Growth following single fraction and fractionated total body irradiation for bone marrow transplantation

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Abstract. Total body irradiation (TBI) is used as a preparative regimen prior to bone marrow transplantation (BMT). Since there are more long-term survivors, follow up studies are important. We have performed a retrospective analysis of growth for 49 children, who had undergone treatment with cyclophosphamide and TBI before BMT. Of these patients 26 received single fraction (SF) TBI as a dose of 900–1000 cGy, whereas 23 received fractionated (FF) TBI as a total dose of either 1200 cGy divided in six fractions or 1440 cGy divided in eight fractions over 3 days. Half of the patients in the SF-TBI group, and 9 in the FF-TBI group had received low-dose cranial irradiation prior to TBI. In all groups a decrease in height SDS was observed. By evaluating the major factors leading to growth impairment the influence of cranial irradiation, which was demonstrable in the 1st year after TBI, could not be shown after 3 years. At this time growth was significantly more impaired in the SF group with a mean height SDS of −0.9 (± SD 0.9) compared to a mean height SDS of −0.22 (1.02) in the FF group (P < 0.05). Measurement of segmental proportions showed a significant difference in SDS for sitting height in comparison to SDS for subischial leg length, irrespective of the TBI regimen. This was already evident 1 year after TBI and decreased during the following years. Twenty four of the patients (17 in the single fraction and 7 in the fractionated TBI group) were treated with growth hormone, but demonstrated an inappropriate response with absent catch-up growth in their legs. In conclusion, growth is seriously affected in children after BMT, especially if SF-TBI is administered. Decreased growth rates were also observed after FF-TBI, but to a lesser degree, despite the higher total dose of irradiation.

Key words: Leukaemia – Total body irradiation – Bone marrow transplantation – Growth – Growth hormone

Introduction

Bone marrow transplantation (BMT) has been a treatment for haematological disease for nearly 20 years. In the treatment of leukaemia, achievement of a cure is only possible using an intensive preparative regimen prior to the BMT, in order to eradicate the underlying haematological disorder or malignancy, and to suppress the immune system. This regimen included high dose chemotherapy and total body irradiation (TBI), which at our hospital was given in a single fraction (SF-TBI) of 900 to 1000 cGy until July 1987. This type of irradiation has been associated with growth impairment and endocrine dysfunction, particularly thyroid failure [18], permanent gonadal failure [19, 20], and growth hormone (GH) deficiency [11, 16]. From 1987 onward TBI was given in a fractionated manner in an attempt to reduce damage sustained by normal tissues. Thus a total dose of 1200 cGy is divided in six fractions (18 patients) or 1440 cGy is divided into eight fractions (5 patients), both given over 3 days. It is already known that, using this method of delivery there is reduced cataract formation [1]. In the present study we have compared the growth of 49 children, of whom 26 had received TBI as a single fraction whilst 23 had received fractionated TBI (FF-TBI). All but 4 were prepubertal at the time of TBI.

Since cranial irradiation, administered prior to BMT, adversely influences GH production and contributes to growth impairment [13, 22, 23], we subdivided our main groups into those who had been previously irradiated in addition to their TBI, and those who had received TBI alone.

Patients

Between 1981 and 1991, 100 children at The Hospital for Sick Children underwent BMT for acute lymphoblastic leukaemia (ALL) and a variety of myeloproliferative disorders. Of the 66 survivors, 49 conformed to the criteria for investigation which consisted of preparation with high-dose cyclophosphamide and TBI, and a minimum survival of 18 months post transplant.

Of the patients in the SF group 26 received their TBI before July 1987, 23 patients in the FF group were treated after July 1987. We
were only able to compare the two dose regimens in series as a longitudinal study.

The mean age at TBI, pubertal status and previous cranial irradiation are summarized in Table 1. The mean age at diagnosis of ALL was similar in both groups. Those transplanted in first remission, which included patients with myeloproliferative disorders and those with ALL having a WBC > 100 × 10^9/l at presentation, had not been previously irradiated. None of our patients received spinal irradiation, except as a part of TBI. Boys with ALL were routinely irradiated at the time of TBI with an additional testicular boost of 400 cGy to prevent testicular relapse, and two boys in the SF group and one in the FF group had been treated with 2400 cGy testicular radiation for local relapse. The mean time between our analysis and TBI was 5.7 years in the SF-TBI group, and 2.7 years in the FF-TBI group. At the time of their endocrine assessment all but one were in good health.

