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Original Research

Growth deceleration in children treated with imatinib for chronic myeloid leukaemia ☆

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Abstract ***Purpose:*** The aim is to study statural growth in a large cohort of children with chronic myeloid leukaemia (CML) treated with front-line imatinib.
Methods: Retrospective data from 81 children less than 18 years of age with CML identified in the French pediatric registry were analysed. Height was expressed as standard deviation score (SDS).
Results: A gradual decrease in height SDS was observed over time since starting imatinib. The height SDS was significantly lower 12 months and 24 months after the start of imatinib overall

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($p < 10^{-4}$) irrespective of gender and pubertal age. The height SDS was significantly ($p < 10^{-4}$) lower 12 months after the start of imatinib in boys and girls, and in the prepubertal age group as well as in the postpubertal age group, respectively. A similar finding was observed in the subgroups of boys and girls starting imatinib at a prepubertal or postpubertal age. Loss in height SDS 12 months after the start of imatinib was of the same range in boys when compared to girls and in patients who started imatinib at a prepubertal age compared to those who started at a postpubertal age.

Conclusion: Growth velocity was altered during the first years of imatinib treatment in boys as well as in girls and in prepubertal age patients as well as in adolescents.

1. Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder characterised by the constitutively activated BCR-ABL tyrosine kinase oncoprotein. CML is a very rare disease in children accounting for 2–3% of leukaemias in this age range [1]. We have demonstrated that imatinib, a tyrosine kinase inhibitor, is an effective treatment for children with newly diagnosed CML [2]. Long term imatinib therapeutic benefit has been reported in continuously treated chronic-phase (CP) adult patients with CML [3,4]. Imatinib inhibits the tyrosine kinase activity of BCR-ABL as well as platelet-derived growth factor receptor (PDGF-R), macrophage colony-stimulating factor receptor (c-fms) and stem cell factor receptor (c-Kit) involved in bone metabolism [5–7]. Indeed altered bone and mineral metabolism has been reported in adults and children treated with imatinib leading to concerns regarding the effects of prolonged administration of this drug on growth of children and adolescents [8,9]. Growth deceleration has been described in case reports [10–12] and in small cohorts of children in India and in Japan [13,14]. We reported for the first time in 2009 preliminary results indicating growth deceleration in a cohort of children and adolescents with CML receiving imatinib enrolled in the French prospective trial Glivec Phase IV [15]. The present study was conducted in order to assess long term growth in an extended group of 81 children and adolescents with CML treated with imatinib.

2. Patients and methods

The analysis presented here was confined to patients under 18 years of age treated with imatinib front-line for newly diagnosed chronic phase CML in the 33 paediatric haematology units in France between July 2001 and August 2012 including the 44 patients enrolled between March 2004 and December 2008 in the French prospective study Glivec Phase IV [2]. For all patients initial Imatinib dose was 260 mg/m^2 which is equivalent in terms of drug exposure to the standard dose of 400 mg in adults. The analysis was focused on long-term follow-up of growth in this cohort of patients. Heights at the start of imatinib and every three months were considered until the most recent assessment or treatment discontinuation. Weight data at the same timepoints were considered to allow for body mass index (BMI) calculation. The follow up regarding growth was censored within 1 month after imatinib discontinuation for alternative therapy (stem cell transplantation or switch to second generation tyrosine kinase inhibitors according to our national recommendations). For patients who became 18 during therapy, the follow up was performed by the adult teams without any interruption of the data collection. Height was expressed as standard deviation score (SDS). Height SDS was calculated using French growth standard [16], as patient height minus mean height for age and sex, divided by standard deviation of height for age and sex. Pre-pubertal age was defined as being younger than 9 years for girls or 11 years for boys. Informed consent to register data was obtained from patients and/or parents according to French national health ethics rules.

2.1. Statistical analyses

Differences between independent groups were assessed by the use of the Wilcoxon rank sum test. For paired analyses of the variation of the height SDS between different time points, the Wilcoxon rank signed test was used. To address the question of some potential biases, these paired data were analysed overall and then adjusted on individual body mass index (BMI). All delays were calculated from the onset of imatinib. The follow-up of patients who discontinued imatinib was censored one month after discontinuation for alternative therapy (stem cell transplantation or switch to second generation tyrosine kinase inhibitor). All tests were two-tailed and $p < 0.05$ was considered statistically significant. Data analyses were performed using SAS software (SAS institute, Cary, NC).

3. Results

Data were collected retrospectively from a total of 81 children and adolescents (50 boys and 31 girls) with CML in chronic phase treated with imatinib. Median