THE EUTOS Long-Term Survival score was tested in 350 children with chronic myeloid leukemia in first chronic phase treated with imatinib and registered in the International Registry for Childhood Chronic Myeloid Leukemia. With a median follow up of 3 years (range, 1 month to 6 years) progression and/or death (whichever came first) occurred in 23 patients. For the entire cohort of patients the 5-year progression-free survival rate was 92% (95% CI: 87%-94%) and the 5-year survival accounting for chronic myeloid leukemia deaths was 97% (95% CI: 94%-99%). Of the 309 patients allocated to low (n=199), intermediate (n=68) and high (n=42) risk groups by the EUTOS Long-Term Survival score, events (progression and/or death) occurred in 6.0%, 8.8% and 26.2%, respectively. Estimates of the 5-year progression-free survival rates according to these three risk groups were 96% (95% CI: 94%-99%), 88% (95% CI: 76%-95%) and 67% (95% CI: 48%-81%), respectively. Differences in progression-free survival according to these risk groups were highly significant (P<0.0001, overall). The EUTOS Long-Term Survival score showed better differentiation of progression-free survival than the Sokal (<45 years), Euro and EUTOS scores in children and adolescents with chronic myeloid leukemia and should be considered in therapeutic algorithms. (Trial registered at: www.clinicaltrials.gov NCT01281735)

Introduction

Prognostic scores such as the Sokal score, the Euro score and the EUTOS score based on clinical and biological features at diagnosis have proven their usefulness in predicting the outcome of adults receiving defined treatment for chronic myeloid leukemia (CML). While the Sokal score for patients less than 45 years...
 old and the Euro score were defined in cohorts of patients including children, the usefulness of these prognostic scores has not been formally established in the pediatric population. Limited data are available regarding the utility of the EUTOS score in the pediatric population. Recently, a new EUTOS score, the EUTOS Long-Term Survival (ELTS) score was validated in the adult population and showed better discrimination of the probability of dying of CML than had previous prognostic scores.6

The International Registry for Chronic Myeloid Leukemia in children and adolescents (I-CML-Ped Study registered at www.clinicaltrials.gov as NCT01281735) gave us the opportunity to compare risk group allocations and outcome between these prognostic scores in the pediatric population.

### Methods

The I-CML-Ped Study was established to assess the epidemiology, management and outcome of CML in the pediatric population. Newly diagnosed children and adolescents less than 18 years old with Philadelphia chromosome-positive CML in chronic or advanced phase diagnosed later than January 2000 were eligible for this study. The calculations for the Sokal (for patients less than 45 years), Euro and EUTOS scores and into low risk, intermediate risk or high risk groups for the Sokal low risk or high risk for the ELTS score. The phase of the disease was determined according to the European leukemiaNet (ELN) recommendations as previously reported.7 The study protocol was approved by the institutional review committee of the university hospital of Poitiers (France). Written informed consent was obtained from the children and/or their guardians. For analyses of progression-free survival, events of interest included progression to accelerated phase or blast crisis and death, irrespective of cause, whichever came first.8 For analysis of survival, the event of interest was death from CML disease, deaths from other causes being considered as competing events, as initially designed in the ELTS score model. The follow up of patients was not censored at the time of switching to other drugs or allogeneic hematopoietic stem cell transplantation (HSCT). Estimates of progression-free survival were calculated using the Kaplan-Meier method and comparisons were performed using the log-rank test. For the estimation of cause-specific death in a competing model, the Gray test was used for comparison.9 The level of statistical significance was 0.05.

### Results

Between January 2011 and June 2016, 350 patients with CML in chronic phase at diagnosis treated with standard dose (260 to 300 mg/m2 daily) imatinib front line were registered from 13 countries. The patients’ median age at diagnosis of CML was 12.2 years (range, 8 months to 18 years old). Between January 2011 and June 2016, 350 patients with CML in chronic phase at diagnosis treated with standard dose (260 to 300 mg/m2 daily) imatinib front line were registered from 13 countries. The patients’ median age at diagnosis of CML was 12.2 years (range, 8 months to 18 years old).
years) and 56% were male; a palpable spleen was noted in 77% of the patients and the median spleen size was 5 cm (range, 0 to 32 cm) below the costal margin; the median white blood cell count and the median hemoglobin level were 228x10^9/L (range, 4.8x10^9/L to 1037x10^9/L) and 94 g/L (range, 31 g/L to 170 g/L), respectively.

