GROWTH OF CHILDREN DURING AND AFTER TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

A biometric study to the causal factors for growth retardation

J.J. Groot-Loonen
Chapter 1 General introduction

1.1 Introduction 6
1.2 Acute lymphoblastic leukemia 6
  1.2.1 Disease characteristics of ALL
  1.2.2 Treatment of ALL
  1.2.3 Nutritional state
1.3 Human growth 8
  1.3.1 Introduction
  1.3.2 The growth plate
  1.3.3 Growth hormone
  1.3.4 Growth hormone binding protein
  1.3.5 Insulin-like growth factors
  1.3.6 IGF receptors
  1.3.7 IGF binding proteins
  1.3.8 Paracrine factors
  1.3.9 Thyroid hormone
  1.3.10 Vitamin D
  1.3.11 Growth in puberty
1.4 Influence of cranial irradiation on growth 16
1.5 Influence of corticosteroids on growth 17
1.6 Influence of chemotherapy on growth 18
1.7 Aim of the study 19
1.8 Patients and methods 20
  1.8.1 Introduction
  1.8.2 Treatment of patients in this study

Chapter 2 Influence of treatment modalities on prepubertal growth in children with acute lymphoblastic leukaemia
Pediatric Hematology and Oncology 1995; 12:343-353

2.1 Abstract 29
2.2 Introduction 29
2.3 Patients and methods 30
2.4 Results 32
2.5 Discussion 33

Chapter 3 Chemotherapy plays a major role in the inhibition of catch-up growth during maintenance therapy for childhood acute lymphoblastic leukemia
Pediatrics 1995; 96:693-695

3.1 Abstract 44
3.2 Introduction 44
3.3 Patients and methods 45
3.4 Results 47
3.5 Discussion 47
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Catch-up growth in acute lymphoblastic leukaemia; influence of treatment modalities on timing.</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>Intensity of catch-up growth during and after treatment for acute lymphoblastic leukaemia</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>Shortened and diminished pubertal growth in boys and girls treated for acute lymphoblastic leukaemia</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>Influence of treatment modalities on body weight in acute lymphoblastic leukemia</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>General discussion</td>
<td>112</td>
</tr>
<tr>
<td>9</td>
<td>Summary</td>
<td>122</td>
</tr>
</tbody>
</table>
Chapter 10 Samenvatting 128

Chapter 11 References 135

List of abbreviations 149

Dankwoord

Curriculum vitae

List of publications
CHAPTER 1

GENERAL INTRODUCTION
1.1 Introduction

The incidence of cancer in children < 16 year is one per 10,000. In the Netherlands 350-400 new cases are diagnosed annually. Acute Lymphoblastic Leukemia (ALL) is one of the most common malignancies in children. Out of 350-400 patients with childhood cancer approximately 80 patients are diagnosed to have ALL.

Since the introduction of central nervous system (CNS) prophylaxis and the development of more intensive chemotherapeutic regimens, the overall event free survival rate in ALL improved from 4% in 1972-1973 to 66% in 1988-1991. Therefore it is important to pay attention to the late sequelae of therapy. Growth retardation is a well-known side-effect in children treated for ALL. The causal factors for disturbed growth in these patients can be: the disease itself, the treatment modalities: chemotherapy, radiotherapy and corticosteroids and loss of weight due to illness or treatment. Especially cranial irradiation (CI) as CNS prophylaxis has been associated with a significant loss of standard deviation score (SDS) for height at final height. About the influence on height at final height, of treatment without CI, conflicting results have been published. Holm et al reported about normal final height of these patients while in another study significant decrease in final height was noticed.

1.2 Acute Lymphoblastic Leukemia

1.2.1 Disease characteristics of ALL

Acute lymphoblastic leukemia (ALL) is a disorder characterized by the uncontrolled growth and proliferation of immature lymphoid cells. The signs and symptoms of the child presenting with ALL reflect the degree of bone marrow infiltration with leukemic cells and the extent of extramedullary disease spread.
General Introduction

In the pathogenesis of ALL genetic factors are presumed to play a significant role\textsuperscript{101}. Evidence for this relationship is based on several observations including the association between various constitutional chromosomal abnormalities and childhood ALL, the occurrence of familial leukemia, the high incidence of leukemia in identical twins and the demonstration of karyotypic abnormalities in leukemic cells of children with this disease. In addition to genetics environmental factors, viral infection and immunodeficiency may predispose to leukemia\textsuperscript{101}.

Morphologic, immunologic, cytogenetic and biochemical characterizations of leukemic lymphoblasts have confirmed that ALL is a biological heterogeneous disorder. The heterogeneity reflects the fact that the leukemia may develop at any point during the multiple stages of normal lymphoid differentiation.

Although ALL can occur at any age, the peak incidence of ALL occurs at approximately 4 years of age.

1.2.2 Treatment of ALL

Without effective antileukemic therapy, ALL is an uniformly fatal disease. The recognition that ALL is a heterogeneous disease and that children can be stratified into various risk groups has profoundly influenced therapy. Modern ALL treatment regimens divide therapy into four main treatment elements: remission induction, central nervous system preventive therapy, consolidation and maintenance therapy.

In the treatment of ALL, combination chemotherapy is the primary therapeutic modality. In the Netherlands, children with ALL are treated according to the protocols of the Dutch Childhood Leukemia Study Group (DCLSG) since 1972. In the period of 1972-1995 the DCLSG has implemented eight protocols for the treatment of childhood acute lymphoblastic leukemia.

Protocol 1 represented a non-invasive treatment protocol\textsuperscript{147}. The protocols 2 to 6 (1973-1988) were based on Pinkel’s principle of “Total Therapy”\textsuperscript{100}. Pinkel laid the foundation of the current treatment strategy for childhood ALL. He was the first to design a treatment protocol which turned out to be curative for patients with
Chapter 1

ALL. The general procedure of Pinkel consisted of 1. remission-induction therapy with multiple antimetabolite chemotherapy and prednisone. 2. prophylactic central nervous system therapy with cranial irradiation and intrathecal methotrexate, early during complete remission, to eliminate residual leukemic cells in the central nervous system and 3. continuation chemotherapy, consisting of simultaneously administered multiple drugs for 2 to 3 years to eradicate all remaining leukemic cells 100.

Cranial irradiation has been associated with late sequelae, notably with neuropsychologic dysfunction and growth retardation 66,91,106,131 and has therefore, since 1984, been omitted from the Dutch protocols.

The protocols 7 and 8 (1988-1995) were developed after the German Berlin-Frankfurt-Münster (BFM) group 54. In these protocols patients were no longer treated on a uniform or standard treatment regimen but patients were assigned into different risk groups on the basis of prognostic factors, stratifying treatment according to the prognostic factors.

1.2.3 Nutritional state

Both ALL as a serious illness and the treatment modalities applied in the treatment for ALL can have a negative influence on the appetite of the patients leading to a bad nutritional state. Bad nutrition followed by loss of weight can affect growth 4.

1.3 Human growth

1.3.1 Introduction

Height is a strongly genetically determined characteristic and under favourable conditions a child will growth according to a predominated growth curve 4. Under normal conditions, parental heights can give a good indication of the target height to which a child is aiming. Tanner described growth as a target-seeking function 136 and he postulated that growth is controlled by a central regulator which senses body size to a setpoint for target size and accelerates or decelerates growth rate accordingly. Measurement of growth is important for monitoring the health of a child. In children with ALL both the disease and
the treatment can have an influence on growth. These environmental influences on the growth process are at their maximum when growth is at its fastest.

In childhood three principal phases of growth can be distinguished: 1. the rapid and rapidly decelerating growth of infancy, representing the last phase of fetal growth, 2. the steady and slowly decelerating growth of midchildhood and 3. growth of puberty. Growth during infancy is regulated principally by nutrition and local growth factors, while growth during childhood is largely determined by growth hormone (GH) secretion and thyroid hormones. Growth during puberty is beside growth hormone and thyroid hormones also endocrinological dependent of sex steroids. The sex steroids have a direct anabolic action and a modulating effect on GH secretion. A clear rise in GH secretion occurs during puberty.

1.3.2 The growth plate

Growth of the long bones is a remarkable integrated process with a coordinated interaction of systemic and local factors in the developmental process. Elongation of bones proceeds by endochondral ossification, whereby a cartilaginous growth plate moves progressively distal from the diaphyseal centre, leaving a front of newly ossified bone. Control of the pace of the growth process is largely an endocrine phenomenon, while local control by paracrine and autocrine factors is essential to coordinate cellular and matrix events. (figure 1.1).

Figure 1.1: The long bone.
1.3.3 Growth hormone

The principle hormone influencing midchildhood growth is growth hormone (GH). GH secretion occurs in a pulsatile fashion. The secretion of GH is regulated by neurotransmitters and by hormonal and metabolic substrates\(^35\) (figure 1.2).

The final common pathway for integration of these signals involves two hypothalamic neuropeptides; growth hormone releasing hormone (GHRH) and somatostatin (SS). GHRH controls synthesis and release of GH, while SS modulates its pulsatile secretion\(^56\).

Secretion of GH results in production of IGF-1 especially by the liver. The regulation of

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**Figure 1.2:** The general pattern of endocrine regulation of growth. (GHRH: growth hormone releasing hormone, SS: somatostatin, GH: growth hormone, IGF-1: insulin-like growth factor 1).
GH release is also influenced by the production of IGF. IGF-1 inhibits basal GH gene transcription, suggesting a feedback role for IGF-1 in GH regulation \(^{154}\). The somatotroph populations of the pituitary are differentially responsive to IGF-1 and SS. SS is a much more effective inhibitor of total GH release than IGF-1 and appears to affect most, if not all, somatotrophs \(^{58}\). At the cellular level it would appear that IGF-1 inhibits only the secretion of newly synthesized GH, while SS inhibits both stored and newly synthesized GH pools \(^{124}\).

Secretion of GHRH is also inhibited by IGF-1 in vitro \(^{125}\). GH regulation is largely dependent on GHRH/SS equilibrium and probably controlled by GH and IGF-1 forming systemic and local feedback loops (figure 1.3).

The human growth hormone (hGH) gene is present on the long arm of chromosome 17 and is part of the hGH gene cluster which consists of five very similar genes \(^{56}\). Transcription of the hGH\(_1\) gene leads to the synthesis of hGH a protein with a molecular weight of 22 kD, which accounts for 90% of the GH synthesized. The excision of the second intron of the hGH\(_1\) gene leads to an alternative splicing site. This alternative splicing forms the basis of the 20 kD variant of hGH which comprises 5-10% of total pituitary hGH \(^{76}\). The two forms are co-secreted and similar forms are observed in the plasma with the 22 kD form predominant at 75%, the 20kD variant 20% and acidic hGH 5%. The molecular forms of hGH secreted in vivo are independent of the secretory stimuli applied to the somatotroph. GHRH, exercise and sleep related GH-secretory bursts all produce the GH forms: 22 kD, 20 kD and acidic GH \(^{12}\).

1.3.4 Growth hormone binding protein

In plasma, large forms of GH can be detected with molecular weights in the order of 40-70 kD \(^{56}\), representing the interaction of GH with a circulating protein \(^{10}\). This high-affinity, low capacity binding protein for hGH represents the extracellular portion of the monomeric GH receptor \(^{11}\). It has more affinity for the 22 kD form than for the 20 kD variant and approximately 50% of circulating 22 kD hGH is estimated to be in a complexed form with it \(^{9}\). The hypothesis is that the binding protein may have an
Figure 1.3: Pituitary GH release as a net result of an intricate interplay between two hypothalamic hormones, the stimulatory GH-releasing hormone (GHRH) and its inhibitory counterpart somatostatin (SS). The stimulating effect of GHRH does not occur before the concentration of SS, in the hypophyseseal portal level, is low.
important effect on the in vivo kinetics of GH, prolonging the biological persistence of GH in vivo.

The pattern of secretion of GH may play an important role in the control of body growth. The rapid changes in circulating GH levels require efficient adaptation of the somatogenic receptors to induce the specific signals necessary to promote growth. It has been speculated that the low basal level of GH between pulses is important in that it allows receptor recovery. The rapid changes in GH secretion must be reconciled with the buffering effect of two factors: the presence of near constant circulating levels of IGF-1 bound to specific IGF-binding proteins and the fairly well-conserved levels of GH-binding protein in physiological and pathological conditions.

The effect of GH on the growth plate, to effect growth, is complex. It is thought that GH acts on growth via a dual mechanism (figure 1.4):

- A direct stimulation through specific receptors on growth plate chondrocytes.
- An indirect action through insulin like growth factor-1 (IGF-1).

1.3.5 **The insulin-like growth factors**

There are 2 insulin-like growth factors of which at least one (IGF-1) is GH dependent. These peptide factors mediate many of the anabolic and mitogenic actions of GH. The IGF’s were so named because of their evolutionary and structural relationship with proinsulin. The diverse actions of the factors include:

- Stimulation of DNA synthesis and cell multiplication.
- Promotion of the incorporation of sulphate into cartilage.
- Insulin-like activity in extraskeletal tissues for instance lipolyse.

IGF-1 is a basic peptide of 70 amino acids and IGF-2 is a slightly acidic peptide of 67
Figure 1.4: The effect of growth hormone on the epiphyseal growth plate.

- GH stimulates precursor cells.
- Differentiating cells become IGF-1 responsive.
- The gene encoding for IGF-1 is expressed in these cells, resulting in increased local synthesis of IGF-1.
- Locally produced IGF-1 acts by autocrine and paracrine mechanisms.
- The local IGF-1 production controls cell multiplication and differentiation.

amino acids. The human IGF-1 gene spans approximately 95 kb of genomic DNA on the long arm of chromosome 12. The human IGF-2 gene is located on the short arm of chromosome 11, immediately adjacent to the insulin gene and spans 35 kb of genomic DNA. Complex control of IGF gene expression contributes to variability in tissue expression. The liver is a major site of IGF production and is the main contributor to the circulating pool of IGF-1. However, many other cells and tissues produce IGF-1. Locally produced IGF-1, stimulated by GH, acts via an autocrine/paracrine mechanism probably distinct from the endocrine circulating IGF-1.
IGF-1 is considered an important postnatal growth factor because of rising levels at term in humans. IGF-2 has been regarded as an essential fetal growth factor as it is expressed in diverse tissues throughout gestation, however serum IGF-2 levels remain significant and constant during the human lifespan. The postnatal role of IGF-2 in humans is unresolved. Expression of IGF-2 messenger RNA has been demonstrated in diverse primary tumours and malignant cell lines, including many sarcomas, Wilms’ tumor, phaeochromocytoma, neuroblastoma and hepatoblastoma. Investigators speculate that tumor growth is stimulated by IGF-2 autocrine action.

In the human foetus serum IGF-1 levels increase with gestational age. IGF-1 levels in human newborn serum are generally 30-50% of adult levels. Serum concentrations rise gradually during childhood attaining adult levels by the onset of sexual maturation. During puberty IGF-1 concentration rise to levels 2-3 times those seen in adults. Accordingly IGF-1 levels during adolescence correlate better with stages of puberty than with chronological age.

From findings that patients with GH receptor defects show a pubertal rise in serum IGF-1 despite a decline in GH levels it has been concluded that there is a direct effect of sex steroids upon IGF-1. Serum IGF-1 levels demonstrate a progressive age-associated decline in adults.

Serum IGF-2 levels do not follow the developmental pattern of IGF-1 levels. Human newborn concentrations of IGF-2 are approximately 50% of adult levels. Adult concentrations are attained by 1 year of age without the marked pubertal rise seen with IGF-1. There is little, if any, subsequent decline.

1.3.6 IGF-receptors

The IGF’s can bind with low affinity to insulin receptors but two distinct IGF receptors are discriminated. The type-1 IGF receptor is capable of binding both IGF-1 and IGF-2 with high affinity. The type-2 IGF receptor is entirely distinct from the insulin and type-1 IGF receptors and bears no structural similarity to them. Studies have indicated that the classic mitogenic and metabolic actions of both IGF-1 and
IGF-2 are mediated through the type-1 IGF receptor. Several experimental observations provide evidence for IGF-2 actions mediated by the IGF-2 receptor. Minniti et al reported that IGF-2 appears capable of acting as an autocrine growth factor for human rhabdomyosarcoma cells, actions apparently mediated through the type-2 receptor. This study provides a potential mechanism for signal transduction through the type-2 IGF receptor, but it is still generally assumed that most actions of IGF-2 are mediated by the type-1 IGF receptor.

1.3.7 IGF-binding proteins (IGFBP's)

The IGF's circulate in plasma complexed to a family of binding proteins. To date six IGFBP's have been characterized. These IGFBP's regulate IGF availability between tissues and the circulation, extent the serum half life of the IGF peptides, transport IGF's to target cells and modulate the interaction of the IGF's with their cell surface receptors. In the circulation about 75% of the IGF's are complexed with IGFBP-3. The remainder of circulating IGF's are bound to lower molecular weight IGFBP's, mainly IGFBP-1,-2 and -4. All members of the IGFBP family bind IGF-1 and IGF-2 with approximately equal affinity. The amount of free IGF in serum is very low and constitutes approximately 1-5% of the total serum IGF concentration.

The IGFBP synthesis is influenced by hormonal (GH, insulin, IGF’s, glucocorticoids) as well as metabolic and nutritional factors. The IGFBP's are differentially expressed in various tissues depending on the stage of development and the type and age of the organ system.

Local modulation of the IGFBP's (and therefore of IGF activity) can be achieved through proteolytic modification by proteases derived from chondrocytes or at the metaphyseal interface from osteoblastic cells.

The physiological significance of limited proteolysis of IGFBP's is that protease activity results in decreased affinity of the IGFBP for IGF peptides, leading to increase bioavailable IGF peptides when needed.

IGFBP's have been found in all biological fluids. The concentrations of the various IGFBP's...
vary among biological fluids. IGFBP-1 is the major IGFBP in human amniotic fluid, and IGFBP-2 is prominent in cerebrospinal fluid. IGFBP-3 is the major IGFBP in normal human serum and demonstrates clear GH dependence.

1.3.8 Thyroid hormone
Thyroxine has both an indirect and direct effect on the growth plate. An euthyroid state is essential for normal pituitary GH secretion.

1.3.9 Vitamin D
1,25(OH)₂ vitaminD₃, which could be included as an endocrine factor in the steroid family, regulates calcium absorption and availability. Chondrocytes can convert the 25(OH) vitamin D to the active form for action on vitamin D receptors in the proliferative and hypertrophic zones of the growth plate. 1,25(OH)₂D₃ shows a biphasic effect on growth, stimulating in-vitro chondrocyte proliferation at low doses and inhibiting at higher doses.

