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Influence of Treatment Modalities on Body Weight in Acute Lymphoblastic Leukemia

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Weight for height of 92 patients (51 girls and 41 boys) treated for acute lymphoblastic leukemia (ALL) was evaluated in a longitudinal study. Fifty-four patients received cranial irradiation (CI) with a dose of 18 or 24 Gy and 38 patients did not receive CI. Seventy-seven patients were treated according to a normal-risk protocol and 15 patients received more intensive chemotherapy according to a high-risk protocol. In most of the patients the duration of follow-up was 12 years for irradiated patients and 4.5 years for the nonirradiated patients.

Thirty of 92 patients were treated according to a protocol without CI, but with a difference in the use of corticosteroids: 19 patients received dexamethasone during the remission-induction and maintenance treatment and 11 patients received prednisone. The influence of dexametha-

son vs. prednisone, sex, CI and high-dose vs. low-dose chemotherapy on weight for height was evaluated. Patients who received dexamethasone showed a significant increase in weight for height immediately after the start of therapy. In patients who received CI, weight for height significantly increased after the first year of treatment. The overweight in these patients persisted during the whole follow-up period. The weight for height of patients treated with prednisone and of patients who did not receive CI was below the mean of the normal population during treatment but was not different from normal after cessation of therapy. No difference in weight gain was seen between boys and girls and between patients who were treated with high vs. normal-risk protocols. © 1996 Wiley-Liss, Inc.

Key words: ALL, cranial irradiation, weight for height

INTRODUCTION

During the last decade many studies have been published on linear growth of children treated for acute lymphoblastic leukemia (ALL), concluding that retardation of linear growth during treatment is a common observation [1-7]. Data about weight gain in these patients are limited. Malnutrition leading to loss of weight, as a consequence of the disease itself or the side effects of chemotherapy, might be one of the causal factors of early growth deceleration. Our clinical impression, however, is that several patients showed excessive weight gain during and after treatment. Other authors also noticed obesity in a number of children during and after treatment for ALL [8-13], but it is not clear if all the treatment modalities are associated with a higher risk for developing obesity.

In this study we evaluated weight development during and after treatment for ALL in order to answer the following questions:

1. Does the Z-score of weight for height decline during the period of treatment of children treated for ALL?
2. Is the pattern of body weight development influenced by treatment?
3. Could we identify treatment factors related to the pattern of weight development in these patients?

PATIENTS AND METHODS

Patients

Ninety-two consecutive patients with ALL treated at the Department of Paediatric Oncology of the University Hospital Nijmegen between 1972 and 1988 were included in the study. Data about age and sex are shown in Table I. Since central nervous system (CNS) involvement could cause hypothalamic dysfunction [14], patients with CNS involvement were excluded from the study. All patients had entered into first remission within 6 weeks after diagnosis. Patients with relapse of their disease were excluded from the study.

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TABLE I. Mean Ages at Diagnosis, the Range of the Ages, and the Sexes of the Patients in Different Treatment Groups

	High-risk (n = 15)	Normal-risk (n = 77)	Protocol 6		CI (n = 54)	Non-CI (n = 38)
			Dexa (n = 19)	Pred (n = 11)		
♂	6	35	11	7	21	20
♀	9	42	8	4	33	18
Mean age (years)	6.7	5.2	5.5	5.5	5.5	5.5
Range	1.1–15.9	0.6–15.5	2.3–12.3	1.6–13.9	0.6–15.9	1.1–14.4

Treatment

Depending on the risk factor of leukemia, patients were divided into two groups. Group I included 77 patients with normal-risk leukemia, i.e., they had a leukocyte count in the peripheral blood $<50,000/\text{mm}^3$, without mediastinal enlargement. This group was treated according to the consecutive protocols 2, 3, 5, and 6 of the Dutch Leukemia Working Group. Protocols 2, 3, and 5 comprised induction treatment with vincristine (VCR), prednisone (Pred), with or without L-asparaginase (L-Asp), and maintenance treatment with 6-mercaptopurine (6-MP), methotrexate (MTX) alternated with VCR and Pred.

