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

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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. In 27 patients maintenance therapy 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.***

ABBREVIATIONS. ALL, acute lymphoblastic leukemia; CI, cranial irradiation; VCR, vincristine; Dexa, dexamethasone; Pred, prednisone; L-asp, L-Asparaginase; MTX, methotrexate; 6-MP, 6-mercaptopurine; ARA-C, cytosine-arabinoside; Z_r score, relative standard deviation score.

Growth retardation during treatment for acute lymphoblastic leukemia (ALL) has been demonstrated in many studies.[1–8] Diminished growth during treatment could be caused by several factors including the disease itself, infections, and poor nutrition, but cranial irradiation (CI), chemotherapy, and corticosteroids have been proposed as the main etiologic agents.[2,3,5–8] The greatest part of the growth retardation occurred during the remission induction therapy, a phase of intensive chemotherapy. Catch-up growth did not occur before cessation of therapy.[1,3–5,7,8] Maintenance therapy seemed not to affect growth to a great extent; however, maintenance therapy did prevent a catch-up growth to occur. Several authors assumed that this inhibition of catch-up growth is mainly due to the effect of steroids.[3,6,7] In this study we investigated the influence of corticosteroids on growth during maintenance therapy. We evaluated growth of children with ALL treated according to two different protocols: in the first protocol corticosteroids were a part of the maintenance therapy, in the second protocol maintenance therapy only comprised chemotherapy.

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METHODS

Patients

Forty-six patients (19 girls and 27 boys) with ALL treated at the Department of Paediatric Oncology of the University of Nijmegen Hospital between 1984 and 1991 were included in the study. Patients with high-risk ALL, defined as leucocyte counts >50.000/mm^3 and/or mediastinal enlargement and patients with central nervous system involvement at time of diagnosis were excluded. To avoid the influence of pubertal growth spurt only children less than 10 years of age at diagnosis were included in the study. Age distribution was 1.6 to 9.9 years, median age, 5.1 years.

Treatment

Twenty-seven patients were treated with chemotherapy according to protocol 6 of the Dutch Leukemia Working Group. Protocol 6 comprised: a) Induction treatment with vincristine (VCR), dexamethasone (Dexa) or prednisone (Pred) with L-asparaginase (L-Asp) and two doses of methotrexate (MTX) and prednisone intrathecally; b) Central nervous system prophylaxis with high-dose MTX intravenously, and three doses MTX plus prednisolone intrathecally; and c) Maintenance treatment with 2 weeks of VCR plus Pred or Dexa alternated with 5 weeks 6-mercaptopurine (6-MP), 50 mg/m^2 daily, plus MTX 30 mg/m^2 once a week and 8 courses of MTX, prednisolone and cytosine-arabinoside (ARA-C) intrathecally.

Seventeen out of 27 patients treated according to protocol 6 received Dexa, 6 mg/m^2, during induction and maintenance treatment and in 10 patients Dexa was replaced by Pred, 40 mg/m^2. The duration of induction treatment and central nervous system prophylaxis was 3 months, so maintenance therapy started 3 months after diagnosis. Total duration of treatment was 2 years.

Nineteen patients were treated according to protocol 7 of the Dutch Leukemia Working Group. Protocol 7 comprised: a) Induction treatment with VCR, Pred, daunorubicin, L-asp, cyclophosphamide, ARA-C, and 6-MP and three doses MTX intrathecally; b) central nervous system prophylaxis with high-dose methotrexate (MTX) intravenously, 6-MP orally, and four doses of MTX intrathecally; c) Reinduction treatment with VCR, Dexa, adriamycin, L-asp, cyclophosphamide, ARA-C and 6 thioguanine, and two doses of MTX intrathecally; and d) Maintenance treatment with 6-MP, 50 mg/m^2 daily, and MTX, 20 mg/m^2 once a week. The maintenance treatment started 7 months after diagnosis. Total duration of treatment was 1.5 years. None of the patients in this study received cranial irradiation. In this study we investigated statural growth during 1.5 years of therapy.

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.[9] 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 regular time intervals (3 months) were obtained by interpolation of the individual standard deviation score curves. To measure the influence of therapy properly the relative standard deviation score (Z_r score) was calculated, defined as: $Z_r = Z_t - Z_0$ (Z_t: standard deviation score at time point t after diagnosis, Z_0: standard deviation score at time of diagnosis).

Statistical comparison was made using the *t* test on the Z_r scores. Z_r 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_r 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 ≥.10).

DISCUSSION

Growth retardation during treatment for ALL is of multifactorial etiology.[5] CI as central nervous system prophylaxis in the treatment for ALL has been implicated as the main etiologic agent.[8] 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.[3–5,7,8] Children treated for ALL with chemotherapy and corticosteroids but without CI also showed a diminished growth rate during treatment.[4,7,8] Apart from impaired growth, retardation of bone age development has also been reported during treatment for ALL.[10] 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.[10] 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.[11,12] 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.[13,14] 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.[12] 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,[15] 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.