1.3.10 Paracrine and other growth factors
The relative roles of GH and the IGF’s in cartilage and bone development are not entirely clear. A current hypothesis is that GH is necessary within the growth plate for stimulating recruitment of the germinal/progenitor chondrocyte cells to stimulate them to clonal proliferation which is sustained by locally generated (GH dependent) or systemically derived IGF-1 (figure 1.4).

These endocrine stimuli, essential to normal growth, can be regarded as outside factors which provide the fuels and determine the pace for bone growth. However, locally expressed autocrine or paracrine factors govern the precise timing and coordinate cellular and matrix events which permit growth to proceed in an orderly manner.

Other growth factors such as transforming growth factor-b, the bone morphogenic proteins, platelet-derived growth factor, basic fibroblast growth factor, cytokines IL-1b, IL-6 and IL-8 and the IGF’s interact at many levels with the functions of each of the others, cells and matrix constituents to enhance or inhibit processes and induce proliferation, differentiation,
enzyme expression and cell death \(^{55,117}\).

### 1.3.11 Growth in puberty

The pubertal growth spurt encompasses the most rapid phase of growth after the neonatal period. The pubertal growth spurt begins in girls prior to the onset of secondary sexual characteristics \(^{138}\). Growth spurt in boys starts on the average 2 years after the average age of onset in girls.

The pubertal growth spurt is mediated by several endocrine influences. Sex steroids exert a direct effect upon the growing cartilage and stimulate local production of IGF-1 \(^{5}\). Increasing sex-steroid production stimulates increased amplitude (but not increased frequency) of growth hormone secretion at puberty. The increased growth hormone secretion in turn stimulates increased production of IGF-1. Thus pubertal growth is not only accompanied by higher levels of sex steroids but by increased episodic secretion of growth hormone and serum IGF-1 \(^{53}\). These direct and indirect effects of sex steroids cause the increased growth rate characteristic of the pubertal growth spurt. Thyroid hormone is necessary in sufficient amounts to allow the pubertal spurt to proceed \(^{132}\).

When the pubertal growth spurt be analysed by means of individual height velocity curves, the phase differences between the individual curves must be taken into account.

### 1.4 Influence of cranial irradiation on growth

Cranial irradiation (CI) can cause damage to the hypothalamic-pituitary function \(^{20,106,123,148}\). The radiation-induced damage may result in single or multiple pituitary hormonal deficiencies \(^{29}\). The prevalence of hormonal deficiencies is dependent on the dose and fractionation schedule of the irradiation administered to the hypothalamic-pituitary axis as well as the time elapsed since irradiation \(^{20,29}\). The higher the dose of irradiation, the higher the incidence and the shorter the lag time between treatment and development of GH deficiency. The age of the patient at the time of irradiation may also be an important variable, with younger patients being more vulnerable than adults \(^{128}\).
Growth hormone deficiency (GHD) is the most frequent pituitary abnormality that occurs after CI $^{20,29,30,106}$. GHD appears to develop following CI which exposes the hypothalamic-pituitary region to doses in excess of 18-20 Gy $^{106}$. Radiation-associated GH deficiency appears to result from damage to the hypothalamus, although at very high doses (>50Gy) the pituitary itself may also suffer direct damage $^{1,106,122}$. Although the mechanism of radiation damage to the hypothalamus or pituitary is not known, it must involve a direct injury to the cells responsible for hormonal secretion, an injury to the stroma or its microvasculature or an injury to the vascular channels that transfer the hypothalamic hormones to the pituitary. The correlation between the frequency of TRH-dependent hypothyroidism and the interval between treatment and evaluation is compatible with both vascular injury and damage to parenchymal cells which have a slow rate of turnover $^{29}$.

In the treatment for ALL prophylactic CI, with a dose of 18-24 Gy, has been used to protect patients against central nervous system relapse. Growth hormone deficiency, as a sequela of CI, has been suggested to be the major factor for the growth retardation in these patients. However Brauner et al $^{20}$ showed in a prospective study that in children treated with CI no significant growth retardation could be attributed to GHD during the first two years after CI while in children with ALL growth retardation occurred immediately after start of therapy. Dacou-Voutetakis described in 1977 an immediate suppressive effect of irradiation upon the hypothalamic-pituitary function, suggesting that the poor growth velocity shown by children during the first year of treatment is due to radiation-induced transient GH deficiency. These findings could not be confirmed by other investigators. In a longitudinal study Marky et al $^{83}$ showed no difference in GH secretion during the period of treatment, between patients who received no irradiation and patients who received irradiation with a dose of 18-24 Gy as CNS prophylaxis. So the early growth retardation in children treated for ALL cannot be ascribed to GH deficiency caused by CI.

Another well recognized side-effect of CI, which can influence final height, is development of precocious puberty. Early onset of puberty mainly occurs after high-dose CI but this side effect has also been described in girls treated for ALL with CI in a dose of 18-24 Gy $^{73,128,143}$.
1.5 Influence of corticosteroids on growth

In the treatment of ALL remission-induction therapy always comprises corticosteroids. Several protocols also include corticosteroids during maintenance therapy. Long-term treatment with corticosteroids during childhood is a well recognized cause of growth impairment.

The mechanisms of growth suppression by corticosteroids are multifactorial with altered endocrine and tissue/end-organ responsiveness to many physiological regulators of the growth process. Corticosteroids regulate a vast array of synthesis pathways thereby controlling the production of various enzymes, structural proteins, receptor proteins and growth regulatory peptides and proteins (e.g. growth hormone, the growth hormone receptor, IGF-1 and most of the IGF-binding proteins). High non-physiological levels of corticosteroids distort the fine balance of these factors. Acute and chronic exposure to corticosteroids may stimulate or inhibit pituitary growth hormone release through a mixture of hypothalamic and pituitary effects on growth hormone releasing hormone, somatostatin and growth hormone synthesis.\textsuperscript{45}

The effect of excessive corticosteroids on the growth plate is shrinkage. As cell proliferation slows, the columns of proliferative chondrocytes become shorter and intercellular matrix components are disrupted by enzyme digestion.\textsuperscript{78} It is likely that similar effects are occurring in adjacent bone, with a shift in balance from mineral accretion toward mineral loss which eventually leads to osteoporosis.\textsuperscript{78} Collagen synthesis is reduced, yet degradation is increased as proteolytic enzymes are released to enhance degradation of the intercellular cartilage and bone matrix.

Some of these effects are part of a more generalized catabolic milieu resulting from the wider systemic impact of corticosteroids on fuel metabolism and anabolic processes.\textsuperscript{13,109}
1.6 Influence of chemotherapy on growth

Chemotherapy is the major part of the treatment for ALL and is administered both intravenously and intrathecally. The duration of chemotherapy in the treatment for ALL is at least 1.5-2.0 years. Little is known about the influence of chemotherapy on the growth process. Histologic examination of specimens of the distal femoral growth plates of 8 patients treated for osteosarcoma with preoperative chemotherapy did not show complete growth arrest. In these patients the gross thickness of the plates was preserved. Columnar arrangement of the cells was minimally disrupted. The number of proliferative cells in each column was decreased and the number of hypertrophic cells was increased slightly. The metaphysis showed longitudinal trabeculations with a high chondroid content. Growth arrest lines were evidenced by transverse trabeculations with a high osteoid content, alterations which were ascribed to chemotherapy.

1.7 The aim of the study

The relative contributions of the disease, chemotherapy, corticosteroids or cranial irradiation to the growth failure noted after treatment for childhood ALL are not well understood.

To investigate the influence on growth of the distinct entities: the disease ALL itself, nutritional status reflected by weight, chemotherapy, radiotherapy and corticosteroids. Could risk factors in the treatment for ALL be identified being responsible for growth retardation?

In order to answer these questions a retrospective analysis of longitudinal growth data of
Chapter 1

children treated for ALL in the University Hospital Nijmegen, is performed.

In chapter two growth during the period of treatment and 2.5 years after cessation of therapy is analysed. Only prepubertal patients are included in this analysis. The different influences of chemotherapy versus radiotherapy, high-dose chemotherapy versus low-dose chemotherapy and radiotherapy with a dose of 18 Gy versus radiotherapy with a dose of 24 Gy are investigated.

In chapter three growth during maintenance therapy is analysed. Growth of patients who received both chemotherapy and corticosteroids during maintenance therapy is compared with growth of patients who only received chemotherapy during this phase of therapy. The patients included in this study didn't receive cranial irradiation as central nervous system prophylaxis.

In the chapters four and five catch-up growth is investigated. The different influences of cranial irradiation, chemotherapy and corticosteroids on the timing of catch-up growth is described in chapter four and the influences of the different treatment modalities on the intensity of catch-up growth is described in chapter five.

In chapter six growth during puberty of boys and girls is analysed. The patients in this study all received cranial irradiation as central nervous system prophylaxis. Additionally data about final height, age at menarche and bone age development of these patients is described.

The influence of body-weight development during and after treatment for ALL is analysed in chapter seven. The influence of dexamethason versus prednison, cranial irradiation and high-dose versus low-dose chemotherapy on weight for height is evaluated.
1.8 Patients and Methods

1.8.1 Introduction

In our centre treatment for ALL has been given according to the consecutive protocols of the Dutch Childhood Leukaemia Study Group (DCLSG). Patients treated from 1972 to 1980 received as CNS prophylaxis cranial irradiation with a dose of 24 Gy. From 1980 to 1984 the irradiation dose for cranial irradiation was reduced to 18 Gy. In 1984 cranial irradiation was omitted from the DCLSG protocols. In the period 1972 to 1988 the maintenance therapy consisted of the combination of chemotherapy and corticosteroids. In the protocols commenced after 1988 the maintenance therapy did not comprise corticosteroids. The build up of the different protocols enabled us to investigate the influence of cranial irradiation in two different dose schedules, of chemotherapy and of corticosteroids on growth.

1.8.2 Treatment of patients in this study

37 Patients treated from 1972 to 1980 received cranial irradiation with a dose of 24 Gy as central nervous system prophylaxis (DCLSG protocols 2 to 4).

15 Patients treated from 1980 to 1984 received cranial irradiation with a dose of 18 Gy (DCLSG protocol 5).

46 Patients were not irradiated but received chemotherapy as central nervous system prophylaxis (DCLSG protocols 6 and 7).

Of the 46 patients who didn't receive cranial irradiation, 27 patients received maintenance therapy comprising chemotherapy and corticosteroids (protocol 6) and of 19 patients maintenance therapy comprised only chemotherapy (protocol 7).

Of the 27 patients who received both chemotherapy and corticosteroids during maintenance therapy, the treatment of 17 patients comprised dexamethason and 10 patients received prednison (table 1.1).

Height and weight of each patient were measured by experienced staff. A stadiometer was used to measure height. During the period of treatment patients were measured 8 to 12 times.
Chapter 1

per year and during the period of follow-up 1 to 4 times per year.
The analysis of the curves and statistical methods used are described in the various chapters.

Table 1.1  Numbers of patients in various treatment protocols.

<table>
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32
General Introduction
CHAPTER 2

INFLUENCE OF TREATMENT MODALITIES ON PREPUBERTAL GROWTH IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA


Pediatric Hematology and Oncology 1995; 12:343-353
2.1 Abstract

Statural growth of 85 prepubertal children treated for acute lymphoblastic leukaemia was evaluated in a longitudinal study over 4.5 years. Patients were divided into three groups according to central nervous system prophylaxis: 37 received cranial irradiation with a dose of 24 Gy, 15 received 18 Gy and 33 were not irradiated. According to the risk of leukaemia, patients were divided into normal-risk (n=74) and high-risk patients (n=11). Duration of treatment was two years. All patients showed growth retardation during treatment. The relative standard deviation score for height declined from 0 to -0.7 for the irradiated patients and to -0.2 for the non-irradiated group (p=0.0001). No difference in growth pattern was seen between cranial irradiation with 18 versus 24 Gy and chemotherapeutical treatment according to high-risk versus normal-risk protocols. However, we demonstrated a synergistic negative effect of more intensive chemotherapy and cranial irradiation on growth.

2.2 Introduction

In the treatment of acute lymphoblastic leukaemia (ALL) introduction of central nervous system (CNS) prophylaxis and intensification of cytoreductive therapy, have led to an increased number of children with long-term survival. It is therefore important to pay attention to the late sequelae of therapy. Cranial irradiation (CI), with a dose of 18-24 Gy, as CNS prophylaxis in the treatment of ALL has been associated with late sequelae, notably with neuropsychologic dysfunction and growth retardation. In an attempt to avoid these side effects CI has been omitted from the Dutch protocols since 1984. Although much attention has already been paid to the statural growth of children treated for ALL several items are still under discussion:
Prepubertal growth in ALL

- Is there a difference in height of children treated with CI with a dose of 18 Gy compared to those irradiated with 24 Gy?
- What is the influence of chemotherapy (CT) on height of children treated for ALL?

Results of the various studies are often difficult to compare due to differences in treatment, the inclusion of both prepubertal and pubertal patients, the variable methods of analysis and the mixture of cross sectional and longitudinal observations.

In this paper a longitudinal study on statural growth of prepubertal children treated for ALL is presented. To avoid pubertal influence, the follow-up of the patients in this study is confined to 4.5 years, as there is an indication that after treatment for ALL further growth retardation occurs during puberty. The height of children treated with CT alone is compared to the height of patients who received CI. The influence of two different radiation protocols (18 and 24 Gy) and the influence of more versus less intensive CT on height of children treated for ALL is investigated.

2.3 Patients and methods

Patients. Eighty-five patients (47 girls and 38 boys) with ALL treated at the Department of Paediatric Oncology of the University Hospital Nijmegen, between 1972 and 1988, were included in the study. Children with CNS involvement at the time of diagnosis were excluded. To avoid the influence of pubertal growth spurt, only children with age at diagnosis less than 10 years were included in the study. The age distribution of the patients is shown in figure 2.1. The data of the girls were only used for analysis up to the age of 13.0 and boys till the age of 14.5 years. None of the patients selected according to these criteria showed pubertal development during the study period. All patients had entered into first remission within 6 weeks after diagnosis and 5 patients relapsed. They remained in the study till the time of relapse.
**Treatment.** Depending on the risk factor of leukaemia, patients were divided into two groups:

I. Patients with normal-risk leukaemia, defined as leucocyte count in the peripheral blood $< 50,000/mm^3$, without mediastinal enlargement, were treated according to the consecutive protocols 2, 3, 5, and 6 of the Dutch Leukaemia Working Group, comprising induction treatment with vincristine (VCR) 2 mg/m$^2$, prednisone (Pred) 40 mg/m$^2$ or dexamethasone (Dex) 6 mg/m$^2$, with or without L-asparaginase (L-Asp) 200 E/kg and maintenance treatment with 6-mercaptopurine (6-Mp) 50 mg/m$^2$ and methotrexate (MTX) 30 mg/m$^2$ alternated with VCR 2 mg/m$^2$, Pred 40 mg/m$^2$ or Dex 6 mg/m$^2$.

II. Patients with high-risk leukaemia, defined as leucocyte count $> 50,000$ mm$^3$ and/or mediastinal enlargement, were treated according to a more intensive high-risk protocol comprising induction treatment with cyclophosphamide (Cyclo) 1200...
Prepubertal growth in ALL

mg/m², vincristine (VCR) 1.5 mg/m², prednisone (Pred) 60 mg/m², L-asparaginase (L-Asp) 200 E/kg, and adriamycin (Adria) 60 mg/m². The maintenance treatment consisted of alternating 6-mercaptopurine (6-MP) 50 mg/m², methotrexate (MTX) 30 mg/m², Cyclo 150 mg/m² alternated with VCR 1.5 mg/m², Pred 40 mg/m², Adria 30 mg/m² and cytosine arabinoside (Ara-C) 100 mg/m². The high-risk therapy was available since 1979.

Depending on the method of available nervous system prophylaxis, patients were divided into three groups:

A: received CI with a dose of 24 Gy in 13 fractions over 17 days and 5 doses MTX 12.5 mg/m² and Pred intrathecally (i.t.) 12.5 mg/m² (1972 - 1980).
B: received CI with a dose of 18 Gy in 10 fractions over 14 days and 5 doses MTX 12.5 mg/m² and Pred i.t. 12.5 mg/m² (1980 - 1984)
C: received no CI. These patients were treated with 3 courses of high dose MTX intravenously combined with MTX 15 mg/m² and Pred i.t. 15 mg/m². During maintenance treatment 8 doses of MTX 15 mg/m², Pred 15 mg/m² and Ara-C 30 mg/m² were given i.t. (1984 - 1988).

Table 2.1: The number of patients treated according the high-risk and normal-risk protocols and the three methods of central nervous system prophylaxis.

<table>
<thead>
<tr>
<th></th>
<th>24 Gy CI (group A)</th>
<th>18 Gy CI (group B)</th>
<th>non-CI (group C)</th>
<th>total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal-risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>leukemia</td>
<td>34</td>
<td>11</td>
<td>29</td>
<td>74</td>
</tr>
<tr>
<td>high-risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>leukemia</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>total number</td>
<td>37</td>
<td>15</td>
<td>33</td>
<td>85</td>
</tr>
</tbody>
</table>

18 Gy and 24 Gy CI: the dose of cranial irradiation; non-CI: non-cranial irradiation.
The numbers of patients treated according to the different protocols and the numbers of patients during the follow-up period of 4.5 years are shown in tables 2.1 and 2.2. The duration of treatment in all patients was two years. In this study we investigated statural growth during the period of treatment and the first 2.5 years after cessation of therapy.

Table 2.2: Number of patients during the 4.5 years of follow-up.

<table>
<thead>
<tr>
<th>follow-up (years)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 Gy CI</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>24 Gy CI</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>CI (total)</td>
<td>52</td>
<td>52</td>
<td>52</td>
<td>52</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>non-CI</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>25</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>high-risk leukemia</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>normal-risk leukemia</td>
<td>74</td>
<td>74</td>
<td>74</td>
<td>67</td>
<td>57</td>
<td>51</td>
</tr>
<tr>
<td>total number</td>
<td>85</td>
<td>85</td>
<td>85</td>
<td>77</td>
<td>67</td>
<td>60</td>
</tr>
</tbody>
</table>

18 Gy and 24 Gy CI: the dose of cranial irradiation; non-CI: non-cranial irradiation.

Measurements. Patients heights and weights were measured by experienced staff. A stadiometer was used to measure patients heights. During the two years of treatment patients were measured 8 to 12 times per year and during the years of follow-up 2 to 4 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 (Z-scores) using Dutch reference values. Z-score 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. By means of interpolation Z-scores at six monthly intervals were calculated. To measure the influence of therapy the relative standard
deviation score ($Z_r$-score) was calculated, defined as $Z_t = Z_t - Z_0$ ($Z_t$: Z-score at time point t after diagnosis, $Z_0$: Z-score at time of diagnosis).