Thirty patients were treated according to protocol 6, 19 of whom (group Ia) received induction treatment with VCR, dexamethasone (Dexa) $6 \text{ mg}/\text{m}^2$, and L-Asp and maintenance treatment with 6-MP, MTX alternated with VCR, Dexa. Eleven patients (group Ib) received the same treatment with only a difference in the corticosteroid medication. In these patients Dexa was replaced by Pred $40 \text{ mg}/\text{m}^2$, a dose nearly equal on the basis of glucocorticoid activity.

Group II included 15 patients with high-risk leukemia, i.e., they had a leukocyte count $>50,000/\text{mm}^3$ and/or mediastinal enlargement. They were treated according to a high-risk protocol comprising induction treatment with cyclophosphamide (Cyclo), VCR, Pred, L-Asp, and Adriamycin (Adria). The maintenance treatment consisted of 6-MP, MTX, and Cyclo alternated with VCR, Pred, Adria, and cytosine-arabioside (Ara-C).

Depending on the method of CNS prophylaxis, patients were divided in two groups. Group A, which included 54 patients treated between 1972 and 1984, received cranial irradiation (CI). Thirty-seven patients received a dose of 24 Gy in 13 fractions over 17 days and five doses of MTX and Pred intrathecally (i.t.) and 17 patients received 18 Gy CI in 10 fractions over 14 days and five doses of MTX and Pred i.t. (1972–1984). None of the patients received spinal irradiation. The timing of the CI was 5–6 weeks after diagnosis for all patients. Duration of follow-up was up to 12 years.

Group B, which included 38 patients treated between 1984 and 1988, did not receive CI. The CNS prophylaxis in these patients consisted of high-dose MTX intravenously combined with MTX and Pred i.t. During mainte-

nance treatment, eight doses of MTX, Pred, and Ara-C were given i.t. Duration of follow-up was up to 4.5 years.

Forty-three of 77 patients with normal-risk and 11 of 15 patients with high-risk leukemia received CI. The number of patients during the follow-up period is shown in Table II.

Measurements and Methods

Patients' heights and weights were measured by experienced staff. During the 2 years of treatment, patients were measured 8–12 times per year and during the years of follow-up one to four times per year. Weight for height was studied. In order to compare the patients' groups with the general population, Z-scores were calculated for weight for height using Dutch reference values [15]. The Z-score is defined as the difference between a patients' weight and the stature and sex appropriate mean divided by the corresponding standard deviation. Weight for height is known to be positively skewed distributed, therefore, a log-transformation after translation $\ln(x-c)$ was applied comparable to the method developed by van 't Hof et al. [16]. The translation (c) is stature and sex dependent. The translation was chosen so that a symmetric distribution with regard to the P_{10} , P_{50} , and P_{90} was obtained. The transformed distribution was used for the calculation of the Z-scores. Estimates of the Z-scores at regular time intervals were obtained by interpolation in the individual Z-score curves.

Statistical Analysis

Statistical comparisons were made using Student's t-test and analysis of variance (ANOVA). Significance was accepted for $P < 0.05$.

RESULTS

In order to investigate the influence of different glucocorticoids on body weight development, we compared the Z-scores of weight for height of patients treated according to protocol 6 of the Dutch Leukemia Working Group with Dexa (group Ia) with the Z-scores of patients who received Pred instead of Dexa (group Ib) (Fig. 1). The chemotherapy in both groups was the same and neither of these patients received CI. At diagnosis, the Z-score of

TABLE II. Number of Patients During Follow-Up (n = 92)*

Duration in follow-up (years)	0	0.25	1	2	3	4	4.5	5	6	7	8	9	10	11	12
CI (group A)	45	54	54	54	54	53	52	51	47	45	42	41	33	26	19
No irradiation, exclusive Dexamethasone patients (group B)															
No irradiation															
Protocol 6: Dexamethasone (group Ia)	14	19	19	19	18	13	7								
Protocol 6: Prednisone (group Ib)	8	11	11	11	6	6	5								
Other protocol	7	8	8	8	8	7	6								

*A number of the initial values were missing. At 3 months after diagnosis all patients had entered the averages.

