Role of Busulfan and Total Body Irradiation on Growth of Prepubertal Children Receiving Bone Marrow Transplantation and Results of Treatment With Recombinant Human Growth Hormone

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Seventy-six prepubertal children receiving autologous or allogeneic bone marrow transplantation (BMT) were enrolled in a prospective study on the impact of different pretransplant preparative regimens on growth. Patients were divided into three groups: group I, consisting of 37 children who had received total body irradiation (TBI) and cytotoxic drugs as preparative regimen; group II, including 17 children receiving prophylactic cranial irradiation before being conditioned with TBI and cytotoxic drugs; and group III, composed of 22 patients transplanted after a busulfan (BU)-containing myeloablative therapy. All patients have a minimum follow-up of 2 years, whereas 48 and 34 patients have been studied until 3 and 4 years after transplant, respectively. Height and growth rate were expressed as standard deviation score (SDS). Growth hormone (GH) secretion in response to pharmacologic stimuli was evaluated after documented growth failure. Patients with GH deficiency were treated with recombinant human GH, and response to therapy was evaluated. The main impairment of growth rate in patients belonging to group II was observed in the first year after TBI (growth rate SDS changing from $-0.12$ to $0.23$ to $-1.23$ to $0.25$, $P < .005$), with only a slight loss in the following years, whereas in group I children growth failure occurred in the third year after TBI ($-1.36$ to $0.28$ SDS in comparison to a pre-BMT SDS of $0.10$ to $0.15$, $P < .005$). Therefore, growth velocity between these two groups differed significantly in the first 2 years ($P < .01$) but subsequently equalized. On the contrary, all BU-treated children but 2 grew normally. GH deficiency was shown in the vast majority of children with growth impairment. Twenty-three children treated with recombinant human GH are evaluable; a successful response was observed in all but 1, with the mean growth rate increasing from $-2.29$ to $0.27$ before treatment to $0.86$ to $0.38$ and to $1.66$ to $0.56$ SDS at 1 and 2 years after treatment, respectively ($P < .001$). In conclusion, growth rate impairment was common in patients receiving TBI, with the speed of onset of both decreased growth velocity and GH deficiency depending mainly on the total dose of radiation. On the contrary, patients receiving BU did not experience significant problems in terms of growth velocity. The timely start of appropriate hormonal replacement therapy may ameliorate the final growth of children undergoing BMT.

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With the increasing use of bone marrow transplantation (BMT) there has been an increasing number of studies reporting on development of growth impairment in children surviving after marrow transplantation.1-4 These studies have shown that children receiving preparative regimens including cytotoxic drugs in combination with total body irradiation (TBI), administered both in single exposure and in fractionated doses, frequently experience a reduction of growth velocity. Total radiation dose, fraction size, and age at the time of treatment were recognized as important factors influencing impairment of linear growth.1,4-8

Growth hormone (GH) deficiency seems to be a major determinant of growth impairment, because the hypothalamic-pituitary axis is sensitive to the deleterious effects of radiotherapy and GH is usually the first anterior pituitary hormone to be affected by cranial irradiation.9-12 On the contrary, data on the effects of intensive chemotherapy on growth velocity are still controversial; for instance, patients with severe aplastic anemia conditioned with cyclophosphamide (CY) have been reported to grow normally.13-15 Because of its ability to permanently impair the self-renewal capacity of hematopoietic progenitors, busulfan (BU), usually associated to CY, has gained increasing use as an alternative to TBI-containing preparative regimens in patients with both malignant and nonmalignant disorders. However, only two studies have specifically focused on the effects of BU on growth velocity and GH production, and conflicting results have been reported.16,17

To evaluate the impact of different pretransplant preparative regimens on growth, we decided to study prospectively growth and, when indicated, GH production in 76 prepubertal children with malignancies or nonmalignant disorders receiving an autologous or allogeneic marrow transplant. Moreover, because limited data on the effects of replacement therapy in children developing GH-deficiency after BMT are available,9,18,19 we also evaluated the response to treatment with recombinant human GH of our patients who developed GH deficiency.