Statistical analysis. Statistical comparison was made using Student t-test and analysis of variance. Significance was accepted for p value < 0.05.

2.4 Results

At diagnosis the mean Z-score for height of all patients was -0.2 (SD 1.0) which was not significantly different from zero.

The $Z_r$-scores for height of patients with and without CI are shown in figure 2.2. During treatment a decline in $Z_r$-score for height was demonstrated in both groups.

Figure 2.2: Mean $Z_r$-scores ($\pm$ SEM) for height of patients treated for ALL with (broken line) and without (solid line) cranial irradiation. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, indicating the t-test significance level.
After the first year of therapy the mean $Z_r$-score was -0.2 (SD 0.3) for the non-irradiated and -0.5 (SD 0.5) for the irradiated patients. The difference between the two groups was statistically significant ($p=0.004$). After two years the mean $Z_r$-score for the non-irradiated patients was still -0.2 (SD 0.4) and for the irradiated patients -0.7 (SD 0.6) ($p=0.0001$). After cessation of therapy an increase in $Z_r$-score for height was shown in both groups. At 3 and 4 years from diagnosis the mean $Z_r$-score was 0.1 (SD 0.4) at both points for the non-irradiated patients and -0.4 (SD 0.7) and -0.3 (SD 0.7), respectively, for the irradiated patients. The differences between the two groups were still significant ($p=0.002$ and $p=0.013$, respectively).

The mean $Z_r$-score for height of patients treated with irradiation dose of 18 Gy compared to those receiving 24 Gy did not show a significant difference.

The mean $Z_r$-score for height of patients treated with normal-risk protocols compared to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2_3}
\caption{Mean $Z_r$-scores ($\pm$ SEM) of height of patients treated according to normal-risk protocols with ( ) and without CI ( ) and high-risk protocols with ( ) and without CI ( ). * = $p<0.05$, indicating the ANOVA significance level. A synergistic negative effect on statural growth of CI and high-dose chemotherapy.}
\end{figure}
those treated according to high-risk protocols are shown in figure 2.3. Comparison of the two groups was made using analysis of variance with correction for irradiation. In the group of non-irradiated patients there was not a significant difference in Zr-scores for height between patients treated with CT according to a normal-risk protocol and patients treated with CT according to a high-risk protocol. In the group of irradiated patients, however, there was a decline of the Zr-score to -0.5 (SD 0.5) of the patients treated according to a normal-risk protocol and a decline to -1.1 (SD 0.7) of the group of patients treated according to a high-risk protocol. The difference between these two groups was significant at 1, 1.5, 2 and 2.5 years from diagnosis (p <0.05). So in the group of patients treated with both high-dose CT and CI there was a synergistic negative effect of these treatment modalities on the mean Zr-score for height.

In none of the treatment protocols the mean Zr-scores for height of boys was significantly different from those for girls.

2.5 Discussion

We performed a longitudinal study to the influence of different treatment modalities on statural growth in prepubertal children treated for ALL. The results are expressed in standard deviation scores which enables comparison over sexes and ages. Growth retardation during the remission induction and continuation periods is a well known observation. This early deceleration in growth has been attributed to the disease itself, poor nutrition, the direct effect of chemotherapy, treatment with corticosteroids or CI. The contribution of the disease itself is minimal as height at diagnosis was not significantly different from the normal population. In the non-irradiated patients we observed growth deceleration during the first six months of therapy. The next 1 1/2 years there was a normal growth rate, but after cessation of therapy a catch-up growth occurred. Underweight could have attributed to the growth deceleration during the first six months of the treatment as in our study the Z-score for weight for height during the first six months was below the mean of the normal population. After six months, however, the patients showed an increase in
weight above the mean of the normal population. If underweight was the only reason for growth retardation the catch-up growth for height should have occurred after six months. Therefore these results suggest that CT and/or corticosteroids directly affect growth. Data of other studies \(^{66,87}\), are in agreement with our results. Moëll et al. \(^{87}\) and Katz et al. \(^{66}\) observed an initial decline in both height and growth velocity in patients who only received CT. Clayton et al. \(^{27}\) saw a catch-up growth in the third year after diagnosis in patients who received 2 years CT. When CT was maintained for a further year, the catch-up growth was delayed by a year. These observations justify the conclusion that there is an involvement of CT and/or corticosteroids in early growth retardation. The effect of CT alone on final height is still under discussion \(^{67,92,127}\), but CT for ALL doesn’t seem to influence final height to a great extent. Growth retardation is clearly more marked in patients who have undergone radiotherapy. The physiologic basis for this growth failure is presumably attributable to a disturbance in the secretion of growth hormone after CI. Growth hormone deficiency (GHD) is the most frequent endocrine abnormality that occurs after CI \(^{20,26,106}\). The occurrence of GHD depends on the estimated radiation dose delivered to the hypothalamus and pituitary \(^{106,121,123}\). The time of occurrence of GHD is also related to the radiation dose \(^{26,88,106}\). Brauner et al. \(^{20}\) demonstrated in a prospective study that, although GHD is an early complication of CI, no significant growth retardation in patients treated for ALL can be attributed to GHD during the first 2 years. The early growth retardation shown in patients after treatment with CI for ALL might be due to an early transient reduction in nocturnal growth hormone secretion as reported by Dacou-Voutetakis et al. \(^{31}\) in combination with the influence of CT and/or corticosteroids.

The effects on growth of CI with a dose of 18 GY or 24 GY in our study were indistinguishable. Similar results have been described by others \(^{131,149}\). On the contrary, Cicognani et al. \(^{25}\) and Logghe et al. \(^{79}\) found different effects of 18 GY and 24 GY CI on growth. Cicognani et al. \(^{25}\) suggested that the follow-up of the patients in the earlier mentioned studies \(^{131,149}\) of 1/2 - 1 year was too short to find such a difference. However, our study with a follow up of 2 1/2 years after cessation of therapy did not show any difference between either 18 or 24 GY CI. The irradiation schedules were comparable in all
studies. The explanation for the different outcome could be differences in CT. In the study of Logghe et al. 79 high-risk patients received CT with a total duration of 5 years, while normal-risk patients received CT during 2 or 3 years. Their evaluation of growth in both groups was 5 years after diagnosis, so a number of patients, all in the 24 Gy CI group, did not have the opportunity to show a catch-up growth, as they just finished their treatment. Additional differences were that normal-risk patients were irradiated with 18 Gy and high-risk patients with 24 Gy and that the intensity of CT was different in both groups. Longer duration of chemotherapeutic treatment and more intensive CT can affect growth velocity. In this longitudinal study we demonstrated that high-risk patients receiving CI showed a significantly greater decline in height than normal-risk patients treated with the same dose of irradiation. So, more intensive CT and CI have a synergistic negative effect on growth. This finding is supported by Shalet et al. 122, who concluded that the greater growth failure in the patients studied by Kirk et al 68 compared with his own patients, might be due to more intensive CT.

From this study it can be concluded that there is an influence of CT on short-term growth in patients treated for ALL. The influence of CI on statural growth is more pronounced, with a similar negative effect of 18 and 24 Gy. The combination of CI with high dose CT has a synergistic negative effect on statural growth, so in studies comparing the effect on growth of two different radiation protocols the difference in intensity and duration of CT may not be ignored. Before the general conclusion can be drawn that CT doesn’t influence final height, further investigation is mandatory especially in patients treated with combinations of CT different from ALL treatment schedules.
CHAPTER 3

CHEMOTHERAPY PLAYS A MAJOR ROLE IN THE INHIBITION OF CATCH-UP GROWTH DURING MAINTENANCE THERAPY FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA


Pediatrics 1995; 96:693-695
Chapter 3

3.1 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 due 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 to occur during maintenance therapy for ALL.

3.2 Introduction

Growth retardation during treatment for acute lymphoblastic leukemia (ALL) has been demonstrated in many studies. 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. 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. 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. In this study we investigated the influence of...
Inhibition of catch-up growth
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.

3.3 Patients and methods

Patients. Forty-six patients (19 girls and 27 boys) with ALL treated at the Department of Paediatric Oncology of the University Hospital Nijmegen, 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 with age less than 10 years at diagnosis were included in the study. Age distribution was 1.6 - 9.9 year, 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.

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 the 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
Chapter 3

40 mg/m². 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: Re-induction treatment with VCR, Dexa, Adriamycin, L-Asp, Cyclophosphamide, ARA-C and 6 Thioguanine and two doses of MTX intrathecally.

d: Maintenance treatment with 6-MP, 50 mg/m² daily, and MTX, 20 mg/m² 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. 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
Inhibition of catch-up growth

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 $\pm$ the standard deviation.

3.4 Results

The $Z_r$-scores for height of the 27 patients treated for ALL according to protocol 6 (maintenance therapy comprising Pred or Dexam) compared with the $Z_r$-scores of 19 patients treated according to protocol 7 (maintenance treatment without corticosteroids) are shown in figure 3.1. 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 start of therapy the $Z_r$-score of patients treated according to

![Graph showing Zr-scores for height over time.](image)

Figure 3.1: Mean $Z_r$-score (± standard error) for height of patients treated for 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).
Chapter 3

protocol 6 was \( -0.2 \pm 0.2 \). The \( Z_r \)-score remained \( -0.2 \). The \( Z_r \)-score of patients treated according to protocol 7 was \( -0.3 \pm 0.2 \) at 3 months and remained \( -0.3 \) during the whole period of treatment. The differences between the two groups were not significant at any time (all p-values \( 0.10 \)).

3.5 Discussion

Growth retardation during treatment for ALL is of multifactorial etiology \(^{27}\). CI as central nervous system prophylaxis in the treatment for ALL has been implicated as main etiologic agent \(^{49}\). Compared to 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 \(^{27,49,59,77,87}\). Children treated for ALL with chemotherapy and corticosteroids but without CI also showed diminished growth rate during treatment \(^{49,59,87}\). Apart from impaired growth, retardation of bone-age development has also been reported during treatment for ALL \(^{134}\). 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 \(^{134}\). 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 \(^{61,93}\). Short-term treatment with prednisone in a dose of 40 mg/m\(^2\)/day and dexamethasone in a dose of 10 mg/m\(^2\)/day, used during remission induction therapy for ALL have been shown to suppress growth hormone secretion \(^{19,82}\). 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 to children who received corticosteroids during the entire period of treatment. Although in protocol 6 corticosteroids were given intermittently
Inhibition of catch-up growth

(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 due 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 significant different from the normal population, from this we conclude that malnutrition could not be a factor contributing to the inhibition of catch-up growth.
CHAPTER 4

CATCH-UP GROWTH IN ACUTE LYMPHOBLASTIC LEUKAEMIA; INFLUENCE OF TREATMENT MODALITIES ON TIMING.


Submitted
Chapter 4

4.1 Abstract

Catch-up growth was investigated in 76 children treated for acute lymphoblastic leukaemia; 41 patients received cranial irradiation (protocols 2, 3, 5), maintenance therapy comprised chemotherapy and corticosteroids in 61 (protocols 2, 3, 5 and 6) and chemotherapy only in 15 patients (protocol 7). Individual, longitudinal curves for growth-velocity and acceleration were constructed. The Z-velocity was distracted from the Z-score for height. Timing of ONSET, START and PEAK of catch-up growth and timing of accelerated growth were analysed for three groups of patients: 1. Patients who received cranial irradiation as central nervous system prophylaxis and corticosteroids during maintenance therapy (protocols 2, 3 and 5), 2. patients treated without cranial irradiation but with corticosteroids during maintenance therapy (protocol 6) and 3. patients treated without cranial irradiation and without corticosteroids during maintenance therapy (protocol 7).

The Z-velocity increased during treatment. The start of the positive Z-velocity, which is the start of catch-up growth, was respectively 2.0, 1.3 and 1.0 years after diagnosis for the protocols 2-5, 6 and 7. The time-interval from onset to peak of catch-up growth was comparable for all patients. Growth was accelerated immediately after start of therapy. The acceleration decreased during treatment. The end of the accelerated growth was 2.5, 2.2 and 1.9 years after diagnosis for respectively protocol 2-5, 6 and 7. So it can be concluded that acute lymphoblastic leukaemia itself has an influence on growth. The start of the catch-up growth is independent of cessation of therapy. The duration of catch-up growth is not influenced by different treatment modalities.

4.2 Introduction

The growth potential of a person is genetically determined and under favorable conditions each individual will follow a predominated growth curve. Growth retardation, a deflection away from the predicted growth curve, can be caused by various diseases,
Timing of catch-up growth

malnutrition, psychosocial stress or endocrine disorders. When a period of growth retardation ends and favorable conditions are restored, a period of accelerated growth will occur. This acceleration in growth is referred to as "catch-up growth". It is a self correcting response which restores individuals to their original growth channel. The extent to which growth failure can be compensated for depends on timing, severity and duration of the growth failure, as well as on the aetiology and pathogenesis of the disease restricting growth.

Growth retardation during treatment for acute lymphoblastic leukaemia (ALL) has been demonstrated in a number of studies. Treatment for ALL comprised 1. induction therapy with chemotherapy (CT) and corticosteroids, 2. central nervous system (CNS) prophylaxis with radiotherapy or CT and 3. maintenance therapy with CT with or without corticosteroids. The treatment modalities CT, corticosteroids and cranial irradiation (CI) have been proposed as the main etiologic factors for growth retardation in these patients. After cessation of therapy catch-up growth was demonstrated in all patient groups. In patients treated without CI growth returned completely to the predicted growth curve whereas in patients who received CI as a part of their treatment the catch-up growth was incomplete.

This study was performed to investigate the effects of the different treatment modalities: chemotherapy, irradiation and corticosteroids, on catch-up growth of children treated for ALL. To gain more insight into the growth patterns of these patients, not only heights achieved at different time points were analysed, but we also analysed velocities as velocity detects alterations in growth regardless of the stature achieved.

4.3 Patients and methods

Patients. Seventy-six consecutive patients (39 girls and 37 boys) with ALL treated at the Department of Pediatric Oncology of the University Hospital Nijmegen between 1972 and 1991 were included in the study. To avoid the influence of the pubertal growth spurt only
patients with age at diagnosis of less than 7 years were included. The patients had entered into first remission within 6 weeks after diagnosis. The follow-up of the patients was at least two years after cessation of therapy. Patients who relapsed were excluded. As CNS involvement can cause hypothalamic dysfunction, patients with CNS involvement at the time of diagnosis were also excluded.

**Treatment.** According to the year of diagnosis of ALL, patients were treated according to the protocols 2, 3, 5, 6 and 7 of the Dutch Leukemia Working Group. Patients were divided into three groups: 1. patients treated according to the protocols 2, 3 and 5. These patients received both cranial irradiation as CNS prophylaxis and corticosteroids and chemotherapy during maintenance therapy (n=41). 2. Patients treated according to protocol 6. These patients did not receive CI as CNS prophylaxis, the maintenance therapy comprised both chemotherapy and corticosteroids (n=20). 3. Patients treated according to protocol 7 received neither CI as CNS prophylaxis nor corticosteroids during maintenance therapy (n=15).

**Protocol 2, 3, 5:** these protocols were used for patients diagnosed in between 1972-1984.

The protocols 2, 3 and 5 comprised: Induction treatment with Vincristine (VCR) 2 mg/m², Prednisone (Pred) 40 mg/m² with or without L-Asparaginase 200 E/kg.

Maintenance treatment with 5 weeks of 6-Mercaptopurine (6-MP) 50 mg/m² daily and Methotrexate (MTX) 30 mg/m² once a week, alternated with 2 weeks of VCR 2 mg/m² and Pred 40 mg/m². Patients of protocol 2 also received Cyclophosphamide 200 mg/m² every 2 weeks.

CNS prophylaxis: CI with a dose of 24 Gy in 13 fractions over 17 days and 5 doses MTX 12.5 mg/m² and Pred 12.5 mg/m² intrathecally (i.t.) (protocols 2 and 3) (1972-1980). CI with a dose of 18 Gy in 10 fractions over 14 days and 5 doses MTX 12.5 mg/m² and Pred 12.5 mg/m² i.t. (1980-1984) (protocol 5).

The aimed duration of treatment was 2 years.

**Protocol 6:** This protocol was used for patients diagnosed in between 1984-1988.

Protocol 6 comprised: Induction treatment with VCR 2 mg/m², Dexamethasone 6 mg/m² or Pred 40 mg/m² and L-Asparaginase 200 Units/kg.

58
Timing of catch-up growth

Maintenance treatment with 5 weeks of 6-MP 50 mg/m² daily and MTX 30 mg/m² once a week, alternated with 2 weeks of VCR 2 mg/m² and Dexamethason 6 mg/m² or Pred 40 mg/m².

CNS prophylaxis with 3 courses of intermediate-dose MTX 2000 mg/m² intravenously (i.v.) combined with MTX 15 mg/m² and Pred 15 mg/m² intrathecally. During maintenance treatment 8 doses of MTX 15 mg/m², Pred 15 mg/m² and Cytarabine 30 mg/m² were given i.t..

The aimed duration of treatment was 2.25 years.

Protocol 7: This protocol was used for patients diagnosed in between 1988-1991.

Protocol 7 comprised: Induction treatment with VCR 1.5 mg/m², Pred 60 mg/m², Daunorubicin 40 mg/m², L-Asparaginase 10000 E/m², Cyclophosphamide 1000 mg/m², Cytarabine 75 mg/m² and 6-MP 60 mg/m².

Consolidation treatment with VCR 1.5 mg/m², Dexamethason 10 mg/m², Adriamycine 30 mg/m², L-Asparaginase 10000 E/m², Cyclophosphamide 1000 mg/m², Cytarabine 75 mg/m² and 6-Thioguanine 60 mg/m².

Maintenance treatment with 6-MP 50 mg/m² daily and MTX 20 mg/m² once a week.

CNS profylaxis with 4 courses of high-dose MTX 5000 mg/m² i.v. combined with MTX 15 mg/m² i.t. and 6-MP 25 mg/m² orally.

The aimed duration of treatment was 1.5 years.