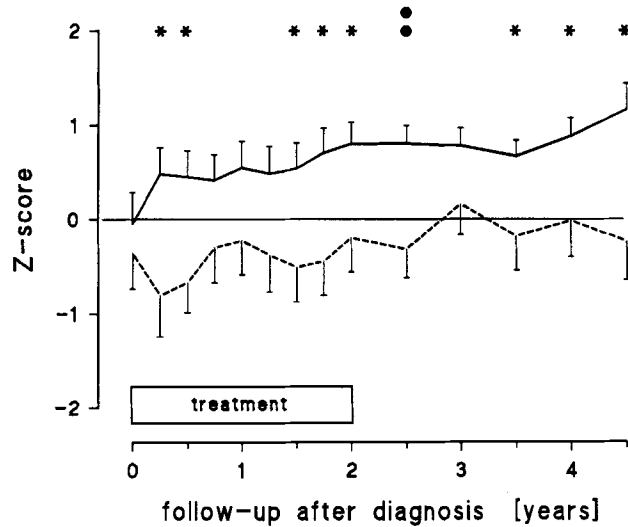


Fig. 1. Mean Z-scores (\pm SEM) of weight for height of patients treated for ALL according to protocol 6 of the Dutch Leukemia Working Group. The patients receiving Dexamethasone (solid line), n = 19, are compared with the patients receiving Prednisone (broken line), n = 11. * $P < 0.05$, ** $P < 0.005$, indicating the t-test significance level.

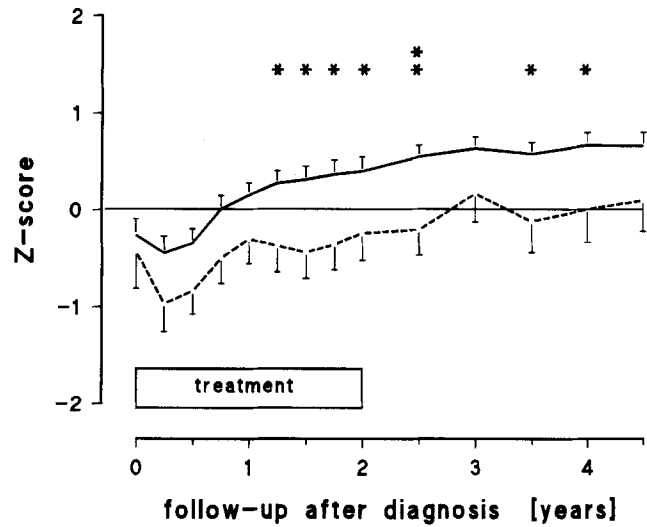


Fig. 2. Mean Z-score (\pm SEM) of weight for height of patients treated for ALL with prophylactic CI (solid line), n = 54, or without prophylactic CI (broken line), n = 19. All patients received Prednisone as corticosteroid. * $P < 0.05$, ** $P < 0.01$, indicating the ANOVA significance level.

weight for height of group Ia was -0.1 ± 1.3 (\pm SD) and of group Ib -0.4 ± 1.1 . This difference is not significant. Three months after start of therapy, the Z-score was 0.5 ± 1.1 for group Ia and -0.8 ± 1.4 for group Ib. The difference is significant ($P = 0.01$). In order to investigate whether the baseline difference in Z-scores of +0.3 in the two groups influenced the significance at 3 months, and to examine whether the difference at 3 months could be an artifact due to the five and three patients that were added to each group, respectively, we calculated the change from the baseline: Z ($Z = Z_x - Z_0$, Z_x is the Z-score at 3 months and Z_0 is the Z-score at diagnosis) of the 14 and 8 patients at 3 months. The Z of the 14 patients treated with Dexamethasone was 0.5 ± 0.8 and of the 8 patients treated with Prednisone was -0.2 ± 0.8 . This difference is also significant ($P = 0.04$). A significant difference between the two groups persisted during the whole follow-up period of 4.5 years.