Patients and Methods

Seventy-six prepubertal children (55 males and 21 females) receiving an autologous (31 patients) or allogeneic (45 patients) marrow transplant at the Department of Pediatrics of the University of Pavia and at the Istituto G. Gaslini of Genoa, Italy, were enrolled in this study after obtaining written informed consent from the parents. The patient’s age at time of BMT ranged from 0.5 to 12 years.
with the median age being 7 years; only 3 children were near pubertal age (age >11 years for boys or >9 years for girls). Details on patient’s age at BMT, sex, original disease, and conditioning regimen used before transplant are reported in Table 1. Patients with acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), non-Hodgkin’s lymphoma (NHL), and neuroblastoma had been previously treated using protocols established by the Italian Association for Pediatric Hematology/Oncology (AIEOP), whereas, before marrow transplant, children with chronic myeloid leukemia (CML) had received hydroxyurea.

Fifty-four patients received a conditioning regimen including fractionated TBI (12 Gy divided in 6 fractions over 3 days). Seventeen patients affected by ALL or NHL also had received previous prophylactic cranial irradiation (18 Gy divided in 12 fractions over 16 days) during first-line chemotherapy with a median time interval between cranial irradiation and TBI of 18 months (range, 7 to 36 months). An 11-year-old girl affected by NHL received radiotherapy at a dose of 36 Gy on the skull and 18 Gy on the neck during the pretransplant treatment. Twenty-two children were transplanted after a myeloablative therapy consisting of BU (16 mg/kg administered orally over 4 days) and CY, with (12 patients) or without (10 patients) L-PAM. None of the children receiving BU had received previous cranial irradiation and none of the 15 patients with neuroblastoma had received limited field radiotherapy during first-line chemotherapy.

To define the role of different conditioning regimens and the impact of radiotherapy on growth rate and GH production, we divided patients into three groups: group I, consisting of 37 children receiving TBI and cytotoxic drugs as preparative regimen; group II, including 17 children receiving prophylactic cranial irradiation during first-line chemotherapy before TBI and cytotoxic drugs; and group III, comprising 22 children transplanted after a BU-containing myeloablative therapy. All patients have a minimum follow-up of 2 years; 48 patients (27 of group I, 10 of group II, and 11 of group III) were evaluable 3 years after BMT and 34 (20 of group I, 7 of group II, and 7 of group III) have been studied until 4 years or more after transplant. Details on observation time and subdivision between patients with malignant or nonmalignant disorders for each of 3 groups are reported in Table 1.

During the study period all patients were in continuous complete hematologic remission from their original disease and remained in a prepubertal stage. Children receiving an allogeneic transplant did not present chronic graft-versus-host disease (GVHD) and at time of evaluation they were no longer receiving steroid therapy since at least 6 months.

Standard auxologic assessment was performed before marrow transplant and, starting at a minimum of 6 months after BMT, every 6 months. Height of patients and their parents were measured using a stadiometer by standard anthropometric techniques. Height and growth rate were expressed as standard deviation score (SDS), calculated for height as (height – mean height for age and sex) ÷ standard deviation (SD) of height for age and sex, and calculated for growth rate as (growth rate – mean growth rate for age and sex) ÷ SD of growth rate for age and sex, using a computer-based algorithm. Bone age was assessed using the method of Greulich and Pyle.

GH secretion in response to pharmacological stimuli (insulin, arginine, and/or L-dopa) was evaluated after documented growth failure, namely loss of growth rate greater than 2 SD. In detail, GH production was evaluated after insulin-induced hypoglycemia (0.1 UI/kg intravenously [IV]), arginine (0.5 g/kg, infused IV over 30 minutes), and/or L-dopa (0.5 g/1.73 m², administered orally). GH deficiency was defined as a response less than 10 ng/mL to at least two pharmacologic tests. Patients showing reduced growth velocity but with normal or borderline GH secretion underwent repeat tests after 6 months until a definite result was obtained. To establish damage level on the hypothalamic-pituitary axis, a number of patients showing impaired GH secretion were evaluated after IV administration of synthetic GH-releasing hormone (GHRH) 1-29 (1 μg/kg). After the first endocrine assessment, clinical follow-up of patients was obtained every 3 months.

Thyroid function was evaluated every 6 months after BMT by measuring serum thyroid-stimulating hormone (TSH) concentration, as well as serum concentration of T₃, T₄, free-T₃, and free-T₄. Adrenal function was assessed yearly by measuring serum levels of cortisol, androstenedione, dehydroepiandrosterone (DHEA), and its sulforalylated derivative (DHEA-S).