Summary of treatment: 41 patients received cranial irradiation (protocols 2, 3 and 5), 61 patients received chemotherapy and corticosteroids during maintenance therapy (protocols 6 and 7) and 15 patients received only chemotherapy during maintenance therapy (protocol 7).

Measurements. Patients heights were measured by experienced staff using a stadiometer. During the years of treatment patients were measured 12 times per year and during the years of follow-up 4 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 (SDS or Z-scores) using Dutch reference values. Z-score 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.

Velocity and acceleration curves. During a period of catch-up growth, a child is regaining length with respect to its peer group. This implies an increasing Z-score and a period in which the Z-velocity is positive. In order to detect such periods of catch-up growth it is necessary to study changes in Z-velocity, given by the Z-acceleration curve. At the same time also the growth velocity in height itself is changing. To obtain a complete impression of catch-up growth, individual height- and Z-velocity curves are studied together with height- and Z-acceleration curves. For this purpose the statistical technic of the Kernel estimation was used. The Kernel estimation is a smoothing procedure using polynomials up to the degree of 7, holding for a prechosen band width. In this study two different sets of band widths for time, as introduced by Gasser, were

Figure 4.1: Mean Z-score (SDS for height + SEM) of patients treated according to protocol 2-5 ( ) n =41, protocol 6 ( ) n =20 and protocol 7 ( ) n =15.
Timing of catch-up growth

used: 1. a band of 3.1 years for velocity and 3.6 years for acceleration and 2. a band of 3.8 years for velocity and 4.0 years for acceleration. The Kernel estimation was applied on individual, longitudinal measurements. Individual, longitudinal curves for growth velocity and acceleration, from diagnosis to two years after cessation of therapy, were obtained.

Statistics. Comparison of time points derived from the individual velocity and acceleration curves with respect to the 3 treatment protocols were made using one way analysis of variance (ANOVA). Significance was accepted for p values less than 0.05.

4.4 Results

Time curves for Z-scores. The mean Z-scores for height are shown in figure 4.1. At diagnosis there is no significant difference in Z-score between the three treatment groups (ANOVA, p =0.60). This means that the 3 groups were initially comparable.

During the years of therapy a significant growth retardation was found in the patients treated with CI (protocols 2, 3 and 5), (paired t-test, p <0.001) with a mean Z-score = -0.8 (SEM =0.15). The Z-score of this group increased up to -0.5 (SEM = 0.13) after cessation of therapy, indicating an incomplete catch-up growth.

For the protocols 6 and 7, without CI, also a decrease in mean Z-score was found followed by a complete catch-up growth.

Timing of catch-up growth. Figure 4.2 shows the Z-velocity curve and the Z-acceleration curve for a representative patient. Initially the Z-velocity is negative, indicating a period of growth retardation. This period was followed by a period with a positive Z-velocity, where the patient is regaining height compared to the peer group, i.e. the period of catch-up. The end of the catch-up growth is beyond the follow-up of two years after cessation of therapy for most of the patients.
Figure 4.2: Curve of the Z-acceleration (SD/year²) (---) and the Z-velocity (SD/year) (-----) of a representative patient. The timing of the ONSET, the START and the PEAK of catch-up growth are indicated. The vertical (dotted) line indicates the moment of cessation of therapy.

The timing of the catch-up growth is marked by 3 time points i.e.
- The moment were the negative Z-velocity is increasing, marked by a zero Z-acceleration. This time point may be regarded as the ONSET of catch-up growth.
- The moment that the Z-velocity reaches a positive value. This may be regarded as the START of catch-up growth.
- The moment that the Z-velocity reaches its PEAK value, marked by the second time that the Z-acceleration becomes zero.

Such a pattern of catch-up growth was found in 66 out of the 76 patients. For 18 out of the 76 patients the Z-acceleration was already, slightly, positive at diagnosis and the moment of onset of catch-up growth could easily be obtained by backward extrapolation of the Z-acceleration curve, leading to a negative value (before start of therapy) for the onset.

In 6 out of the 76 patients (2 patients of protocol 5, 3 patients of protocol 6 and 1 patient of protocol 7) the Z-velocity was almost zero during the whole period of the study. These
Timing of catch-up growth

patients were "tracking" and no growth retardation or catch-up growth could be observed. In 4 out of the 76 patients (2 patients of protocol 5 and 2 patients of protocol 7) the Z-velocity was negative during the whole study period. These patients suffered from growth retardation without any sign of catch-up growth.

Thus for 66 patients the start of catch-up growth could be identified. On the basis of the Z-acceleration curves it was possible to identify both the minimal (onset of catch-up) and maximal Z-velocity (peak of catch-up) for all 76 patients.

Table 4.1: Mean ± SD (n) of the three moments in catch-up growth for the three groups of patients treated according to the protocols 2-5, 6 and 7 and the corresponding time of cessation of therapy given in years after diagnosis.

<table>
<thead>
<tr>
<th>Moment</th>
<th>protocol 2-5</th>
<th>protocol 6</th>
<th>protocol 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset (n)</td>
<td>Start (n)</td>
<td>Peak (n)</td>
</tr>
<tr>
<td>Onset</td>
<td>0.41±0.48 (41)</td>
<td>0.05±0.46 (20)</td>
<td>-0.08±0.59 (15)</td>
</tr>
<tr>
<td>Start</td>
<td>2.02±0.55 (36)</td>
<td>1.31±0.34 (16)</td>
<td>1.04±0.69 (14)</td>
</tr>
<tr>
<td>Peak</td>
<td>2.99±0.72 (41)</td>
<td>2.45±0.55 (20)</td>
<td>2.51±0.83 (15)</td>
</tr>
<tr>
<td>Cessation of</td>
<td>2.0</td>
<td>2.25</td>
<td>1.5</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all three moments protocols 2-5 are significantly later than protocol 6 and 7 (ANOVA, all p-values < 0.01).

A comparison of the three protocols with respect to the three time points is given in table 4.1. Table 4.1 shows that all three catch-up moments are significant later in the protocols 2, 3 and 5 (with CI) compared to the protocols 6 and 7 (without CI).

On the average the start of catch-up growth in the protocols 2-5 coincides with cessation of therapy, but in protocol 6 and 7 catch-up growth starts in general before cessation of therapy. The time intervals between the three moments of catch-up growth are shown in table 4.2.
Table 4.2: Mean ± SD (n) for the time intervals between the three moments in catch-up growth for the three groups of patients treated according to the protocols 2-5, 6 and 7.

<table>
<thead>
<tr>
<th>Interval</th>
<th>Protocol 2-5 (n)</th>
<th>Protocol 6 (n)</th>
<th>Protocol 7 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset - Start</td>
<td>1.50±0.32 (36)</td>
<td>1.12±0.17 (16)</td>
<td>1.24±0.35 (14)</td>
</tr>
<tr>
<td>Start - Peak</td>
<td>1.13±0.42 (36)</td>
<td>1.31±0.25 (16)</td>
<td>1.36±0.54 (14)</td>
</tr>
<tr>
<td>Onset - Peak</td>
<td>2.58±0.53 (41)</td>
<td>2.41±0.17 (20)</td>
<td>2.47±0.72 (15)</td>
</tr>
</tbody>
</table>

The duration of the interval onset - start is significant different for the three groups (ANOVA, p <0.01).

The only significant difference between the protocols is the duration of the interval onset - start (ANOVA, p <0.01), indicating a larger interval for the protocols 2-5.

The growth velocity on its own is not informative for the timing of catch-up growth since growth velocity is positive also in children treated for ALL. From the acceleration curves obtained by the Kernel estimation, the start of the acceleration of growth could not be indicated in this group of children. Such a point did not appear as, surprisingly, growth was accelerated immediately after start of therapy (figure 4.3). Instead of an acceleration curve changing from negative into positive, which was expected, the acceleration curve changed from positive into negative in all children. The end of the positive acceleration (point a, figure 4.3) was calculated for the different groups of patients.

The mean end of the period of the accelerated growth was 2.52 years (SD 0.72) after diagnosis for children treated according to the protocols 2-5 and 2.18 (SD 0.50) and 1.93 (SD 0.32) years after diagnosis for patients treated according to protocols 6 and 7 respectively. The difference in duration of accelerated growth between the protocols was significant (p =0.004, ANOVA).

In applying the Kernel estimation two different band widths (smoothing parameters) were used. Compared to the results of the 3.1-3.6 band the end of the accelerated growth was
significant later: 0.07 (SD 0.16) year, the timing of the minimal Z-velocity was significantly earlier: 0.06 (SD 0.06) year, the timing of the maximal Z-velocity was 0.04 (SD 0.13) year later and the start of the positive Z-velocity was 0.06 (SD 0.21) year later than in the 3.8-4.0 band. Despite the significant influence of the bandwidth, it may be concluded that the sensitivity to band width choice is only small.

4.5 Discussion

Z-score for height declined during the period of treatment in the three groups of patients. The decrease was most pronounced in the patients who received cranial irradiation as CNS prophylaxis (protocols 2-5) and in this group the catch-up growth was incomplete, which is in agreement with other studies\textsuperscript{27,40,87}. The treatment modalities have been thought to be the main causal factors for growth retardation as catch-up growth did

![Graph showing growth acceleration over time](image)

Figure 4.3: Curve of acceleration of growth (cm/year\(^2\)) of the same patient as figure 4.2. The end of the accelerated growth (a) is indicated. The vertical (dotted) line indicates the moment of cessation of therapy.
not occur during the period of treatment. However, despite growth suppressive therapy, in all patients, acceleration of growth was demonstrated as soon as therapy was instituted. This could imply that the leukemic process is an important causal factor for growth suppression.

The majority of the patients, diagnosed for ALL, present with skeletal lesions. These lesions, observed roentgenographically, are juxtaepiphyseal radiolucent bands, osteoporosis and osteolytic lesions. The pathogenesis of the skeletal lesions in ALL could be understood from the role of the hematopoietic bone-marrow in bone-cell development. Both osteoblasts and osteoclasts originate in the marrow. Cells of the bone and the hematopoietic bone marrow share progenitors and produce and respond to some of the same cytokines and colony-stimulating factors. Disease of the bone marrow will cause disruption of the bone-cell development with growth arrest or disturbed growth in children. In most patients complete remission of ALL will be achieved within six weeks after start of therapy, with recovery of the hematopoiesis and restoration of bone-cell development. So soon after institution of therapy acceleration of growth could occur and our results are in concurrence with this phenomenon.

Despite accelerated growth in this period, the Z-score for height declined during the early phase of therapy.

The decrease in Z-score for height was the most severe in patients who received CI as CNS prophylaxis and especially in these patients the period of acceleration of growth was significantly longer than in the other patients. The more severe growth retardation, during the first months of treatment, of the patients who received CI is not well understood. The physiologic basis for growth failure after CI is thought to be a disturbance in the secretion of growth hormone. However Brauner et al demonstrated in a prospective study that although growth hormone deficiency is an early complication of CI, in patients treated for ALL no significant growth retardation can be attributed to growth hormone deficiency during the first 2 years after CI. In this study we demonstrated an acceleration of growth, in all patients, already in the early phase of therapy. During a period of accelerated growth children are more susceptible to the detrimental effects of growth suppressive therapy and the combination of CT, corticosteroids and CI is more growth suppressive than CT and...
Timing of catch-up growth

corticosteroids alone.

For patients who received CI as a part of their treatment the Z-velocity decreased during the first 5 months of therapy (the onset of catch-up was 5 months after diagnosis, table 4.1). For patients treated according to protocol 6, a decrease of Z-velocity was demonstrated during the first month of therapy. In this phase the greatest loss in Z-score for height occurred. The patients of protocol 7 showed an increase of Z-velocity immediately after start of therapy.

Despite an increase in Z-velocity, during the early phase of therapy, the Z-score for height did not increase before the Z-velocity became positive. So the start of the positive Z-velocity is the beginning of the catch-up growth. The start of the positive Z-velocity was 2 years after diagnosis for patients of the protocols 2-5 and 1.3 and 1.0 years after diagnosis for patients of protocols 6 and 7. For patients treated according to the protocols 2-5 the start of the catch-up growth coincides accidently with the cessation of therapy. These results could, erroneously, support the conclusion that the start of the catch-up growth was related to the cessation of therapy.

The start of the positive Z-velocity was earliest after diagnosis in patients of protocol 7, the patients who, apart from no CI as CNS prophylaxis, did not receive corticosteroids during maintenance therapy. This might lead to the conclusion that growth suppression is prolonged in patients treated with corticosteroids as a part of maintenance therapy. However this is not in concordance with results of a previous study to the influence of maintenance therapy on growth in children treated for ALL 50. In this study we showed that during maintenance therapy the relative Z-score for height of patients treated with CT and corticosteroids was comparable to the relative Z-score for height of patients who received only CT.

As far as the duration of catch-up growth is concerned, the time interval between the onset of catch-up growth and the peak value is important as during this phase the Z-velocity increased. No difference between the protocols was noticed for this time interval. Neither there was a difference in time interval in between the start of catch-up growth and the timing of the peak value, which is not only a period of increase in Z-velocity but also a period of positive Z-velocity. So although the catch-up growth is incomplete in the
irradiated patients, in contrast to the non-irradiated patients who fully regain the previous loss, the duration of the catch-up growth is comparable for all patients.

A limitation in the application of the Kernel estimation could be the choice of the smoothing parameter (band width). Gasser 42 suggested a smoothing parameter of 3.1 year for velocity during puberty, a period of increased growth velocity, and 3.8 year for velocity before puberty. We applied both smoothing parameters. The difference between the two parameters was a small shift of less than one month of the end of the accelerated growth and the timing of the onset, the start and the peak value of catch-up growth.

From this study it can be concluded that:

- Acute lymphoblastic leukaemia, as such, has a negative influence on growth velocity. Growth accelerates as soon as therapy is instituted.
- The causal factor for the decrease in Z-score for height, despite accelerated growth and increase in Z-velocity during treatment, is the suppressive effect on growth of the treatment modalities instituted.
- The strongest growth suppressive effect is cranial irradiation.
- The start of the catch-up growth, which is the start of the positive Z-velocity, is independent of the moment of cessation of therapy.
- The duration of catch-up growth is comparable for all patients, regardless the treatment protocol.

Acknowledgments: The authors thank Mrs. A.E. van ’t Hof-Grootenboer and Miss H. Vogt for their technical assistance.
CHAPTER 5

INTENSITY OF CATCH-UP GROWTH DURING AND AFTER TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKAEMIA.


Submitted
5.1 Abstract

Catch-up growth was investigated in 76 children treated for acute lymphoblastic leukaemia; 41 patients received cranial irradiation and 35 patients were not irradiated. Curves for Z-acceleration and Z-velocity were distracted from the Z-scores for height. To describe the intensity of catch-up growth: the minimal Z-velocity, the maximal Z-velocity and the difference between minimal and maximal Z-velocity were analyzed for patients with and without irradiation. The magnitude of the minimal Z-velocity of the irradiated patients was significantly lower. The magnitude of the maximal Z-velocity was comparable in both groups. The difference between the minimal and the maximal Z-velocity, which is a degree for the intensity, was significantly higher in the irradiated patients. The SDS for height at maximal Z-velocity was significantly lower in the irradiated patients. So despite a more intensive catch-up growth, the irradiated patients have a significantly greater loss in height SDS, which supports the hypothesis of a reset of the mechanism which recognizes normal body size, to a smaller body size by cranial irradiation.

5.2 Introduction

Normal human growth is characterized by growth according to a predicted growth channel. This growth channel is genetic determined and observed from the peer group. A negative deflection away from this predicted growth channel can be caused by various conditions such as chronic diseases, malnutrition or endocrine disorders. Catch-up growth towards the original growth curve, will occur after a period of growth retardation, provided that the favourable conditions are restored.

A disease which is attended with growth retardation is acute lymphoblastic leukaemia (ALL). The causal factors for growth retardation in ALL could be the disease itself or treatment with chemotherapy, radiotherapy and corticosteroids.
In a previous study to the timing of catch-up growth in ALL it was shown that growth velocity was already low at diagnosis. From this we concluded that the disease ALL has an influence on growth. After institution of treatment with chemotherapy, corticosteroids and with or without radiotherapy, acceleration of growth was noticed. So despite the growth suppressive effects of the treatment modalities, growth accelerated as soon as therapy commenced. However during the early period of treatment the attained growth velocity was below the growth velocity of the normal population leading to a decrease in standard deviation score for height. After a period of time the patients growth velocity was above the growth velocity of the normal population and catch-up growth appeared. In patients who received prophylactic, cranial irradiation to protect against central nervous system (CNS) relapse, the catch-up growth was incomplete whereas in patients who only received intrathecal chemotherapy to prevent CNS leukemia, height returned to the initial predicted growth curve. The duration of catch-up growth was comparable for both irradiated and non-irradiated patients.

In this study we investigated the intensity of catch-up growth in patients treated for ALL, in relation to different treatment modalities.

5.3 Patients and methods

Patients. Seventy-six consecutive patients (39 girls and 37 boys) with ALL treated at the Department of Pediatric Oncology of the University Hospital Nijmegen between 1972 and 1991 were included in the study. Inclusion criteria:

- Age at diagnosis < 7 years, to avoid the influence of the pubertal growth spurt.
- Achievement of complete remission within six weeks after start of therapy.
- Follow-up of at least 2 years after cessation of therapy.
- No relapse of ALL during treatment and within two years after cessation of therapy.
- No CNS involvement as CNS involvement can cause hypothalamic dysfunction.
Chapter 5

Treatment. According to the year of diagnosis of ALL, patients were treated according to three consecutive protocols 2 up to 7 of the Dutch Leukemia Working Group.

Protocols 2,3 and 5 were used for patients diagnosed in between 1972 and 1984 (n=41). These protocols comprised cranial irradiation (CI) with a dose of 18 or 24 Gy as CNS prophylaxis and patients received corticosteroids and chemotherapy during maintenance therapy.

CI commenced 6 weeks after start of therapy.

Protocol 6 was used for patients diagnosed in between 1984 and 1988 (n=20). This was a protocol without CI as CNS prophylaxis with chemotherapy and corticosteroids during maintenance therapy.

Protocol 7 was used for patients diagnosed in between 1988 and 1991 (n=15). This protocol did neither comprise CI as CNS prophylaxis nor corticosteroids during maintenance therapy. Detailed information about chemotherapy is described in a previous paper.