As treatment with Dexamethasone has a clear influence on weight

for height, 19 patients treated with Dexamethasone, all from protocol 6, were excluded from further analysis.

By means of two-way ANOVA, the influence of sex and CI on weight for height was studied. The Z-scores of weight for height of the irradiated group compared with the Z-scores of patients who did not receive CI are shown in Figure 2. No significant differences between the groups were shown during the first year of therapy. At 2 and 4 years from diagnosis, the Z-scores were, respectively, -0.2 ± 1.1 and 0.0 ± 1.2 for the non-CI group and 0.4 ± 1.1 and 0.7 ± 0.9 for the patients who received CI. These differences are significant, P values, respectively, 0.04 and 0.05.

Figure 3 shows the Z-scores of weight for height of the irradiated patients during the follow-up period of 12 years. At the end of treatment, 2 years after diagnosis, the Z-score was 0.4 ± 1.1 . Two years after cessation of therapy, the Z-scores were more positive: 0.7 ± 0.9 . The Z-score remained above the mean of the normal

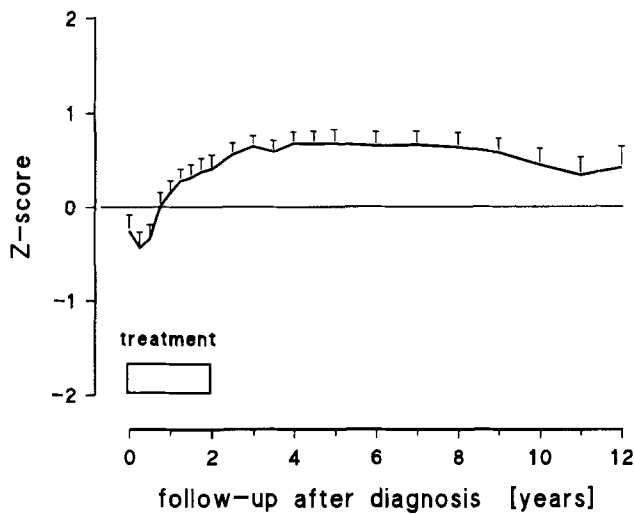


Fig. 3. Mean Z-scores (\pm SEM) of weight for height of the irradiated patients with follow-up of 12 years.

population during the whole period of follow-up. The Z-score 12 years after diagnosis was 0.4 ± 1.0 .

No differences in body weight development were noticed between boys and girls and between patients treated according to a normal-risk protocol vs. patients treated according to a more intensive high-risk protocol.

DISCUSSION

At diagnosis, the weight for height of patients in this study was not significantly different from the weight for height of the normal population. All patient groups, with the exception of the group of patients treated with Dexamethasone, showed loss of weight during the first 3 months of treatment. The underweight of these patients during this phase of therapy could have attributed to the impairment of height growth, which was also demonstrated in our patients [17]. During the next 3–6 months, weight for height of the patients increased to normal, however, weight for height of the irradiated patients further increased during the second year of treatment and the first year after cessation of therapy. After this period, the weight for height of these patients stabilized but the Z-score remained above the mean of the normal population during the whole follow-up.

All studies [8–13,18] but one [19], with respect to weight, reported an increased weight velocity during or after treatment for ALL. Different factors as lack of physical exercise and poor dietary habits [9,13] have been suggested to contribute to the excess weight gain in these patients who have suffered a serious illness. In this study, however, there is clear evidence that two treatment modalities, i.e., craniospinal irradiation and treatment with Dexamethasone, are associated with excessive weight gain. Patients treated without craniospinal irradiation and

patients who received Pred instead of Dexamethasone showed normal weight development during the second year of therapy and after finishing treatment. Another study [13] has also identified craniospinal irradiation as a risk factor for developing obesity. Craniospinal irradiation is also associated with impaired height growth [13,18]. Some authors [13,18] suggested that compromised height is a major contributor of obesity and occurs when height compromise is not accompanied by parallel weight compromise. However, in the study of Schell et al. [18], patients receiving craniospinal irradiation were shown to be at increased risk for abnormally short stature but not for obesity. This finding suggests that other factors than just compromised height are responsible for obesity.