Patients with GH deficiency received substitutive therapy with human recombinant GH, administered subcutaneously at the dose of 0.6 IU/kg/wk over 4 to 6 days. Criteria for inception of treatment were normal result of oral glucose tolerance test (blood glucose less than 120 mg/dL 2 hours after challenge with 40% glucose solution, 1.75 g/kg body weight, with a maximum of 75 g), bone age less than 12 years without signs of puberty, and written informed consent from the parents.

Table 1. Characteristics of the 76 Patients Enrolled in the Study

| Age at BMT (median, range) | 7 (0.5-12) |
| Sex (M/F) | 55/21 |
| Diagnosis |  |
| ALL | 22 |
| AML | 20 |
| NHL | 2 |
| CML | 3 |
| Neuroblastoma | 15 |
| Thalassemia major | 5 |
| Inborn errors | 9 |
| Allogeneic/autologous BMT | 45/31 |
| Conditioning regimens |  |
| TBI/Cy | 20 |
| TBI/VCY/Cy | 16 |
| TBI/L-PAM | 18 |
| BU/Cy/L-PAM | 9 |
| BU/Cy | 13 |
| Median time of observation from BMT (mo) for each group |  |
| Group I | 50 |
| Group II | 42 |
| Group III | 37 |
| Malignant/nonmalignant disorder ratio for each group |  |
| Group I | 35/2 |
| Group II | 17/0 |
| Group III | 10/12 |

Data analysis and presentation. Data were stored, analyzed, and reported with the packages STATISTICA/w (StatSoft, Inc, Tulsa, OK), and Fig.P (Biosoft, Cambridge, UK), both run on a Power Exec EL (AST, Irvine, CA) personal computer. Results were expressed as mean ± SEM. Normal distribution of data was tested with the Shapiro-Wilk’s W test. Differences in mean growth velocity and height during time and among the three different groups after BMT were compared using two-way repeated measures ANOVA. Because only 48 patients had a follow-up of 3 years after BMT and only 34 patients a follow-up of 4 years, three different ANOVA analyses were performed, the first comparing data on growth velocity and height pre-BMT 1 year and 2 years after BMT, the second one comparing data obtained 2 years and 3 years after BMT, and the third one comparing data obtained 3 and 4 years after BMT. To
confirm our conclusions, a two-way ANOVA for repeated measures including only the 34 children with a complete follow-up of 4 years was also performed, as well as an analysis not based on a longitudinal repeated measures model and including all 76 children. Only results confirmed by the three analyses were reported in the text. Moreover, because dropouts were mainly children with an important growth impairment who, after evaluation for GH secretion, started replacement hormonal therapy, most of the children without a complete follow-up of 4 years were those with the worst growth velocity. On the basis of this consideration, the bias thus introduced was against rejection of the null hypothesis; therefore, the validity of our conclusion remained unaffected.

One-way ANOVA for repeated measures was used to test significance of GH treatment results. Tukey HSD test for unequal sample sizes (Sprott and Stoline test) and Scheffé test were used to compare differences between groups and within groups. Given the high number of comparisons performed, only P values less than .01 were considered to be statistically significant.

RESULTS

Height and growth rate. Both pretransplant height and growth rate did not significantly differ among patients belonging to the three groups (Figs 1 and 2), even though group I children as a whole were taller. In detail, the mean pretransplant growth rate SDS was +0.10 ± 0.15 in group I children (receiving TBI plus chemotherapy), −0.12 ± 0.23 in children belonging to group II (TBI plus previous prophylactic cranial irradiation), and −0.16 ± 0.12 in children of group III (chemotherapy only). Mean pre-BMT height of the three different groups were +0.28 ± 0.19, −0.28 ± 0.22, and −0.62 ± 0.19 SDS, respectively (Fig 2).