Patients with ALL had been previously treated using protocols established by the Medical Research Council [5], the United Kingdom Children’s Cancer Study Group [12] or by the Hospital for Sick Children [4]. Intrathecal methotrexate and/or cytosine was used in all patients to prevent leukaemic meningeal infiltration. Patients with acute myeloid leukaemia were treated with either daunorubicin, cytosine arabinoside and thioguanine alone (Medical Research Council, acute myeloid leukaemia VIII) or with two courses of this prior to one course of M-AMSA, azacytidine and etoposide VP16. The preparative regimen prior to the transplant consisted of cyclophosphamide 60 mg/kg intravenously in 2 consecutive days and TBI was administered in either the single fraction or fractionated regimen.

Four patients developed chronic graft-versus-host disease post transplant. Two boys in the SF-TBI group were treated with long-term oral corticosteroids for 2.5, and more than 7.0 years. One girl in the same group had inhaled corticosteroids for 2 years. In the FF-TBI group one girl was treated with oral corticosteroids for 10 months post transplant.

### Table 1. Clinical data of 49 patients at the time of administration of TBI

<table>
<thead>
<tr>
<th>Group (no. of patients)</th>
<th>Diagnosis</th>
<th>Age, years (range)</th>
<th>Pubertal status</th>
<th>Previous irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF (26)</td>
<td>ALL (21)</td>
<td>8.7 (2.3–15.8)</td>
<td>23 prepubertal</td>
<td>13 cranial</td>
</tr>
<tr>
<td></td>
<td>AML (5)</td>
<td>6.5 (1.4–10.7)</td>
<td>3 pubertal</td>
<td></td>
</tr>
<tr>
<td>FF (23)</td>
<td>ALL (19)</td>
<td></td>
<td>22 prepubertal</td>
<td>9 cranial</td>
</tr>
<tr>
<td></td>
<td>AML (4)</td>
<td></td>
<td>1 pubertal</td>
<td></td>
</tr>
</tbody>
</table>

AML, acute myeloproliferative leukaemia

### Methods

Growth data were documented in all patients from the time of initial diagnosis. Height and sitting height (SH) were measured using a stadiometer by standard anthropometric techniques [2]. Parental heights were measured using the same technique. Puberty was staged by the method of Tanner [28] and testicular volume was assessed using an orchidometer [33]. To determine the stage of puberty the appearance of the genitalia was used, because the testicular volume is often inappropriate after destruction of the germ cells by irradiation [10, 20]. Height standard deviation score (SDS) was calculated using the formula SDS = \((x - \bar{x})/S\), where \(x\) is the height of the patient, \(\bar{x}\) the mean height for chronological age, and \(S\) the standard deviation [2]. In a similar way, sitting height SDS and subischial leg length (SLL) SDS were calculated. Growth standards were from British Children [29]. GH was administered at a dose of 15 IU/m² per week given as a daily subcutaneous injection which approximates to a physiological replacement dose. If an inadequate growth response was obtained the dose regimen was increased to 20 IU/m² per week. Patients were monitored post transplant with regular anthropometric and bone age assessments at 3- to 6-monthly intervals. Skeletal maturation was assessed by one observer (R.S.) using the method of Tanner et al. [30].

### Statistical methods

Height SDS in each group were compared using Students’ paired t-test. Regression coefficient was calculated to demonstrate the rate of change of height SDS in each group. ANOVA was used to evaluate the influence of TBI received and previous cranial irradiation on linear growth.

### Results

#### Total height

Figure 1 illustrates height SDS in the two main groups without further subdivision irrespective of whether they had been previously treated with cranial irradiation. Height SDS 1 year before, at TBI, and in the consecutive 3 years as well as height SDS for the corresponding corrected midparental heights are shown. In the SF-TBI group the comparison of consecutive years demonstrates a highly significant loss of height SDS after TBI, whereas in the FF-TBI group there was only a minimal reduction in height SDS in the first 2 years. Nevertheless, in both groups height SDS after 3 years was significantly decreased in comparison to that at TBI. In the SF group height SDS changed from -0.29 (0.95) to -0.90 (0.90) \((P < 0.0001)\), while in the FF group a change from -0.09 (1.22) to -0.22 (1.02) \((P < 0.02)\) was observed. Only in the SF group did the height SDS of the patients in each consecu-

![Fig. 1. Height SDS of 49 patients treated with either SF (solid columns) or FF (shaded columns) TBI from 1 year prior to 3 years following treatment. Data for corrected midparental height are shown. Numbers of patients are indicated. Horizontal bar represents 1 SD. NS, non significant; * \(P < 0.01\); ** \(P < 0.005\). The test of significance is compared to the previous year](image-url)