Measurements. Patients heights were measured by experienced staff. A stadiometer was used to measure patients heights. During the period of treatment, patients were measured 12 times per year and during the follow-up period, 4 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 (Z-scores or SDS-scores) using Dutch reference values. The Z-score is defined as the difference between a patients height and the age and sex appropriate mean of the population relative to the corresponding standard deviation.

Catch-up growth is most clearly defined as regaining height (relative to the peer group) and can be quantified as positive changes in Z-score over time. Therefore Z-velocities and Z-accelerations play an important role in the study of catch-up growth.

Velocity and acceleration curves. For the calculation of velocities and accelerations the Kernel estimation was used. The Kernel estimation is a smoothing procedure using polynomials up to a degree of 7, holding for a pre-chosen band width for time.
Intensity of catch-up growth

Figure 5.1: Curve of the Z-acceleration (SDS/yr$^2$) and the Z-velocity (SDS/yr) of a representative patient. The minimal Z-velocity (MiVZ), the maximal Z-velocity (MaVZ) and the difference between the MiVZ and the MaVZ (ΔVZ) are indicated. The vertical dotted line indicates the moment of cessation of therapy.

In this study two different sets of band widths, as introduced by Gasser, were used: band 1 of 3.1 years for velocity and 3.6 years for acceleration and band 2 of 3.8 years for velocity and 4.0 years for acceleration.

As catch-up growth is defined as growth velocity above the growth velocity of the normal population, Z-velocity and Z-acceleration were distracted from the Z-scores for height. Using the Kernel estimation time curves for Z-velocity and Z-acceleration, from diagnosis to two years after cessation of therapy, were obtained.

To describe the intensity of catch-up growth two events were analysed: minimal Z-velocity (MiVZ) and maximal Z-velocity (MaVZ) (see figure 5.1).

Estimated from the time curves for Z-velocity and Z-acceleration were:

1. The moment of MiVZ, defined as the timing after start of therapy of the minimum Z-velocity (= zero Z-acceleration) in years.
2. The magnitude of MiVZ expressed as gain in Z-score per year (SDS/year).
3. The moment of MaVZ, defined as timing after start of therapy of maximum Z-velocity (= zero Z-acceleration) in years.
4. The magnitude of MaVZ expressed in Z-score per year (SDS/year).
5. The gain in Z-velocity (= magnitude of MaVZ-MiVZ = VZ) which is a measure of intensity for catch-up growth.

Statistics. The points MiVZ and MaVZ were analysed for the different treatment protocols. In addition the Z-values for height at diagnosis at MiVZ and MaVZ were compared between the protocols. For statistical analysis Students’ t-test was used. Significance was accepted for p-value < 0.05.

5.4 Results

The curve of the Z-velocity and the curve of the Z-acceleration of a representative case are shown in figure 5.1. In 58 of the 76 patients the Z-velocity decreased during the first period of therapy. The Z-acceleration started negative and increased immediately after start of therapy. The timing of the start of the positive

Table 5.1: Mean (±SD) for minimal Z-velocity (MiVZ in SDS/yr) and maximal Z-velocity (MaVZ in SDS/yr) and VZ (in SDS/yr) for the different treatment protocols.

<table>
<thead>
<tr>
<th>protocol number of</th>
<th>MiVZ</th>
<th>MaVZ</th>
<th>MiVZ - MaVZ (VZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-5 with CI</td>
<td>41</td>
<td>-0.38 ± 0.27</td>
<td>0.25 ± 0.17</td>
</tr>
<tr>
<td>6 + 7 without CI</td>
<td>35</td>
<td>-0.18 ± 0.14</td>
<td>0.22 ± 0.13</td>
</tr>
<tr>
<td>p-value t-test</td>
<td>0.000</td>
<td>0.508</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI = cranial irradiation.

76
Z-acceleration, which is the moment of the minimal Z-velocity (MiVZ), could be indicated. In 18 of the 76 patients the Z-acceleration was already positive at diagnosis and the Z-velocity increased immediately after start of therapy. In these patients the timing of the MiVZ was obtained through backward extrapolation. No difference was noticed in the timing, after diagnosis, of the MiVZ and the MaVZ of patients treated according to protocol 6 (without CI but with corticosteroids during maintenance therapy) and patients treated according to protocol 7 (without CI and without corticosteroids during maintenance therapy). The moment of the MiVZ for these patients was 0.02 (SD 0.54) years and the MaVZ 2.44 (SD 0.67) years after start of therapy. For the irradiated patients (treated according to protocol 2-5) the MiVZ was 0.41 (SD 0.48) and the MaVZ 2.99 (SD 0.72) years after diagnosis. The difference in timing of both points between the irradiated and the non-irradiated patients was significant (p-values respectively 0.001 and 0.002, t-test). However the time-interval in between MiVZ and MaVZ was comparable for all the patients (mean duration 2.5 years, SD 0.5). So the decrease of the Z-velocity was significantly prolonged in patients who received CI but the duration of the increase in Z-velocity was comparable for both groups. Analysis of the intensity of catch-up growth didn't show differences between the patients of protocol 6 and patients of protocol 7, with the only exception of the Z-velocity at MaVZ which was 0.27 SDS/yr (SD 0.11) for patients treated according to protocol 6 and 0.17 SDS/yr (SD 0.12) of patients of protocol 7 (p =0.017, t-test). Since the differences are only marginal it was decided to compare only two different groups of patients during further analysis: 1. patients who received CI (protocols 2-5) and 2. patients treated without CI (protocols 6 and 7). The magnitudes of MiVZ and MaVZ are shown in table 5.1 and the values of the SDS for height at diagnosis, MiVZ and MaVZ are shown in table 5.2. Heights of patients at diagnosis were not significantly different. The magnitude of the MiVZ of the irradiated patients is, in comparison to the magnitude of the MiVZ of the non-irradiated patients, significantly lower (table 5.1). However at this point there is no difference in height SDS between the irradiated and the non-irradiated patients (table 5.2). The magnitude of the MaVZ was comparable for both irradiated and non-irradiated
Table 5.2: Z-score (+SD) for height at diagnosis, at minimal Z-velocity (MiVZ) and at maximal Z-Velocity (MaVZ) for the different treatment protocols.

<table>
<thead>
<tr>
<th>protocol</th>
<th>number of patients</th>
<th>diagnosis MiVZ</th>
<th>MiVZ</th>
<th>MaVZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 with CI</td>
<td>41</td>
<td>-0.3 ± 1.1</td>
<td>-0.5 ± 1.0</td>
<td>-0.7 ± 1.0</td>
</tr>
<tr>
<td>6 + 7 without CI</td>
<td>35</td>
<td>-0.2 ± 0.9</td>
<td>-0.2 ± 0.9</td>
<td>-0.1 ± 1.0</td>
</tr>
</tbody>
</table>

p-value t-test: 0.466 0.102 0.012

CI = cranial irradiation.

patients (table 5.1). So despite a lower Z-velocity at MiVZ the irradiated patients are capable to increase the Z-velocity to the same maximum as the non-irradiated patients. However despite this capacity there is a significant loss in height SDS of the irradiated patients at MaVZ (table 5.2).

In table 5.1 the difference (VZ) is shown between the minimal Z-velocity and the maximal Z-velocity for irradiated and non-irradiated patients. The difference for the irradiated patients is 0.63 (± 0.31) SDS/year which is significantly more than the difference for the non-irradiated patients: 0.41 (± 0.21) SDS/year. So the irradiated patients have a significant more intensive catch-up growth.

In applying the Kernel estimation in this study, two different band widths (smoothing parameters) were used: the 3.1 3.6 band and the 3.8 4.0 band. The sensitivity to band width choice appeared to be vary small.
5.5 Discussion

After treatment for childhood ALL, CI as a component of CNS prophylaxis is significantly associated with reduced final height \(^{67,127}\). Apart from more severe growth retardation during treatment \(^{49,87}\) and blunted pubertal growth \(^{52,90}\), patients who received CI also have incomplete catch-up growth, while patients treated for ALL without CI, during the catch-up growth fully compensate for the preceding growth deficit \(^{49,87}\).

In this study we demonstrated that the decrease of the Z-velocity was significantly longer and the MiVZ was significantly lower, in the irradiated patients, as compared to the non-irradiated patients. The treatment during the decrease of the Z-velocity comprised chemotherapy and corticosteroids in all the protocols and only patients treated according to protocol 5 received CI during this phase of therapy. This implies that cranial irradiation with a dose of 18 Gy has a direct, negative effect on growth velocity and that growth retardation due to CI develops in the early phase of therapy. A remarkable finding is that after the Z-velocity increased, even the patients who received CI can reach a maximal Z-velocity which is comparable to the maximal Z-velocity of patients treated without CI (table 1). This increase of Z-velocity is a degree for the intensity of catch-up growth. So the catch-up growth in patients who received CI is significantly more intensive. Despite a more intensive catch-up growth, the height SDS is significantly lower for the irradiated patients at MaVZ (table 2). This loss in height SDS despite a more intensive catch-up growth in irradiated patients cannot be explained by a difference in duration of catch-up growth as the duration of the catch-up growth is comparable for all patients.

The underlying mechanism for catch-up growth has not yet been fully elucidated. From animal studies \(^{84,94}\) it has become clear that growth hormone plays a role in the accelerated growth during the period of catch-up growth. More recent data suggest that especially the frequency of growth hormone pulses may be a factor in triggering catch-up growth \(^{2,94}\). It is however improbable that disturbance in growth hormone secretion is a causal factor for incomplete catch-up growth after CI. Marky et al. \(^{83}\) performed a longitudinal study of
growth hormone secretion during treatment for childhood ALL. They didn't show any difference in the spontaneous GH secretion during treatment between patients who received no CI and those who received 18 or 24 Gy CI as CNS prophylaxis.

Crowne et al. performed an analysis of 24-hour serum GH profiles using 20-minute sampling of 21 longterm survivors of ALL who received CI with a dose of 18 Gy and 23 normal children. They showed an abnormality of periodicity and a quantitative reduction in GH secretion in patients treated for ALL, which appeared to be restricted to puberty. In the prepubertal children the spontaneous GH secretion was normal and no significant differences in mean number of pulses or mean pulse amplitudes between the irradiated and the control groups were found.

The prevailing explanation for catch-up growth involves a central mechanism which relates body size to a reference point for target size and accelerates or decelerates growth rate accordingly. Experimental data tend to support the hypothesis of a central control of catch-up growth. In animal studies it has been demonstrated that irradiation of the head results in stunted growth. Stunted head-irradiated rats are capable of catch-up growth after fasting, but only to the stunted body-size. This finding suggests that the mechanism which recognize normal body size and which determines the limit of catch-up growth is reset for a smaller body size by head irradiation. In this study we demonstrated that the duration of catch-up growth of patients who received CI is comparable to the duration of catch-up growth of the non-irradiated patients and that the catch-up growth in the irradiated patients is more intensive. Nevertheless the catch-up growth of the irradiated patients is incomplete. These findings support the hypothesis of a reset of the mechanism which recognizes normal body size, to a smaller body size by cranial irradiation.

Acknowledgement: The authors thank Mrs A.E. van ’t Hof-Grootenboer and Miss H. Vogt for their technical assistance.
Intensity of catch-up growth
SHORTENED AND DIMINISHED PUBERTAL GROWTH IN BOYS AND GIRLS TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA


Acta Pediatrica 1996; 85:1091-1095
Chapter 6

6.1 Abstract

Statural growth during puberty was studied longitudinally in 28 patients treated for acute lymphoblastic leukaemia. All patients received prophylactic cranial irradiation. Age at diagnosis was < 7 years, age at final investigation was > 16 years for girls and > 18 years for boys. Growth was analyzed using the Kernel estimation. In girls the onset of puberty and menarche was at a younger age, as compared to reference values, and the duration of the pubertal growth spurt was shorter. Compared to early maturing girls growth velocity at peak height velocity was lower. This resulted in a final height which was shorter than expected on the basis of height standard deviation score before the start of puberty. In boys the duration of the pubertal growth spurt was shorter and the height gain during the growth spurt less than in the reference population. In both sexes the bone age development was accelerated.

6.2 Introduction

Growth disturbances during treatment are frequently reported in children with acute lymphoblastic leukaemia (ALL), particularly when they received cranial irradiation (CI) as central nervous system (CNS) prophylaxis. Central premature puberty and reduction in growth hormone secretion during puberty have also been demonstrated in these children. The combination of early or precocious puberty and growth hormone insufficiency may lead to severe growth impairment during puberty causing a further reduction in final height. One of the most important markers for early detection of puberty is the age at onset of the pubertal growth spurt (PS). The PS starts about one year prior to the onset of thelarche in girls. A method for a more differentiated analysis of growth during puberty and onset of the PS is the statistical concept of the "structural average curve", the so-called Kernel estimation. With the Kernel estimation, truly longitudinal curves can be obtained for velocity and
acceleration. From these curves various phases of pubertal growth can be analyzed in terms of timing, intensity and duration.

In this paper we present the analysis of the PS of 28 patients (11 boys and 17 girls) treated for ALL using the Kernel estimation. Besides, data about final height (FH), age at menarche and bone age development of these patients are presented.

6.3 Patients and Methods

Twenty-eight patients (11 boys and 17 girls) treated for ALL at the University Hospital Nijmegen, between 1972 and 1980 were included in the study. Age at onset of the disease was < 7 years in all patients. Age of final observation was > 16 years for girls and >18 years for boys. The patients were treated according to the consecutive protocols of the Dutch Leukaemia Working Group. Chemotherapy comprised: induction treatment with Vincristine (VCR), Prednisone (Pred.) ± L-Asparaginase and maintenance treatment with 6-Mercaptopurine (6-MP) plus Methotrexate (MTX) alternated with VCR, Pred. ± Cyclophosphamide. Patients received CI with a dose of 24 Gy as CNS prophylaxis and MTX plus Pred. intrathecally. None of the patients received either spinal or total body irradiation.

Measurements. Height was assessed at 6-12 months’ intervals using standard anthropometric techniques. To standardize the results and to allow comparison of children of different ages and sexes, values for height were transformed into standard deviation scores (SDS), using Dutch reference values \(^{112}\). Final height (FH) was defined at the moment that there was a 6-month growth less than 0.2 cm/year and/or at a bone age (BA) of 16 years for girls and 18 years for boys. BA was calculated according to Tanner and Whitehouse \(^{137}\).

Statistical analysis. For the estimation of velocity and acceleration on the longitudinal
growth data, the Kernel estimation was used \(^{41,42}\). Kernel estimation is a smoothing procedure using polynomials up to the degree of 7, holding for a pre-chosen band width for age. For reasons of comparability the band width applied by Gasser \(^{41}\) during puberty of 3.1 year (velocity) and 3.6 year (acceleration) was chosen in this study. Velocity and acceleration curves were plotted for each child. Extracted from the velocity curve were: the age at onset of the PS, defined as the age of minimal velocity (= zero acceleration) before the PS, the age at peak height velocity (PHV), defined as the age of maximal velocity (= zero acceleration) during the PS and the velocity (V) and height (H) reached at these ages. The time of the end of the PS was extracted from the acceleration curve, and expressed as age of maximal deceleration.

Table 6.1: The age, height and growth velocity at the onset of puberty, at peak height velocity (PHV) and at the end of PS (pubertal growth spurt), and the final height of girls treated for ALL \((n=17)\) compared to Swiss reference values \((n=45)\) \(^{43}\).

<table>
<thead>
<tr>
<th></th>
<th>Girls treated for ALL</th>
<th>Swiss reference values for girls</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset PS</td>
<td>8.9 ± 0.2</td>
<td>9.7 ± 1.0</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td>PHV</td>
<td>10.6 ± 0.7</td>
<td>12.2 ± 0.8</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td>End PS</td>
<td>12.1 ± 0.8</td>
<td>13.8 ± 0.8</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td>Duration PS</td>
<td>3.2 ± 0.9</td>
<td>4.1 ± 0.5</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td><strong>HEIGHT (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset PS</td>
<td>134.6 ± 7.1</td>
<td>136.3 ± 7.3</td>
<td>(p = 0.4)</td>
</tr>
<tr>
<td>PHV</td>
<td>146.1 ± 7.5</td>
<td>150.4 ± 6.0</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>End PS</td>
<td>155.9 ± 7.9</td>
<td>160.6 ± 6.0</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>Height gain</td>
<td>20.9 ± 5.3</td>
<td>24.7 ± 2.6</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td><strong>GROWTH VELOCITY (cm/year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset PS</td>
<td>5.7 ± 1.0</td>
<td>4.8 ± 0.6</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td>PHV</td>
<td>7.8 ± 0.8</td>
<td>7.0 ± 1.0</td>
<td>(p &lt; 0.0001)</td>
</tr>
<tr>
<td><strong>FINAL HEIGHT (cm)</strong></td>
<td>160.8 ± 5.8</td>
<td>165.3 ± 5.8</td>
<td>(p &lt; 0.01)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. Reference groups. The Netherlands third nation wide survey \(^{112}\) was used for the SD scores.
For evaluation of the longitudinal pubertal data two reference groups were used. Age, height and velocity data about the PS in boys and girls were compared to the original Swiss reference values as no Dutch values are available for the onset of puberty.

Data about PHV, age at menarche, BA and FH were also compared to Dutch reference values. In order to enable this comparison the Kernel estimation was applied to the longitudinal growth data of these Dutch references. Statistical comparison was made using Student’s t test. Significance was accepted for p-value < 0.05.

### 6.4 Results

The data on PS of girls treated for ALL compared to Swiss reference values are shown in table 6.1. The ages at onset of puberty, at PHV and at the end of PS were significantly lower in girls treated for ALL. The duration of PS in girls treated for ALL was also significantly shorter. The height at onset of puberty was not significantly different in girls treated for ALL. Heights at PHV and at the end of puberty were significantly lower in ALL girls compared to Swiss reference values. However, growth velocity at the onset of puberty and at PHV was significantly higher in girls treated for ALL compared to Swiss girls. This resulted in a final height which was significantly different between the two groups. The adult height of normal Dutch girls, however, is 168.3 cm (SD 6.2).

Age, height, growth velocity and BA at PHV of 17 girls treated for ALL compared to Dutch reference values are shown in table 6.2. Compared to our Dutch reference group the age at PHV of girls treated for ALL was significantly lower. The girls treated for ALL were significantly shorter at PHV. Between the two groups there was no difference in growth velocity and BA at the time of PHV.