In group II, comparison among consecutive years after BMT showed a significant decrease of growth rate, already detectable after 1 year, with the growth rate SDS changing from −0.12 ± 0.23 to −1.23 ± 0.25 (P < .005). On the contrary, the growth rate SDS in the first year after BMT remained normal for group I and group III children. The growth rate of patients belonging to group II further decreased slightly in the second year after BMT, with the mean SDS value being −1.83 ± 0.28 (P < .001 if compared with the pretransplant value and P = not significant [NS] if compared with 1 year after transplant mean SDS). In group I, the SDS of growth velocity 2 years after transplant showed only minimal reduction (−0.52 ± 0.21 SDS; P = NS when compared with the value observed 1 year after BMT). All patients but 2 (both affected by AML) who received a BU-based myeloablative therapy had a normal growth rate also in the second year after transplant (Fig 1). During the third year after BMT, growth rate showed an impressive decrease for group I patients, reaching a value of −1.36 ± 0.28 SDS (P < .005 if compared with pretransplant, 1 year, and 2 years after BMT growth rate SDS). Because children belonging to group II showed a further but not statistically significant decrease in growth rate, the difference in growth velocity SDS 1 year and 2 years after marrow transplant between these two groups (P < .01 in both cases) tended to disappear 3 years after BMT (P = NS; Fig 1). All BU-treated patients, with the exceptions mentioned above, continued to grow normally 3 years after BMT. A further, but less pronounced and not statistically significant, loss in growth velocity was observed in those patients belonging to group I and group II who reached the fourth year of observation. Difference between these two groups was not significant, even though growth impairment was more evident in the patients who had received previous cranial irradiation (Fig 1). The 7 patients of group III who were evaluable 4 years after BMT had a growth rate SDS of +0.95 ± 0.51, higher than that observed at the beginning of the study.

Overall, the main impairment of growth rate in patients belonging to group II developed during the first year after
TBI, with only slight decrease in the following years, whereas in group I children growth failure was delayed until the third year after TBI. This difference had the consequence that, whereas growth velocity between these two groups differed significantly in the first 2 years, it subsequently tended to equalize. During the whole period of observation, BU-treated children grew normally and significantly better in comparison with those who received TBI. To determine whether the original disease had an influence on growth pattern, we considered group III children affected by malignant (10 patients) or nonmalignant disorders (12 patients) separately; however, we were not able to find any difference, a similar slope being observed in these two subgroups (data not shown). In conclusion, previous cranial irradiation was the only factor significantly influencing growth rate in the first and second year of observation, whereas in the third and fourth year exposure to TBI significantly influenced growth rate independently of other variables considered.

Although height SDS mimicked the behavior of growth rate SDS in group II and III children (Fig 2), some differences were observed for group I children during the whole observation period. In fact, height SDS of patients in this group decreased only slightly, from +0.28 ± 0.19 before BMT to reach values of −0.38 ± 0.24 and −0.39 ± 0.32 at 3 and 4 years after transplant, respectively. In our view, this finding may be mainly attributed to the longer time needed to detect significant reduction in height in comparison to that required for growth rate impairment.

In all patients with growth impairment, bone age was only slightly reduced in comparison with chronologic age, with the mean bone age/chronologic age ratio being 0.85, a value greater than 0.70, which is considered to be indicative of significant delay in skeletal maturation.24

GH secretion. Observation of significant impairment of growth velocity led to investigation of GH secretion predominately in patients treated with radiation (21 of group I, 14 of group II, and 2 of group III). GH deficiency was shown in 20 of the 21 patients of group I and in 13 of 14 patients who had received prophylactic cranial irradiation. Group I and II patients were investigated at a median of 3 and 2 years after BMT, respectively. The two BU-treated patients presenting growth impairment showed a blunted GH secretion in response to the provocative stimuli when tested 2 years after marrow transplantation.

Among the 14 patients with impaired GH secretion in whom response to GHRH was tested, it was found to be reduced in 6 and normal in 8 patients.

GH treatment. No child showed either spontaneous catch-up growth or spontaneous recovery from GH deficiency during the follow-up period antecedent the beginning of treatment.

We treated with recombinant human GH 27 children with GH deficiency; 23 (12 of group I, 10 of group II, and 1 of group III) of them were evaluable, having completed a minimum time of 1 year of treatment. Eight children were excluded from treatment because of lack of parental consent or nonacceptance of treatment by the patient (4 children), abnormal glucose tolerance test (2 patients), or advanced bone age at the time of final diagnosis of GH deficiency (2 patients).