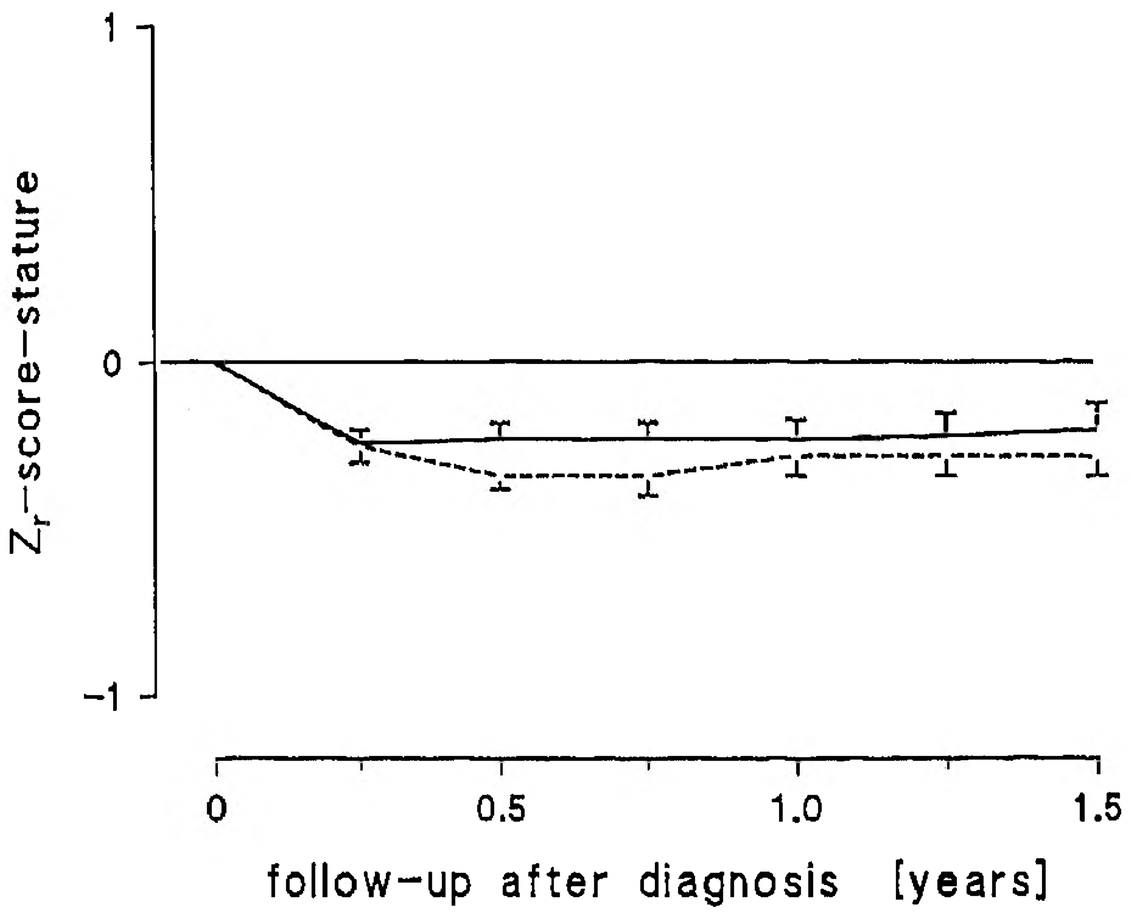

Figure. Mean Z_r score (±standard error) for height of patients treated for acute lymphoblastic leukemia (ALL) according to protocol 6 (maintenance therapy comprising prednisone or dexamethasone, n = 27) (solid line) and according to protocol 7 (maintenance treatment without corticosteroids, n = 19)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

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NOTICE REGARDING THE AMERICAN ACADEMY OF PEDIATRICS NUTRITION AWARD 1996

Nominations for the 1996 AAP Nutrition Award are now being solicited.

Nominations must be in writing and should be limited to one per nominator. The letter should contain a description of the nominee's achievements and state clearly the basis for the recommendation (including references to the literature which describes his/her work). It is requested that the nominee's bibliography be submitted with the nominating letter, together with copies of available reprints. Letters supporting the nomination (*no more than five*) are to be solicited and screened by the nominator and forwarded to the attention of:

Edgar O. Ledbetter, MD, Director
Department of Maternal, Child and Adolescent Health
American Academy of Pediatrics
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Please note that the deadline for award nominations is December 14, 1995.

The Academy appreciates your effort to assist in the appropriate selection of a deserving person for this award.

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The Nutrition Award of the American Academy of Pediatrics was established in 1944. The award is made possible by a grant from the Infant Formula Council.

The Nutrition Award provides an honorarium of $3000 to be awarded under the following stipulations:

1. The award will be made for outstanding achievement in research relating to the nutrition of infants and children.
2. That the award be made for research, which has been completed and publicly reported.
3. That the award be made for research, conducted by residents of the United States and Canada.
4. That the award be made to one individual or for one project.
5. The award is open to all regardless of age. No current member of the Committee on Nutrition shall be eligible for the award.

The Nutrition Award also includes round trip tourist class airfare as well as two days lodging at $150 per diem for the recipient and another person of his/her choice to attend the Annual Meeting of the Academy.

The selection of the Award recipient is made by the Committee on Nutrition of the American Academy of Pediatrics, approved by the Board of Directors, and the award is presented at the Annual Meeting of the Academy.