' height and weight was measured by experienced staff. During the study period patients were measured 12 times per year. To standardize the results and to allow comparison of children with different ages and sexes, values for height were transformed into standard deviation scores using the Dutch reference values. Standard deviation score for height is defined as the difference between a patient's height and the age- and sex-appropriate mean of the population divided by the corresponding standard deviation. Estimates of the standard deviation scores at different time points can be calculated, defined as: $Z_t = Z_r + Z_0$ (where $Z_r$ is the standard deviation score at time point $t$ after diagnosis, $Z_0$ is the standard deviation score at time of diagnosis).

Statistical comparison was made using the $t$ test on the $Z$ scores. $Z$ scores are presented with ± the standard deviation.

RESULTS

The $Z_r$ scores for the height of each of the 27 patients treated for ALL according to protocol 6 (maintenance therapy comprising Pred or Dexa) compared with the $Z$ scores of 19 patients treated according to protocol 7 (maintenance treatment without corticosteroids) are shown in the Figure. Height at diagnosis was not significantly different from the normal population. During treatment a decline in $Z_r$ score for height was shown in both groups. Three months after the start of therapy, the $Z_r$ score of patients treated according to protocol 6 was $-0.2 ± 0.2$. The $Z_r$ score remained $-0.2$. The $Z_r$ score of patients treated according to protocol 7 was $-0.3 ± 0.2$ at 3 months and remained $-0.3$ during the whole treatment period. The differences between the two groups were not significant at any time (all $P$ values $≥0.10$).

DISCUSSION

Growth retardation during treatment for ALL is of multifactorial etiology. CI as central nervous system prophylaxis in the treatment for ALL has been implicated as the main etiologic agent. Compared with patients who were not irradiated, children who received CI showed more severe growth retardation and during the period of catch-up growth these patients did not fully regain the previous loss. Apart from impaired growth, retardation of bone age development has also been reported during treatment for ALL. Bone age retardation in patients who received CI was the same as in patients who were not irradiated, suggesting a direct influence of chemotherapy and/or corticosteroids on skeletal maturation. The influence of chemotherapy alone on growth and bone age development is not known, but long-term corticosteroid therapy has been associated with growth inhibition and delayed skeletal maturation.

Short-term treatment with Pred in a dose of 40 mg/m²/day and Dexa in a dose of 10 mg/m²/day, used during remission induction therapy for ALL have been shown to suppress growth hormone secretion. This temporary inhibition of growth hormone secretion could contribute to the diminished growth during the early phase of therapy. In this study both groups of patients showed loss of height standard deviation score during the initial phase of therapy. The question was whether patients who did not receive corticosteroids during maintenance treatment would show a different growth pattern compared with children who received corticosteroids during the entire period of treatment. Although in protocol 6 corticosteroids were given intermittently (2 weeks on steroid treatment, 5 weeks off), this mode of treatment has also been associated with impaired growth. However, the growth pattern in both groups of patients during maintenance therapy proved to be the same; none of the patients showed catch-up growth. So we may conclude that corticosteroids were not the causal factor for inhibition of catch-up growth, but that this phenomena was mainly attributable to chemotherapy with 6-MP and MTX. Treatment with MTX has been associated with enteropathy, which could result in malnutrition. For patients treated according to protocol 7 (without corticosteroids during maintenance therapy) weight for height was not significantly different from the normal population; we conclude from this that malnutrition could not be a factor contributing to the inhibition of catch-up growth.

REFERENCES


Figure. Mean Z score (standard error) for height of patients treated for acute lymphoblastic leukemia (ALL) according to protocol 6 (maintenance therapy comprising prednisone or dexamethasone, n = 27) and according to protocol 7 (maintenance treatment without corticosteroids, n = 19).
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