Group I children started their treatment at a median of 3.5 years after BMT, group II children at a median of 2.5 years, and patients of group III at 1.9 years. A successful response to treatment was observed in all patients but 1. In fact, growth rate, evaluated 1 and 2 years after starting treatment, increased from −2.29 ± 0.27 before treatment to +0.86 ± 0.38 and to +1.66 ± 0.56 SDS at 1 and 2 years of treatment, respectively (P < .001).

Among 2 patients belonging to group I we observed an increase of TSH from 4.7 to 7.0 and from 4.7 to 11.6 U/mL, respectively; normal values, 0.3 to 3.8 U/mL) in the first year after the beginning of GH therapy; levels of T4 and FT4 were normal. Thyroxine replacement therapy was associated to GH treatment in these patients. No abnormality in adrenal function was found in any patient during the study.

DISCUSSION

Growth impairment is an emerging frequent long-term complication of BMT in children, and radiotherapy used, together with cytotoxic drugs, during the preparative regimen for transplant has been reported to adversely affect subsequent growth and development in survivors.2,4,6-8

A great proportion of children receiving TBI as single exposure have been reported to experience growth failure,
which is especially evident with increasing time from transplant.\textsuperscript{1,4,7} Fractionated TBI, although to a lesser degree, was also shown to impair growth velocity, thus suggesting that dose fractionation does not substantially eliminate the negative impact of radiation on growth.\textsuperscript{1,15,25}

In our cohort of children, we have been able to confirm that patients conditioned with fractionated TBI are at risk of developing growth impairment. The inclusion of only prepubertal children and the exclusion of patients with thyroid abnormalities, patients with chronic GVHD, and those who had received steroid therapy in the 6 months before evaluation ruled out interference by factors capable of influencing either growth rate or GH secretion or both. This finding allowed us to identify a homogeneous population of patients in which the role of total dose of radiation delivered and that of length of time after treatment were sorted out and more exactly defined. In fact, during consecutive years of observation, the degree of loss of growth rate SDS differed significantly, depending on whether children had or had not received prior prophylactic cranial irradiation. Previous cranial radiotherapy was the major determinant affecting growth velocity in the first 2 years after transplant because during this period group II children grew significantly less than the other patients studied. This observation is in accordance with previously published studies showing that growth impairment occurs earlier and with higher incidence in patients having received both TBI and prophylactic cranial irradiation before marrow transplantation.\textsuperscript{2,7,14,19} These children received the highest doses of radiotherapy and total dose of radiation is the major determinant of the speed of onset as well as of the incidence and severity of anterior pituitary hormone deficiency.\textsuperscript{10,26}

With increasing time after BMT (ie, during years 3 and 4 of observation) group I children, not receiving prior cranial radiotherapy, also showed reduced growth velocity; at this time, the most important factor significantly contributing to decreased growth appeared to be exposure to TBI. These findings were not unexpected because the prevalence of GH insufficiency increases with time from TBI, suggesting that exhaustion of GH secretion is a progressive phenomenon and that a long observation time is needed to appreciate the effect of TBI on anterior pituitary hormone function.\textsuperscript{4,27,28} Moreover, the impact of radiotherapy on cartilage growth may have progressively contributed to growth rate impairment, as previously reported.\textsuperscript{8,25} Thomas et al\textsuperscript{8} showed that children receiving TBI had disproportional segmental growth, with more evident effect on the spine, probably due to the greater number of epiphyses per unit surface area leading to a more important cumulative loss of growth.