It is well known that especially endocrine disorders causing blunted growth are attended with overweight such as hypothyroidism, hypercortisolism, and growth hormone deficiency. Hypothalamic-pituitary dysfunction involving corticotropin and thyroid-stimulating hormone has not been demonstrated in children treated for ALL [20,21]. The impaired linear growth seen in children after craniospinal irradiation has been thought to be attributed to minor abnormalities in the secretion of growth hormone [22,23]. Dacou-Voutetakis et al. [22] showed transient alterations in growth hormone secretion early after craniospinal irradiation in children treated for ALL. A quantitative reduction in growth hormone secretion during puberty of children treated for ALL has been shown by Crowne et al. [23], suggesting that craniospinal irradiation causes damage to the hypothalamic-pituitary axis affecting the secretion of growth hormone. The hypothalamus seems more vulnerable to radiation damage than the anterior pituitary [24]. Hypothalamic damage per se may cause obesity, however, the reported cases of hypothalamic obesity in children with ALL have always been demonstrated in patients with leukemic infiltration of the brain [14]. Studies on growth hormone profiles of children after low-dose craniospinal irradiation [23] or total body irradiation [25] show a disturbance of frequency modulation of growth hormone secretion. Both studies [23,25] postulate that disturbance of somatostatin secretion is the underlying mechanism for this observation. Our hypothesis is that neurosecretory dysfunction is responsible for the excessive weight gain in patients who received craniospinal irradiation.

Excess of weight gain during and after treatment for ALL is also shown in children treated with Dexamethasone, whereas children treated with Pred in an equivalent dose showed normal weight development. Besides the well-known peripheral effects of corticosteroids on growth and weight [26], glucocorticoids also exert an effect on the regulation of growth hormone secretion [27]. High-dose Pred (40 mg/m²/day) used in the treatment for ALL resulted in decreased growth hormone secretion during deep sleep as well as in response to arginine, insulin, and growth hormone releasing hormone administration [28]. Dexamethasone, in a dose of 10 mg/m²/day, completely suppressed the spontaneous growth hormone secretion in patients treated

for ALL [29]. The inhibiting action of corticosteroids on growth hormone responses seems to be mediated by an enhancement of the somatostatin effect at the pituitary level [27].

Increase of weight in patients treated with Dexamethasone is immediately shown after start of treatment, while all other patients show loss of weight during this phase of intensive chemotherapy. The loss of weight of most patients during the first months of therapy is presumably due to the side effects of cytotoxic drugs such as nausea and vomiting resulting in inadequate nutrition. Dexamethasone, and not Prednisone, appears to circumvent this action and leads immediately after the start of treatment to excessive weight gain. It could be speculated that excessive weight gain after treatment with Dexamethasone is also a consequence of neurosecretory dysfunction and that Dexamethasone exerts a stronger central effect than Prednisone.

In patients who had undergone cranial irradiation, the overweight persisted during the whole follow-up period of 12 years. In view of the age distribution of the patients included in the study, we may conclude that, compared to age and height matched controls, the overweight of these patients persisted during puberty and adolescence. It is not yet clear if overweight in the Dexamethasone-treated patients also persists during such a long period of time.

Dexamethasone has proven in *in vitro* studies to have a stronger antileukemic effect than Prednisone [30]. So, in the future, Dexamethasone could become a more common drug in the treatment of ALL. As obesity has serious long-term psychological and medical consequences, awareness of this potential complication could contribute to its prevention.

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