Age, height, growth velocity and BA at PHV of early maturing girls treated for ALL compared to early maturing Dutch reference values are also shown in table 6.2. We defined early maturing as PHV before the age of 11 years. Thirteen out of 17 ALL girls
Chapter 6

Table 6.2: Age, height, growth velocity and bone age at peak height velocity (PHV) of all girls (total) treated for ALL (n=17) compared to Dutch reference values (n=86) [17] and of the early maturing girls (n=13) compared to early maturing Dutch references (n=17) [17]. Early maturing is defined as PHV before the age of 11.

<table>
<thead>
<tr>
<th></th>
<th>Girls treated for ALL</th>
<th>Dutch reference values for girls</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10.6 ± 0.71</td>
<td>11.9 ± 0.84</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Early</td>
<td>10.3 ± 0.6</td>
<td>10.7 ± 0.3</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>HEIGHT (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>146.1 ± 7.5</td>
<td>152.9 ± 5.6</td>
<td>p &lt; 0.0005</td>
</tr>
<tr>
<td>Early</td>
<td>144.7 ± 5.7</td>
<td>151.8 ± 3.5</td>
<td>p &lt; 0.005</td>
</tr>
<tr>
<td>GROWTH VELOCITY (cm/year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.8 ± 0.8</td>
<td>8.2 ± 1.2</td>
<td>p = 0.1</td>
</tr>
<tr>
<td>Early</td>
<td>8.0 ± 0.6</td>
<td>9.2 ± 1.4</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>BONE AGE (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.2 ± 0.9*</td>
<td>11.4 ± 0.7</td>
<td>p = 0.5</td>
</tr>
<tr>
<td>Early</td>
<td>11.1 ± 1.0**</td>
<td>10.6 ± 0.5</td>
<td>p = 0.2</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, * n = 11, ** n = 9.

Table 6.3: Age, bone age and height at the menarche of girls treated for ALL compared to normal Dutch girls.

<table>
<thead>
<tr>
<th></th>
<th>Girls treated for ALL</th>
<th>Dutch reference values for girls</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE MENARCHE (years)</td>
<td></td>
<td>12.0 ± 0.4</td>
<td>p &lt; 0.0005</td>
</tr>
<tr>
<td>BONE AGE MENARCHE (cm)</td>
<td></td>
<td>12.7 ± 0.5</td>
<td>p = 0.53</td>
</tr>
<tr>
<td>HEIGHT MENARCHE (years)</td>
<td></td>
<td>152.5 ± 3.0</td>
<td>p &lt; 0.0005</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.
and 17 out of 86 Dutch reference girls met this criterium. Compared to early maturing Dutch girls, age, height and growth velocity of girls treated for ALL were significantly different. The ALL girls reached PHV at a younger age, they were shorter and the growth velocity was lower at PHV. Again there was no difference in BA between the two groups. Table 6.3 shows the age, BA and height at the time of menarche of girls treated for ALL compared to Dutch reference girls. The age at menarche of girls treated for ALL was significantly lower than that of normal Dutch girls. The BA at menarche was comparable in both groups. The height at menarche of girls treated for ALL was significantly shorter than that of the Dutch references. In patients treated for ALL the median time interval between PHV and menarche was 1.35 years (SD 0.47) and the median growth after menarche was 7.1 cm (SD 2.0), which are both within the normal range.

The data about the PS of boys treated for ALL compared to Swiss reference values are shown in table 6.4. There were no differences in the age at onset of puberty, at PHV and at the end of the PS, but the duration of the pubertal growth was significantly shorter in boys treated for ALL. Height at onset of puberty of boys treated for ALL was not different from that of Swiss boys. Height at PHV and at the end of the PS and the height gain during puberty were significantly lower in boys treated for ALL. Growth velocity at onset of puberty and at PHV was comparable in both groups. Final height of boys treated for ALL was significantly shorter. However, final height of normal Dutch boys is 182.0 cm (SD 6.7). Figure 6.1 shows the difference between BA and calender age (CA) (+ SEM) of boys and girls treated for ALL, from diagnosis to puberty. The difference between BA and CA at diagnosis was 0.23 year (+ 0.20). During treatment a retardation in bone maturation occurred: BA - CA at the moment of finishing therapy was -0.48 year (+ 0.16). After cessation of therapy an acceleration in bone age development occurred: BA - CA before the onset of puberty was -0.18 year (+ 0.30). This acceleration continued throughout puberty: BA - CA at PHV was 0.43 year (+ 0.26) and at menarche 1.06 year (+ 0.22). The SDS for heigth of the 28 patients was -0.51 before the start of puberty. At the moment of PHV the SDS for height was declined to -1.48 and at final height the SDS was -1.33.
Table 6.4: The age, height and growth velocity at the onset of puberty, at peak height velocity (PHV) and at the end of PS (pubertal growth spurt) and final height of boys treated for ALL (n=11) compared to Swiss reference values (n=45) [5].

<table>
<thead>
<tr>
<th></th>
<th>Boys treated for ALL</th>
<th>Swiss reference values for boys</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset PS</td>
<td>11.2 ± 0.7</td>
<td>10.9 ± 1.1</td>
<td>p = 0.3</td>
</tr>
<tr>
<td>PHV</td>
<td>13.7 ± 0.6</td>
<td>13.9 ± 1.0</td>
<td>p = 0.3</td>
</tr>
<tr>
<td>End PS</td>
<td>15.0 ± 0.7</td>
<td>15.4 ± 0.9</td>
<td>p = 0.1</td>
</tr>
<tr>
<td>Duration PS</td>
<td>3.8 ± 0.3</td>
<td>4.5 ± 0.6</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td><strong>HEIGHT (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset PS</td>
<td>140.8 ± 6.1</td>
<td>143.6 ± 6.8</td>
<td>p = 0.2</td>
</tr>
<tr>
<td>PHV</td>
<td>156.0 ± 7.7</td>
<td>161.4 ± 6.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>End PS</td>
<td>166.0 ± 8.6</td>
<td>172.4 ± 6.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Height gain</td>
<td>25.9 ± 3.1</td>
<td>28.8 ± 4.0</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td><strong>GROWTH VELOCITY (cm/year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset PS</td>
<td>4.2 ± 0.6</td>
<td>4.3 ± 0.5</td>
<td>p = 0.6</td>
</tr>
<tr>
<td>PHV</td>
<td>8.9 ± 1.3</td>
<td>8.3 ± 0.8</td>
<td>p = 0.1</td>
</tr>
<tr>
<td><strong>FINAL HEIGHT (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>170.8 ± 7.6</td>
<td>177.5 ± 6.7</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.

6.5 Discussion

One of the most important late sequelae after treatment for ALL is impaired adult height and it is clear that in a number of patients there is not only a loss in height potential during the treatment for ALL but a further loss in height prognosis occurs during puberty. Especially children treated for ALL with cranial irradiation as CNS prophylaxis are at risk for short stature from two mechanisms: growth hormone insufficiency and
early pubertal growth \textsuperscript{73,74,81}. The occurrence of early puberty after CI is well documented but less is known about statural growth of these children during puberty. Therefore we performed a longitudinal study on growth during puberty in 11 boys and 17 girls treated for ALL, using the Kernel estimation \textsuperscript{41,42}.

Data about PS in boys and girls were compared to Swiss reference values as no Dutch references are available for the onset of puberty and on these Swiss data the Kernel estimation was applied. Median age of menarche of Swiss girls is 13.4 years \textsuperscript{72} and of Dutch girls 13.28 years \textsuperscript{104} so the timing of puberty of Swiss and Dutch girls is comparable. Final height of Swiss girls and boys is less than Dutch children \textsuperscript{102,112}, therefore for height data the general Dutch references were used. In our study the onset of puberty was, in comparison to Swiss children, significantly earlier in girls treated for ALL but within normal limits for boys. This is in agreement with another study \textsuperscript{97} that reported that after low dose CI (18 - 24 Gy) the high incidence of early puberty was

![Figure 6.1](image-url)

Figure 6.1: Bone age (BA) minus calendar age (CA) (± SEM) at diagnosis (a: n=16, 12), at the end of therapy (b: n=20, 15), prepubertal (c: n=11, 8), at peak height velocity (d: n=14, 11) and at menarche (e, n=13).
predominantly noticed among girls. Damage to the hypothalamic-pituitary axis due to CI can cause early secretion of gonadotrophin releasing hormone and be associated with precocious puberty. There is a sex difference in the response to gonadotrophin releasing hormone and it has been postulated that the CNS control on the onset of puberty is more easily disrupted in girls than in boys. We found that the duration of the PS, in both boys and girls treated for ALL was significantly less than in healthy Swiss children. The consequence was that the height SDS of the 28 patients decreased from -0.51 before the onset of puberty to -1.33 at final height.

At peak height velocity growth velocity of ALL girls was comparable to that of Dutch girls. However as it is known that the earlier children enter puberty, the greater should be their peak height velocity, to compensate for their shorter growth period, we also compared the early maturing ALL girls with early maturing Dutch girls. From this comparison we learned that growth velocity of the ALL girls was significantly less. Height velocity is predominantly controlled by growth hormone pulse amplitude. It has been reported that the expected increase in growth hormone secretion during puberty is absent in children who have undergone low-dose cranial irradiation although in the mentioned study the mean pulse amplitudes of children treated with 18 Gy CI were not significantly different from normal. We found that in the girls treated for ALL age and height at PHV and menarche were significantly different from the mean of the normal Dutch girls. Bone ages at both points were not different. In girls treated for ALL growth after menarche was within the normal range. So the loss in height potential occurs in the early pubertal growth. This is concomitant with the loss of growth velocity in the increment of the early pubertal acceleration.

During treatment the difference between BA and CA, in this and another study, showed a retardation of BA development with a catch-up of BA maturation after cessation of therapy. Moreover we showed that a further acceleration of BA development occurred during puberty.

It has to be emphasized that the Kernel estimation provides us with a method for more differentiated analysis of growth during puberty independent of pubertal characteristics. Especially in boys treated for ALL, testicular size as an indicator for the onset of pubertal
development is not always reliable as it has been reported that testicular size can be influenced by chemotherapy.\textsuperscript{105}

In conclusion, in girls the onset of puberty occurred at a younger age than in references, the duration of PS was shorter, and the BA development was more rapid which resulted in further loss in final height. In boys the onset of puberty was at a normal age but the duration of PS was shorter and the BA maturation was more rapid also resulting in a loss of final height.

A consequence of these conclusions is that the height SDS during puberty, of patients treated for ALL, cannot be compared with age matched references without correlation to the stage of pubertal development.
CHAPTER 7

INFLUENCE OF TREATMENT MODALITIES ON BODY WEIGHT IN ACUTE LYMPHOBLASTIC LEUKEMIA.


Medical and Pediatric Oncology 1996; 27:92-97
Chapter 7

7.1 Abstract

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 non-irradiated patients.

Thirty out 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 dexamethasone versus prednisone, sex, cranial irradiation and high-dose versus low-dose chemotherapy on weight for height was evaluated. Patients who received dexamethasone showed a significant increase in weight for height immediately after 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 versus normal risk protocols.

7.2 Introduction

The last decade many studies have been published on linear growth of children treated for ALL concluding that retardation of linear growth during treatment is a common observation. 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 \textsuperscript{16,88,118,131,135,155}, 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?

Table 7.1: Mean ages at diagnosis, the range of the ages and the sexes of the patients in different treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>high-risk (n=15)</th>
<th>normal-risk (n=77)</th>
<th>protocol 6 dexamethasone (n=19)</th>
<th>protocol 6 prednisone (n=11)</th>
<th>CI (n=54)</th>
<th>non-CI (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age</td>
<td>6</td>
<td>35</td>
<td>11</td>
<td>7</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>(years)</td>
<td>9</td>
<td>42</td>
<td>8</td>
<td>4</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>range</td>
<td>1.1-15.9</td>
<td>0.6-15.5</td>
<td>72.3-12.3</td>
<td>1.6-13.9</td>
<td>0.6-15.9</td>
<td>1.1-14.4</td>
</tr>
</tbody>
</table>

(CI: cranial irradiation)
7.3 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 7.1. Since central nervous system (CNS) involvement could cause hypothalamic dysfunction, patients with CNS involvement were excluded from the study. All patients had entered into first remission within six weeks after diagnosis. Patients with relapse of their disease were excluded from the study.

**Treatment.** Depending on the risk factor of leukemia, patients were divided into two groups:

I: **Normal-risk leukemia** (n=77), defined as leucocyte count in the peripheral blood < 50,000/mm³, without mediastinal enlargement, were 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 (6MP), methotrexate (MTX) alternated with VCR and Pred.

Thirty patients were treated according to protocol 6, 19 of these patients (group Ia) received induction treatment with VCR, Dexamethasone (Dexa) 6 mg/m² 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 mg/m², a doses nearly equal on basis of glucocorticoid activity.

II: **High-risk leukemia** (n=15), defined as leucocyte count > 50,000/mm³, and/or mediastinal enlargement, were treated according to a high-risk protocol comprising induction treatment with cyclophosphamide (Cyclo), VCR, Pred, L-Asp, and adriamycine (Adria). The maintenance treatment consisted of 6-MP, MTX and cyclo alternated with VCR, Pred, Adria and Cytosine-Arabinoside (Ara-C).
Table 7.2: Number of patients during follow-up (n=92). A number of the initial values was missing. At 3 months after diagnosis all patients had entered the averages.

<table>
<thead>
<tr>
<th>Duration in follow-up (years)</th>
<th>0</th>
<th>0.25</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>4.5</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial irradiation (group A)</td>
<td>45</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>53</td>
<td>52</td>
<td>51</td>
<td>47</td>
<td>45</td>
<td>42</td>
<td>41</td>
<td>33</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>No irradiation, exclusive dca (group B)</td>
<td>15</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>14</td>
<td>13</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No irradiation - protocol 6: dca - group 1a</td>
<td>14</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>13</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- protocol 6: pred - group 1b</td>
<td>8</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- other protocol</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Depending on the method of CNS prophylaxis, patients were divided in two groups:

A: Fifty-four patients treated between 1972 and 1984 received cranial irradiation (CI);
37 patients with a dose of 24 Gy in 13 fractions over 17 days and 5 doses MTX and
Pred intrathecally (i.t.) and 17 patients received 18 Gy CI in 10 fractions over 14
days and 5 doses MTX and Pred i.t. (1972 - 1984). None of the patients received
spinal irradiation. The timing of the CI was 5 to 6 weeks after diagnosis for all
patients. Duration of follow-up up to 12 years.

B: Thirty-eight 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 maintenance treatment 8 doses of MTX, Pred and
Ara-C were given i.t. Duration of follow-up up to 4.5 years.

Forty-three out of 77 patients with normal-risk and 11 out of 15 patients with high-risk
leukemia received CI. The number of patients during the follow-up period is shown in table
7.2.

Measurements and methods. Patients heights and weights were measured by experienced
staff. During the two years of treatment patients were measured 8 to 12 times per year and
during the years of follow-up 1 to 4 times per year. Weight for height was studied. In order
to compare the patients group with the general population Z-scores were calculated for
weight for height using Dutch reference values 112. 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 146. 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-t-test and analysis of
variance. Significance was accepted for p value < 0.05.

7.4 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 dexamethasone (group Ia) with the Z-scores of patients who received prednisone instead of dexamethasone (group Ib) (figure 7.1). The chemotherapy in both groups was the same and neither of these patients received cranial irradiation. At diagnosis the Z-score of weight for height of group Ia was -0.1 ± 1.3 (+ standard deviation) 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.

Figure 7.1: Mean Z-scores (+ 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.
and \(-0.8 \pm 1.4\) 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 three months and to examine whether the difference at three months could be an artifact due to the 5 and 3 patients that were added to each group, respectively, we calculated the change from the baseline: \( Z ( Z = Z_x - Z_0, Z_x \text{ is the Z-score at 3 months and } Z_0 \text{ is the Z-score at diagnosis}) \) of the 14 and 8 patients at three months. The \( Z \) of the 14 patients treated with dexamethasone was 0.5 \( \pm \) 0.8 and of the 8 patients treated with prednisone was -0.2 \( \pm \) 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 2-way ANOVA the influence of sex and cranial irradiation on weight for

![Figure 7.2: Mean Z-score (± SEM) of weight for height of patients treated for ALL with prophylactic cranial irradiation (solid line), n=54, or without prophylactic cranial irradiation (broken line), n=19. All patients received prednisone as corticosteroid. * = p <0.05, ** p <0.01, indicating the ANOVA significance level.](image-url)
height was studied. The Z-score of weight for height of the irradiated group compared with the Z-scores of patients who did not receive CI are shown in figure 7.2. No significant differences between the groups were shown during the first year of therapy. At two and four 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 7.3 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 was more positive: 0.7 ± 0.9. The Z-score remained above the mean of the normal population during the whole period of follow-up. Z-score 12 years after diagnosis: 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 versus patients treated according to a more intensive high-risk protocol.
7.5 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 exception of the group of patients treated with dexamethasone, showed loss of weight during the first three 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. During the next three to six 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 but one 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 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: cranial irradiation and treatment with dexamethasone are associated with excessive weight gain. Patients treated without CI and patients who received prednisone instead of dexamethasone showed normal weight development during the second year of therapy and after finishing treatment. Another study has also identified CI as a risk factor for developing obesity. CI is also associated with impaired height growth. Some authors 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. 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 corticotrophin and thyroid stimulating hormone has not been demonstrated in children treated for ALL. The impaired linear growth seen in children after CI has been thought to be attributed to minor abnormalities in the secretion of growth hormone. Dacou-Voutetakis et al. showed transient alterations in growth hormone secretion early after CI 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., suggesting that CI 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. Hypothalamic damage perse 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. Studies on growth hormone profiles of children after low-dose CI or total body irradiation show a disturbance of frequency modulation of growth hormone secretion. Both studies 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 CI. Excess of weight gain during and after treatment for ALL is also shown in children treated with dexamethasone, whereas children treated with prednisone in an equivalent dose showed normal weight development. Besides the well-known peripheral effects of corticosteroids on growth and weight, glucocorticoids also exert an effect on the regulation of growth hormone secretion. High dose prednisone (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. Dexamethasone in a dose of 10 mg /m² / day completely suppressed the spontaneous growth hormone secretion in patients treated for ALL. The inhibiting action of corticosteroids on growth hormone responses seems to be mediated by an enhancement of the somatostatin effect at the pituitary level.