We did not confirm the observation of Wingard et al\textsuperscript{17} on a comparable impairment of growth rate in children with acute leukemia receiving either TBI or BU as part of the preparative regimen before marrow transplantation. Several hypotheses can be considered to explain this discrepancy. First of all, none of our patients had chronic GVHD or was receiving steroids since at least 6 months of age, whereas 55% of patients described by Wingard et al\textsuperscript{17} had received corticosteroid therapy after transplantation and some patients had chronic GVHD. Moreover, one third of these children receiving BU had received prior irradiation to either head, spine, or both, compared with none of ours. All these factors have been proved to adversely affect growth rate of children and a synergistic effect of BU with previous cranial/spinal radiotherapy cannot be excluded. Also, the composition of the study population may explain some of the discrepancy. Because very young children have been reported to have a lower systemic exposure to BU in comparison with older children,\textsuperscript{29} their presence in our study could have partially contributed to the better growth rate of our patients. Even though the two group III patients with growth impairment were older than 5 years, we have not been able to show a relevant influence of age on growth rate of these children (data not shown). Data on plasma BU concentrations were available in 11 of the 22 patients of group III who had been enrolled also in a cooperative study on BU pharmacokinetics. Whereas 9 children growing normally had comparable plasma busulfan levels, independently of age, the 2 patients with growth impairment had higher BU concentrations than those observed in the other children (data not shown), thus suggesting that the systemic exposure to BU, and not age in itself, may be responsible for growth impairment after BMT. Among our patients only 1 of group III was near pubertal age (a male patient 11.5 years old), and this excludes that the calculated growth rate SDS be influenced by the increased growth rate normally expected during this period. After analyzing separately children with leukemia and children with nonmalignant disorders, we did not find any influence of the original disease. This finding seems to exclude that the discrepancy observed could be attributed to heterogeneity of the diseases transplanted or to the administration of prior chemotherapy. On the contrary, our data are in agreement with those reported by Urban et al\textsuperscript{20} and in thalassemic patients by Manenti et al\textsuperscript{16} even though the children reported in the latter study had received a lower total dose of BU (ie, 14 mg/kg).

The vast majority of our patients developing reduced growth rate after TBI, irrespective of having received or not previous cranial radioprophylaxis, had impaired GH secretion when evaluated in response to provocative stimuli. As previously mentioned, development of radiation-induced hypopituitarism is dose-dependent and the total dose of radiation delivered seems to determine the speed of onset as well as the incidence and the severity of anterior pituitary hormone deficiencies.\textsuperscript{9,10,26} The appearance of GH deficiency also in group I children, who had received a total dose of cranial radiation of 12 Gy, a dose not affecting GH production in adults,\textsuperscript{31} seems to confirm that the central nervous system of children may be more radiosensitive than that of older subjects.\textsuperscript{10} GH deficiency was found also in the 2 children who developed a decreased growth rate after having received BU plus Cy as preparative regimen. Interestingly, as mentioned above, both patients had had higher plasmatic levels of BU when compared also with other children in a study evaluating the pharmacokinetics of the drug.\textsuperscript{29} Considering that cerebral spinal fluid levels of BU are directly related to plasma levels, it can be cautiously hypothesized...
that growth failure and GH deficiency could develop whenever children are exposed to elevated concentrations of the drug.

Children showing growth failure and GH deficiency after BMT can respond to GH treatment with an increase in height velocity, even though the Seattle group has reported a growth rate improvement in these patients after substitutive therapy less satisfactory than that observed in nontransplanted GH-deficient patients, and Thomas et al have reported that prepubertal patients treated with GH after fractionated TBI did not respond with “catch up” growth. On the contrary, our results indicate that GH therapy is of significant benefit in children with radiation-induced GH deficiency. All our patients but 1 presented a significant improvement in growth velocity after the beginning of hormonal replacement therapy with an average first-year increase in growth velocity comparable with that observed in idiopathic GH-deficient patients (unpublished data). In view of studies on children with hypopituitarism showing that the final height of patients receiving GH substitutive therapy depends on the height at the start of therapy and that treatment in Turner syndrome has been associated with better results in youngest patients, we suggest that replacement therapy should be started as soon as possible or, at least, before height has decreased below the third percentile. This approach can provide satisfactory results in terms of definitive height for most children receiving BMT, particularly in those developing impairment of growth rate early after marrow transplantation (namely children receiving prophylactic cranial irradiation).

Our data suggest that growth impairment is common in patients receiving a TBI-containing conditioning regimen and that the speed of onset of both decreased growth velocity and GH deficiency seems to depend mainly on the total dose of radiotherapy. On the contrary, patients receiving BU, with few exceptions, did not experience significant problems in terms of growth velocity. Careful sequential study of growth of transplanted patients aimed at detecting the onset of potential abnormalities, and the timely start of appropriate hormonal replacement therapy, whenever GH deficiency is shown, can help to reduce the negative impact of the conditioning regimen on growth of children undergoing marrow transplantation.

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