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 CI the overweight persisted during the whole follow-up period of twelve 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\textsuperscript{64}. 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.
Body weight in ALL.
CHAPTER 8

GENERAL DISCUSSION
8.1 General discussion

The regulation of human growth, from infancy to adulthood, is a complex mechanism involving many different hormones and growth factors acting at different levels: central, systemic and at the level of the growth plate. In the regulation of growth during childhood three different phases can be distinguished: growth during infancy which is mainly regulated by nutrition and local growth factors, growth of midchildhood regulated by growth hormone and thyroid hormone and growth during puberty which is not only dependent of growth hormone and thyroid hormone but also of sex steroids. This remarkable integrated process of growth regulation will, under normal conditions, result in growth according to a predominated growth curve, a curve which is genetically determined. In view of the complexity of the mechanism it is not astonishing that enviromental factors and diseases in childhood can cause a disturbance of this process resulting in growth retardation.

Growth retardation, a deflection away from the normal growth curve, is a frequent side-effect in children treated for ALL. Many causal factors can contribute to the growth retardation in these patients. The disease ALL itself originates in the bone-marrow and could therefore interfere with control of growth at the level of the growth plate as the hematopoietic bone-marrow plays a role in bone cell development. Each of the three treatment modalities applied in the treatment of ALL: chemotherapy, radiotherapy and corticosteroids can have an influence on growth, while side-effects of chemotherapy and radiotherapy such as nausea and vomiting can lead to malnutrition which influences growth. In this thesis we focussed our attention to 1. the growth of children during and after treatment for ALL, by means of biometry of growth data and 2. the discrete contribution to growth retardation of the different causal factors.

When designing a study on growth and especially on disturbed growth where multiple
causal factors can add to the growth retardation, it is important to standardize the results. The use of standard deviation scores not only enables comparison between sexes and ages but also between different studies.

For the inclusion criteria of a group of children in a growth study, the three different phases of growth during childhood have to be taken into account, notably the pubertal growth spurt can interfere with catch-up growth or mask growth retardation.

The design of a longitudinal study is preferred above a cross-sectional study as a longitudinal study reveals individual differences in growth velocity and in the timing of particular phases of growth such as the pubertal growth spurt.

Biometry of the longitudinal growth data of patients treated for ALL, with cranial irradiation as central nervous system prophylaxis, showed a SDS for height which decreased during the first year of treatment, followed by a period of parallel growth. After cessation of therapy the SDS for height increased, but this catch-up growth was incomplete (chapter 2). After catch-up growth again a period of parallel growth occurred till puberty. During puberty a further decrease of the SDS for height was noticed, caused by an insufficient growth spurt, resulting in a significant loss of height SDS at final height (chapter 6).

The SDS for height of patients treated without cranial irradiation also decreased during the first six months of therapy followed by a period of parallel growth but these patients showed a complete catch-up growth after cessation of therapy (chapter 2). To date no sufficient data are obtained of these patients to describe growth during puberty.

The medical history of a child presenting with ALL is usually short with complaints existing no longer than several weeks to months. In all studies concerning growth during treatment for ALL, the heights of the patients at diagnosis are not significantly different from the mean height of the normal population. From these studies the conclusion has been drawn that the influence of the disease ALL itself is minimal. In chapter 4 of this thesis we did not only study the attained height of the patients but also growth acceleration and
growth velocity. From this study we learned that the growth velocity of a child with ALL is extremely low at diagnosis. Immediately after start of the remission-induction therapy with chemotherapy and corticosteroids, acceleration of growth with increase in growth velocity was demonstrated despite the growth suppressive effects of the treatment instituted. This is a clear indication that there is an influence on growth of the disease ALL which is not surprising in view of the involvement of the bone-marrow function in the growth of the bone.

The duration of the low growth velocity due to ALL is apparently not long enough to cause a significant decrease in height SDS before the diagnosis of ALL is made. In most of the children with ALL, complete remission with restoration of the bone marrow function is achieved within six weeks after start of therapy. So although there is a clear influence of ALL on growth the duration of this influence is limited.

Despite acceleration of growth i.e. an increase in growth velocity immediately after start of therapy, which continued throughout the whole period of treatment, the growth velocity of the patients with ALL remained below the growth velocity of the normal population during the first period of treatment, resulting in a significant decrease of height SDS (chapters 4 and 2).

The suppression of the increase in growth velocity during this phase of therapy is probably a consequence of the growth suppressive effects of the treatment modalities.

The remission-induction therapy in children with ALL always comprises chemotherapy and corticosteroids. The growth suppressive effects of corticosteroids are well known and the possibilities of interferences of corticosteroids, in the complex mechanism of growth regulation, are numerous. If there is an additional growth suppressive effect of chemotherapy during this early phase of therapy could not be investigated as all patients received during this phase the combination of chemotherapy and corticosteroids. Although little is known about the influence of chemotherapy on growth, it can be assumed that chemotherapy, in a certain dosage, will have a growth suppressive effect, as chemotherapy causes aplasia of
the bone-marrow. Bone-marrow aplasia could affect growth factors which originate from the bone-marrow cells and are involved in growth of the bone. Besides chemotherapy might exert a direct growth suppressive effect at the level of the growth plate. In children treated for ALL multiple growth arrest lines are seen on the X-ray of the bone.

In this thesis, indeed, a clear influence of chemotherapy on growth could be demonstrated. In chapter 2 a group of patients was identified with a significantly more severe growth retardation during treatment. These patients received cranial irradiation as central nervous system prophylaxis and chemotherapy and corticosteroids during the remission induction therapy but because of the fact that they had a high risk leukemia these patients received high dose chemotherapy. The growth of these patients was significantly worse than of patients treated with cranial irradiation and normal dose chemotherapy. In patients who were not irradiated no different influences of high dose versus normal dose chemotherapy, on growth, were noticed. Herewith we demonstrated that there is a synergistic negative effect on growth of high dose chemotherapy and cranial irradiation.

From the results described in chapter 3 we learned that the growth suppressive effect of chemotherapy with 6-Mercaptopurine and Methotrexate is as strong as the growth suppressive effect of the same chemotherapy in combination with corticosteroids.

In children who received cranial irradiation as a part of their treatment three moments of blunted growth could be detected.

- During the first year of therapy growth retardation in these children was more severe than in children who didn’t receive cranial irradiation (chapter 2). The pathogenesis of this early growth retardation is unknown. A well known side-effect of cranial irradiation is growth hormone insufficiency or deficiency but in studies that analysed growth hormone secretion in patients who received cranial irradiation it was demonstrated that growth hormone secretion during this phase of therapy was normal.

- In contrast to patients who were not irradiated the catch-up growth of patients who received cranial irradiation was incomplete (chapter 2). In the
study concerning catch-up growth (chapters 4 and 5) it was shown that the duration of catch-up growth was not different for patients treated with and without cranial irradiation. Besides the catch-up growth was even more intensive in the irradiated patients. From these findings it was hard to understand that especially the irradiated patients had an incomplete catch-up growth. However these results do support the hypothesis that the central mechanism which recognizes normal body size and which determines the limit of catch-up growth, is reset for a smaller body size by cranial irradiation.

A third moment of growth retardation after cranial irradiation is the phase of the pubertal growth spurt which is described in chapter 6. In girls who received cranial irradiation the onset of puberty and the menarche were significantly earlier than in the reference population. The causal factor for this early onset of puberty is thought to be cranial irradiation which caused damage to the hypothalamic-pituitary axis leading to early secretion of gonadotrophin releasing hormone and early start of puberty. There is a sex difference in the response to gonadotrophin-releasing hormone and it has been postulated that the control mechanism of the central nervous system, for the onset of puberty is more easily disrupted in girls than in boys. This could be an explanation for the observation that only in girls the onset of puberty is early after cranial irradiation. For both boys and girls it turned out that the duration of the pubertal growth spurt was shorter, the bone-age development was accelerated and the height gain during the growth spurt was less than in the reference population. The diminished growth during puberty of patients who received, at a younger age, cranial irradiation during the treatment for ALL can be due to a relative growth hormone deficiency or growth hormone insufficiency, developed as a late side effect of cranial irradiation.

During the follow-up of patients who received cranial irradiation at a younger age the
aspects of early pubertal development and accelerated bone-age development during puberty must be taken into account. It is important not only to measure height and weight but also to be aware of pubertal development and to analyse bone-age. Height measured during the follow-up period always must be related to the development of pubertal characteristics and bone age development.

In patients who have a significant loss in height SDS due to treatment for ALL, an indication can arise for treatment with growth hormone during puberty. It is important to start such a treatment early, or in combination with gonadotrophin-releasing hormone agonists, as the time over which the treatment can be applied is limited.

In the literature there is much debate over the different influences on growth of cranial irradiation with a dose of 18 or 24 Gy. In our study described in chapter 2 we didn’t find a significant difference in height SDS, during and 2.5 years after treatment, of children treated with 18 or 24 Gy. Considering our observation of a synergistic negative effect on growth of high dose chemotherapy and cranial irradiation (chapter 2) we would emphasize that the (additional) influence of chemotherapy on growth should not be ignored in studies focussed on the comparison the different effects of 18 and 24 Gy. The duration or intensity of chemotherapy could be confounding factors.

Although treatment modalities played an important role in growth retardation of patients treated for ALL, from the velocity and acceleration studies in chapters 4 and 5 we may conclude that the start of the catch-up growth is independent of the moment of cessation of therapy.

The nutritional status of a child can have an influence on growth. Nausea and vomiting, as side effects of chemotherapy and radiotherapy, can cause malnutrition in cancer patients. At present tube-feeding is often used to prevent patients for malnutrition but before tube-feeding was introduced in the supportive care of cancer patients, malnutrition could be an additional factor for diminished growth during treatment. In our study on weight for height (chapter 7) we demonstrated that all patients, with exception of patients who received
dexamethason during the remission induction phase, had a significant loss of weight during the first three months of therapy. In this phase underweight could have an influence on statural growth. During the next months weight for height increased to normal but for patients who received dexamethason and patients who were irradiated, weight for height increased further and the SDS for weight for height remained above the mean of the normal population during the whole period of follow-up.

Next to the fundamental property of human growth that height proceeds according to a predicted growth channel, it is a common experience that, under normal conditions, organisms follow predictable patterns of proportionate growth for height and weight. Data from animal studies favour the existence of a proportionate growth control located in the brain. Especially endocrine disorders such as hypothyroidism, hypercortisolism and growth hormone deficiency, that cause blunted growth, can alter body proportions. Discordant growth in body weight and tail length has occurred in neonatal rats which have been stunted by bilateral irradiation of the head. In patients who received either dexamethason or cranial irradiation as a part of their treatment, the persistence of the overweight during the whole period of follow-up, could indicate a damage to or reset of the central mechanism which regulates proportional growth.

In summary the influences of the studied modalities on growth:

- The disease ALL exerts its effect on growth during the early phase of therapy, probably before complete remission is achieved.
- Chemotherapy and corticosteroids are additional causal factors for growth retardation during the first six months of therapy.
- Chemotherapy plays a role in the inhibition of catch-up growth during the phase of maintenance therapy
- High dose chemotherapy and cranial irradiation have a synergistic negative effect on growth.
Cranial irradiation exerts its negative effect on growth during different phases of growth. During the first six to twelve months of therapy cranial irradiation causes a more severe growth retardation. The catch-up growth is incomplete. In girls early pubertal development appears and the pubertal growth spurt in boys and girls is insufficient.

With exception of patients who received dexamethasone, all patients have underweight, as reflection of a bad nutritional status, during the first three months of therapy. During this period underweight could attribute to growth retardation.

In general it can be concluded that risk factors for significant loss of height at final height are: cranial irradiation in combination with high dose chemotherapy, early onset of puberty in girls and small height at onset of puberty of patients who received cranial irradiation. During the follow-up of patients who have been treated for acute lymphoblastic leukemia these factors have to be taken into account.

In this thesis a survey of the biometry of growth of children treated for ALL is presented. The conclusions of the studies urge the need for further investigations to the underlying mechanisms for the development of growth retardation. The possibilities of interferences in the complex mechanism of the regulation of growth are numerous and will be different for the different entities. It is already known that cranial irradiation can cause growth hormone insufficiency or growth hormone deficiency, which only occurs as a late side effect. The underlying mechanism for the early growth retardation in children treated for ALL is unknown. Besides possible disturbances in the endocrine control of growth there is also a possibility that disturbances in the local control of growth, at the level of the growth plate, already exists at diagnosis of ALL or could develop during treatment with cranial irradiation, chemotherapy and corticosteroids.

In our department a study is ongoing to the endocrine control of growth of children during the early phase of treatment for ALL.
CHAPTER 9

SUMMARY
Chapter 9

9 Summary

The incidence of childhood cancer is one per 10,000 children in the age group of 0-15 years. Acute lymphoblastic leukaemia (ALL) is the most frequent diagnosed malignancy accounting for 30% of all childhood malignancies. Introduction of central nervous system (CNS) prophylaxis in the treatment for ALL and intensification of therapy have resulted in a survival rate of ± 70%. Many of these survivors have to face late side effects. One of the most important late effects after treatment for ALL is growth retardation. Causal factors which could attribute to growth retardation after treatment for ALL are the disease ALL itself, chemotherapy, radiotherapy, corticosteroids and underweight as a sign of bad nutrition due to the disease ALL and to nausea and vomiting during treatment. In the studies presented in this thesis we performed a retrospective, longitudinal study to different influences on growth of the separate entities.

Chapter one presents an overview of the regulation of normal human growth and possible influences on that related to ALL. From this the aim of the study was defined and the studies reported in this thesis were described. The aim of the study is to investigate the influence on growth of the distinct entities: the disease ALL itself, nutritional status reflected by weight, chemotherapy, radiotherapy and corticosteroids in order to identify risk factors in the treatment for ALL which are responsible for growth retardation.

In chapter two we describe the statural growth, from diagnosis to 2.5 years after cessation of therapy, of 85 children treated for ALL. To avoid the influence of the pubertal growth spurt all patients were prepubertal during the study period. According to the central nervous system prophylaxis, the patients were divided into three groups: patients who received cranial irradiation with a dose of 24 Gy, patients who received cranial irradiation (CI) with a dose of 18 Gy and patients who were not irradiated. According to the risk of leukaemia patients were divided into normal-risk and high-risk groups. All patients show a decrease of the standard deviation score (Z-score) for height
during the first 6-12 months of therapy. The patients who received cranial irradiation have a significant further decline of the Z-score for height. After a period of parallel growth all patients show catch-up growth. In contrast to the non-irradiated patients the catch-up growth of the irradiated patients is incomplete.

There is no difference in growth pattern between patients who received CI with 18 versus 24 Gy and chemotherapeutic treatment according to high-risk versus normal-risk protocols. However a synergistic negative effect of more intensive chemotherapy and CI on growth is demonstrated.

In chapter three we describe growth during maintenance therapy. Until 1988 maintenance therapy comprised chemotherapy and corticosteroids. The patients treated according to these protocols didn’t show catch-up growth during this phase of therapy. The protocols which were applied after 1988 only comprised chemotherapy during maintenance therapy. The expectation was that if corticosteroids would be the major causal factor for the inhibition of catch-up growth, catch-up growth could occur during the phase of maintenance therapy in those patients who only received chemotherapy.

In this study we compare the Z-score for height during maintenance therapy of 2 groups of prepubertal patients; one group received chemotherapy and corticosteroids and the other group only received chemotherapy during maintenance therapy. No significant difference in Z-score for height is noticed between the two groups, so it can be concluded that the growth suppressive effect of chemotherapy with 6-Mercaptopurine and Methotrexate is as strong as the growth suppressive effects of the same chemotherapy in combination with corticosteroids. So at least chemotherapy alone has a growth suppressive effect.

In the chapters four and five we describe catch-up growth. After a period of decrease of the Z-score for height and a period of parallel growth, all patients show an increase of the Z-score for height. For the patients who were not irradiated the catch-up growth is complete, however patients who received CI have an incomplete catch-up growth. At this point the irradiated patients lose height with consequences for final height. By means of
analysing growth velocity, growth acceleration, Z-velocity and Z-acceleration curves we investigated the influence of different treatment modalities: chemotherapy, radiotherapy and corticosteroids on catch-up growth.

In chapter 4 the timing and in chapter five the intensity of catch-up growth is described. At diagnosis of ALL the growth velocity of the patients is low. Growth accelerates immediately after start of treatment resulting in an increase in growth velocity. From this observation we may conclude that there is an influence of the disease ALL on growth. Despite an increase of growth velocity after start of therapy and a further increase in growth velocity during the whole period of therapy, an increase in Z-score for height is noticed not before the Z-velocity is positive. So the start of the positive Z-velocity is the start of the catch-up growth. For the irradiated patients the moment of start of the positive Z-velocity is significantly later than for the non-irradiated patients. Although the start of the catch-up growth for the irradiated patients is about the moment of cessation of therapy from this study it is clear that the moment of start of catch-up growth, is independent of the moment of cessation of therapy. The start of the catch-up growth coincides accidently with the cessation of therapy. The duration of catch-up growth is comparable for all patients.

The intensity of catch-up growth is defined as the distance between the minimal and the maximal Z-velocity. The minimal Z-velocity is significantly lower for the irradiated patients and the maximal Z-velocity is comparable for all patients. So catch-up growth is more intensive in the irradiated patients.

The observations that the timing of catch-up growth is comparable for irradiated and non-irradiated patients and that for irradiated patients the catch-up growth is more intensive, while the catch-up growth in irradiated patients is incomplete, support the hypothesis that cranial irradiation causes a reset of the central mechanism, which recognizes normal body size, to a smaller body size.

No different influences on catch-up growth are noticed of maintenance therapy with or without corticosteroids.
In chapter 6 growth during puberty is described of 11 boys and 17 girls. All patients received cranial irradiation with a dose of 24 Gy as CNS prophylaxis. The age at diagnosis for ALL was below 7 years, the age at final investigation was above 16 year for girls and above 18 years for boys. In girls the onset of puberty and menarche is at a younger age as compared to reference values and the duration of the pubertal growth spurt is shorter. Compared to early maturing girls, the growth velocity at peak height velocity is lower. This results in a final height which is shorter than expected on the basis of the height SDS before the start of puberty. In boys the duration of the pubertal growth spurt is shorter and the height gain during the growth spurt less than in the reference population. In both sexes the bone age development is accelerated.

In chapter 7 a longitudinal study to weight for height of 92 patients treated for ALL is described. Fifty-four patients received CI with a dose of 18 or 24 Gy and 38 patients didn’t 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 non-irradiated 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 dexamethasone versus prednisone, CI and high-dose versus low-dose chemotherapy on weight for height is evaluated. Patients who received dexamethasone show a significant increase in weight for height immediately after start of therapy. In patients who received CI, weight for height significantly increases after the first year of treatment. The overweight in these patients persists during the whole follow-up period. The weight for height of patients treated with prednisone and of patients who didn’t receive CI is below the mean of the normal population during treatment but is not different from normal after cessation of therapy. No difference in weight gain is seen between boys and girls and between patients who were treated with high versus normal risk protocols.
Chapter 9

The conclusions of the studies presented in this thesis are discussed in chapter 8. In summary the conclusions are: the disease ALL exerts its effect on growth during the early phase of therapy probably before complete remission is achieved. Additional causal factors for growth retardation during the first six months of therapy are chemotherapy and corticosteroids. Chemotherapy plays a role in the inhibition of catch-up growth during the phase of maintenance therapy. High dose chemotherapy and cranial irradiation have a synergistic negative effect on growth. Cranial irradiation exerts its negative effect on growth during different phases of growth. During the first six to twelve months of therapy cranial irradiation causes a more severe growth retardation. The catch-up growth is incomplete. In girls early pubertal development appears and the pubertal growth spurt in boys and girls is insufficient. Underweight as a reflection of a bad nutritional status could attribute to the growth retardation during the first three months of therapy as during this period all patients, with exception of the patients who received dexamethason, have underweight.
CHAPTER 10

SAMENVATTING
10 Samenvatting

De incidentie van kanker op de kinderleeftijd is één per 10.000 kinderen in de leeftijd van 0 - 16 jaar. In 30% van alle oncologische aandoeningen is er sprake van acute lymfatische leukemie (ALL). ALL is daarmee de meest voorkomende maligniteit op de kinderleeftijd. Na de introductie van centraal zenuwstelsel (CZS) profylaxe in de behandeling van ALL en intensivering van behandeling zijn de genezingskansen van kinderen met ALL gestegen tot + 70%. Echter veel patiënten die genezen zijn van ALL hebben late gevolgen. Eén van de meest voorkomende bijwerkingen na behandeling voor ALL is het achterblijven in groei.

Oorzakelijke factoren die kunnen bijdragen aan groeiachterstand na behandeling voor ALL zijn: de ziekte ALL zelf, chemotherapie, radiotherapie, het gebruik van corticosteroïden en een slechte voedingstoestand als gevolg van de ziekte ALL en ten gevolge van misselijkheid en braken als bijwerkingen van de behandeling. In dit proefschrift worden retrospectieve, longitudinale studies beschreven naar de afzonderlijke bijdrage van de verschillende oorzakelijke factoren aan de groeiachterstand na behandeling voor ALL.

In hoofdstuk 1 wordt een overzicht gegeven van de regulatie van normale groei en de mogelijke invloeden daarop van de ziekte ALL en van de behandeling modaliteiten die worden toegepast bij de behandeling van ALL. Hieruit werd het doel van het onderzoek gedefinieerd. Het doel van het onderzoek is het analyseren van de invloed op de lengtegroei van de verschillende factoren: de ziekte ALL, gewicht als een maat voor de voedingstoestand, chemotherapie, bestraling en therapie met corticosteroïden. Daarbij komt de vraag of er bepaalde risicofactoren zijn die verantwoordelijk gesteld kunnen worden voor het ontstaan van een groeiachterstand na behandeling voor ALL?

In hoofdstuk 2 wordt de lengtegroei beschreven over de periode vanaf diagnose tot 2,5 jaar na het staken van de therapie van 85 patiënten die behandeld zijn voor ALL. Om de
Samenvatting

invloed van de puberteitsgroei spurte te vermijden werden alleen patiënten bestudeerd die prepuberaal waren tijdens de studie periode. Afhankelijk van de CZS profylaxe werden de patiënten ingedeeld in 3 groepen: patiënten die schedelbestraling kregen met een dosis van 24 Gy, patiënten die schedelbestraling kregen met een dosis van 18 Gy en patiënten die geen schedelbestraling kregen. Afhankelijk van de risicofactor van de leukemie werden patiënten verdeeld in een groep met normaal risico en een met hoog risico. Bij alle patiënten wordt een significante daling gezien van de standaard deviatie score (Z-score) voor de lengte gedurende de eerste 6-12 maanden van de behandeling. Bij patiënten die schedelbestraling kregen wordt een significante verdere daling van de Z-score voor lengte gezien gevolgd door een periode van stabiele groeisnelheid waarna bij alle patiënten inhaalgroei wordt waargenomen. De niet bestraalde patiënten haalden het lengteverlies volledig in, echter bij patiënten die schedelbestraling hebben ondergaan wordt een incomplete inhaalgroei gezien.

Er is geen verschil in lengtegroei tussen patiënten die 24 Gy schedelbestraling en patiënten die 18 Gy schedelbestraling kregen. Evenmin is er verschil in lengtegroei na behandeling volgens een protocol voor de normale risico groep en volgens een hoog risico protocol. Er is echter een synergistisch negatief effect op de lengtegroei van hoge dosis chemotherapie en schedelbestraling.

In hoofdstuk 3 wordt de lengtegroei beschreven tijdens de fase van onderhoudstherapie. Tot 1988 bestond de onderhoudstherapie uit een combinatie van chemotherapie en corticosteroïden. De patiënten die deze onderhoudstherapie kregen, toonden geen inhaalgroei tijdens de fase van onderhoudstherapie. In de behandelingsscripten na 1988 bestond de onderhoudstherapie alleen uit chemotherapie. De verwachting was dat, wanneer vooral corticosteroïden een remmende werking hadden op de groei in deze fase van de behandeling, er mogelijk wel inhaalgroei zou kunnen optreden bij die patiënten die in deze fase van de behandeling alleen chemotherapie kregen.

In de studie die beschreven wordt in hoofdstuk 3 wordt de Z-score voor lengte tijdens onderhoudstherapie van 2 groepen prepuberale patiënten vergeleken: één groep kreeg chemotherapie en corticosteroïden en de andere groep kreeg alleen chemotherapie tijdens
onderhoudstherapie. Er wordt geen significant verschil gezien in Z-score voor lengte tussen de twee groepen patiënten. De conclusie van dit onderzoek is dat de groeiremmende werking van chemotherapie met 6-Mercaptopurine en Methotrexaat alleen, gelijk is aan de groeiremmende werking van dezelfde chemotherapie in combinatie met corticosteroïden en dat dus minstens ook chemotherapie een groeiremmende werking heeft.

In de hoofdstukken 4 en 5 wordt de inhaalgroei beschreven. Na een periode van daling van de Z-score voor lengte gevolgd door een periode van constante groeisnelheid, vertonen alle patiënten een toename van de Z-score voor lengte, dus inhaalgroei. In tegenstelling tot de niet bestraalde patiënten is de inhaalgroei voor bestraalde patiënten incompleet en ontstaat er op dit moment lengte verlies dat consequenties heeft voor de eindlengte. Door middel van analyse van curves van groeisnelheid, groeiversnelling, Z-snelheid en Z-versnelling wordt de invloed van de verschillende behandelingsmodaliteiten: chemotherapie, radiotherapie en corticosteroïden op de inhaalgroei bestudeerd.

In hoofdstuk 4 wordt de timing en in hoofdstuk 5 de intensiteit van de inhaalgroei beschreven. Op het moment van het stellen van de diagnose ALL is de groeisnelheid laag. Direct na aanvang van de behandeling wordt een groeiversnelling met een toename van de groeisnelheid gezien. Hieruit kunnen wij concluderen dat de ziekte ALL invloed heeft op de lengtegroei. Ondanks een toename van de groeisnelheid direct na de start van de behandeling met een verdere toename van de groeisnelheid tijdens de hele periode van behandeling, wordt een toename van de Z-score voor lengte pas gezien vanaf het moment dat de Z-snelheid positief wordt. Hieruit kan geconcludeerd worden dat het moment waarop de Z-snelheid positief wordt, het werkelijke begin van de inhaalgroei is. Het moment waarop de Z-snelheid positief wordt is voor bestraalde patiënten significant later dan voor de niet bestraalde patiënten. Hoewel bij bestraalde patiënten het moment waarop de inhaalgroei begint ongeveer gelijk valt met het moment van staken van de therapie, kan uit deze studie geconcludeerd worden dat het begin van de inhaalgroei onafhankelijk is van het moment van staken van de therapie en dat het samenvallen van deze momenten
De intensiteit van de inhaalgroei is gedefinieerd als de afstand tussen de minimale en de maximale Z-snelheid. De minimale Z-snelheid van de bestraalde patiënten is significant lager dan de minimale Z-snelheid van de niet bestraalde patiënten. De maximale Z-snelheid is gelijk voor alle patiënten. Hieruit kan geconcludeerd worden dat de intensiteit van de inhaalgroei hoger is bij de bestraalde patiënten.

De bevindingen dat de duur van de inhaalgroei gelijk is voor bestraalde en niet bestraalde patiënten en dat de intensiteit van de inhaalgroei groter is bij bestraalde patiënten, terwijl toch de uiteindelijke Z-score voor lengte achterblijft, ondersteunen de hypothese dat schedelbestraling een beschadiging geeft van het centrale mechanisme dat de normale lichaamslengte herkent waarbij het mechanisme wordt afgesteld op een kortere lichaamslengte. Er wordt geen verschillende invloed gezien op de inhaalgroei van onderhoudstherapie met en zonder corticosteroïden.

In hoofdstuk 6 wordt de lengtegroei beschreven tijdens de fase van de puberteit van 11 jongens en 17 meisjes. Alle patiënten die in deze studie zijn opgenomen kregen schedelbestraling met een dosis van 24 Gy als CZS profylaxe. De leeftijd van deze patiënten bij het stellen van de diagnose ALL was < 7 jaar en de leeftijd waarop het laatste vervolg onderzoek plaatsvond was > 16 jaar voor de meisjes en > 18 jaar voor de jongens. In vergelijking met de referentie populatie treedt bij meisjes het begin van de puberteit en de menarche op een jongere leeftijd op en is de duur van de puberteitsgroei korter. In vergelijking met meisjes die vroeg in de puberteit komen is de groeisnelheid op het moment van Peak Height Velocity lager. Het gevolg hiervan is dat de bereikte eindlengte korter is dan verwacht op basis van de SDS voor lengte voor de start van de puberteit. Bij jongens is de duur van de puberteitsgroei korter en de lengtewinst tijdens de puberteitsgroei korter dan in de referentie populatie. Bij beide sexen is de ontwikkeling van de botrijpheid versneld.
In *hoofdstuk 7* wordt een longitudinale studie beschreven naar gewicht naar lengte van 92 patiënten. Vierenvijftig patiënten kregen schedelbestraling met een dosis van 18 of 24 Gy en 38 patiënten werden niet bestraald. Zevenenzeventig patiënten werden behandeld met chemotherapie volgens een normaal risico protocol en 15 patiënten kregen een intensievere behandeling met chemotherapie volgens een hoog risico protocol. Bij de meeste bestraalde patiënten was de follow-up duur 12 jaar en voor de niet bestraalde patiënten 4,5 jaar. Dertig van de 92 patiënten werden behandeld volgens een protocol zonder schedelbestraling maar met een verschil in het gebruik van corticosteroïden: 19 patiënten kregen dexamethason tijdens de remissie-inductie en onderhoudsbehandeling en 11 patiënten kregen prednison. De invloed van dexamethason versus prednison, schedelbestraling en hoge dosis versus lage dosis chemotherapie op gewicht naar lengte wordt geanalyseerd.

Patiënten die dexamethason kregen ontwikkelden een significante toename van gewicht naar lengte direct na de start van de behandeling. Bij patiënten die schedelbestraling kregen neemt het gewicht naar lengte significante toe na het eerste jaar van de behandeling. Het overgewicht van deze patiënten blijft tijdens de hele periode van follow-up bestaan. Het gewicht naar lengte van patiënten die behandeld werden met prednison en van patiënten die niet bestraald werden is tijdens de behandeling onder het gemiddelde gewicht van de normale populatie en normaliseert na het staken van de therapie. Er is geen verschil in toename van gewicht tussen jongens en meisjes en tussen patiënten die behandeld werden volgens hoog of normaal risico protocol.

In *hoofdstuk 8* volgt een algemene discussie over de conclusies van het onderzoek. De verschillende factoren die een invloed uitoefenen op de lengtegroei zijn: de ziekte ALL, de drie behandelingsmodaliteiten: chemotherapie, schedelbestraling en corticosteroïden en een slechte voedingstoestand van de patiënt. ALL heeft een negatieve invloed op de lengtegroei tijdens de vroege fase van de behandeling waarschijnlijk tot het moment dat complete remissie is bereikt. Tijdens de eerste zes maanden van de behandeling hebben chemotherapie en corticosteroïden een groeiremmend effect. Chemotherapie heeft een remmende werking op de inhaalgroei tijdens de fase van onderhoudstherapie. Wanneer
de behandeling bestaat uit hoge dosis chemotherapie en schedelbestraling wordt er van beide factoren een synergistisch negatief effect op de groei gezien. Het groeiremmend effect van schedelbestraling treedt op verschillende momenten van de groei op. Gedurende het eerste jaar van de behandeling treedt er een grotere groeiachterstand op dan bij patiënten die geen schedelbestraling kregen. De inhaalgroei van deze patiënten is niet compleet. Bij meisjes begint de puberteit op een jongere leeftijd. De puberteitsgroeispurt van zowel jongens als meisjes verloopt niet optimaal. In de eerste drie maanden van de behandeling hebben alle patiënten, met uitzondering van patiënten die dexamethason kregen, ondergewicht. Gedurende deze periode kan ondergewicht een factor zijn die bijdraagt aan het ontstaan van een groeiachterstand.
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Chapter 11


144


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# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Adria</td>
<td>Adriamycin</td>
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<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukemia</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>Ara-C</td>
<td>Cytosine Arabinoside</td>
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<td>BA</td>
<td>Bone Age</td>
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<tr>
<td>BFM-group</td>
<td>Berlin-Frankfurt-Münster-group</td>
</tr>
<tr>
<td>CA</td>
<td>Calender Age</td>
</tr>
<tr>
<td>CI</td>
<td>Cranial Irradiation</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CT</td>
<td>Chemotherapy</td>
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<td>Cyclo</td>
<td>Cyclophosphamide</td>
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<td>DCLSG</td>
<td>Dutch Childhood Leukemia Study Group</td>
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<td>Dexa</td>
<td>Dexamethason</td>
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<td>FH</td>
<td>Final Height</td>
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<td>Growth Hormone</td>
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<td>GHD</td>
<td>Growth Hormone Deficiency</td>
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<td>GHRH</td>
<td>Growth Hormone Releasing Hormone</td>
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<td>Height</td>
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<td>hGH</td>
<td>human Growth Hormone</td>
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<td>IGF</td>
<td>Insuline-like Growth Hormone</td>
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<td>IGFBP</td>
<td>Insuline-like Growth Hormone Binding Protein</td>
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<td>intra thecathecally</td>
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<td>intravenously</td>
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<tr>
<td>L-Asp</td>
<td>L-Asparaginase</td>
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<tr>
<td>MaVZ</td>
<td>Maximal Z-velocity</td>
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<tr>
<td>MiVZ</td>
<td>Minimal Z-velocity</td>
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<tr>
<td>VZ</td>
<td>Difference of MaVZ and MiVZ</td>
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<td>MTX</td>
<td>Methotrexate</td>
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<tr>
<td>PHV</td>
<td>Peak Height Velocity</td>
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<tr>
<td>Pred</td>
<td>Prednisone</td>
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<tr>
<td>PS</td>
<td>Pubertal Growth Spurt</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SDS</td>
<td>Standard Deviation Score</td>
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<td>se</td>
<td>Standard Error</td>
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<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>6-MP</td>
<td>6-Mercaptopurine</td>
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<tr>
<td>SS</td>
<td>Somatostatin</td>
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<tr>
<td>V</td>
<td>Velocity</td>
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<td>VCR</td>
<td>Vincristine</td>
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<tr>
<td>Z-score</td>
<td>Standard Deviation Score</td>
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<td>Zr-score</td>
<td>Relative Standard Deviation Score</td>
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<td>Zt</td>
<td>Z-score at time point t after diagnosis</td>
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<td>Zo</td>
<td>Z-score at time of diagnosis</td>
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Woorden van dank

Op deze plaats wil ik iedereen bedanken die op enigerlei wijze heeft bijgedragen aan de totstandkoming van dit proefschrift. Met name wil ik noemen:

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Woorden van dank

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Curriculum Vitae


Op 1 februari 1982 begon zij de opleiding tot kinderarts in het St. Radboud ziekenhuis te Nijmegen (Opleiders: Prof. dr. E.D.A.M. Schretlen en Prof. dr. G.B.A. Stoelinga). Vanaf 1 februari 1982 was zij gedurende 2 jaar werkzaam op de afdeling kindergeneeskunde van het Canisius-Wilhelmina ziekenhuis te Nijmegen (Opleider: Dr. P. van Weringen), waarna zij vanaf 1 februari 1984 werkzaam was op de afdeling kindergeneeskunde van het St. Radboud ziekenhuis te Nijmegen. Op 1 februari 1986 werd zij als kinderarts ingeschreven in het Specialisten Register.

Vanaf 1 maart 1986 was zij gedurende twee jaar fellow bij het Koningin Wilhelmina Fonds. Deze aanstelling stelde haar in de gelegenheid zich verder te bekwamen in de kinder-oncologie. Van 1 maart tot 1 december 1986 volgde zij een klinisch fellowship op de afdeling kinder-oncologie van het Emma Kinderziekenhuis te Amsterdam (hoofd: Prof. dr. P.A. Vouëte). Vervolgens was zij gedurende 11 maanden werkzaam op de afdeling hematologie van de Dr. Daniël den Hoed Kliniek te Rotterdam (hoofd: Prof. dr. B. Löwenberg) en tot slot werkte zij gedurende 4 maanden op de afdeling beenmergtransplantatie van The Royal Marsden Hospital te Sutton, Engeland (toenmalig hoofd: Prof. dr. T. McElwain).

Van 1 april 1988 tot 1 november 1989 was zij als kinderarts werkzaam in het St. Anna ziekenhuis te Oss. Sinds 1 november 1989 is zij als kinderarts verbonden aan het Kinder-oncologisch Centrum Zuid-Oost Nederland van het Academisch ziekenhuis Nijmegen.

Zij is gehuwd met Kees Groot, longarts, samen hebben zij drie zonen: Pieter, Maarten en Sebastiaan.
List of publications