The distribution of the children into the risk categories by the Sokal (for patients less than 45 years), Euro, EUTOS and ELTS scores is reported in Table 1. Discordant risk categorizations of the children were observed when comparing the four scores. Regarding the Sokal (for patients less than 45 years) and the ELTS scores, all the children categorized as low risk according to the Sokal system were allocated to the low-risk group according to the ELTS score. By contrast, among the children in the intermediate-risk group according to the Sokal system, only 13% remained in the intermediate-risk group according to the ELTS score while 1% and 86% were allocated to the high-risk group and low-risk group, respectively. Among the children in the high-risk group according to the Sokal system, 30% remained in the high-risk group according to the ELTS score while 39% and 31% were allocated to the intermediate-risk group and low-risk group, respectively. The median follow up of the 350 patients in chronic phase treated with imatinib front line was 3 years (range, 1 month to 6 years). Imatinib was administered with a median observational time of 11 months (range, 1 to 131 months); 149 patients discontinued treatment with imatinib because of progression of their disease, toxicity, failure to achieve optimal response, or physician’s choice (HSCT in optimal response). Progression and/or death (whichever came first) were recorded in 23 patients: progression occurred in 19 (5.4%) patients and death was recorded in 12 (3.4%) children. Among the 19 patients who progressed as first event, five patients progressed to accelerated phase and 14 to blastic phase at a median time of 12 months (range, 3 to 32 months) after diagnosis. Eleven of these 19 children are alive including ten who were transplanted with a graft from a sibling donor (4 patients) or an unrelated donor (6 patients). The remaining 8/19 patients have died including five children who died of uncontrolled CML disease (2 children with recurrent disease after HSCT for disease progression of the disease) and three who died after HSCT because of graft-versus-host disease (n=1) or infection (n=2). In addition, death occurred as the first event in four patients who were transplanted (unrelated donor 1 case, sibling donor 3 cases) in first chronic phase in accordance with the choice of the clinician. The causes of these four deaths were graft-versus-host disease (n=1) and infection (n=3). Overall, considering all 12 deaths, these occurred at a median time of 22 months (range, 12 to 56 months) after the diagnosis of CML.

Figure 1. Progression-free survival stratified according to risk categorization by the four scores. (A) Sokal score, (B) Euro score, (C) EUTOS score, (D) EUTOS Long-Term Survival (ELTS) score. Green represent low risk patients, orange represent intermediate risk patients and red represents high-risk patients.
CML and five were related to CML while the other seven deaths were due to post-transplant complications (graft-versus-host disease 2 cases, infection 5 cases) and for this analysis were considered as non-CML-related deaths.

Overall, the 5-year overall survival rate was 94% (95% CI: 90%-97%), the 5-year progression-free survival rate was 92% (95% CI: 87%-94%) and the 5-year survival rate accounting for competing events was 97% (95% CI: 94%-99%). Among the patients allocated to the low-, intermediate- and high-risk groups by the ELTS score, events (progression and/or death) occurred in 6.0%, 8.8% and 26.2%, respectively. When the patients were stratified according to the Sokal, Euro, EUTOS and ELTS scores, only the EUTOS and the ELTS scores were able to discriminate risk groups with significantly different progression-free survival (P=0.009 and P<0.0001, respectively) (Table 1, Figure 1). None of the Sokal, Euro, EUTOS and ELTS scores was able to discriminate risk groups with significant differences in survival based on CML deaths only (Table 1).

Discussion

The prognosis of adult patients with CML can be predicted with established prognostic scores based on clinical (spleen size) and biological parameters. The characteristics of CML differ with age with larger spleen size and higher leukocyte count at diagnosis in the present population of children and adolescents than reported in adults with CML.10-12 Because of the rarity of CML in children, a specific prognostic score incorporating clinical, biological and molecular features has not been established for this population. The Sokal and Euro scores were developed in a cohort of patients including children with CML in the conventional chemotherapy (busulfan, hydroxyurea) and in the interferon eras, respectively.12 A Sokal score for young patients was established in a cohort of patients less than 45 years old and is still useful in the era of therapy with tyrosine kinase inhibitors.4,5 Subsequently, the EUTOS scoring system was introduced in adult patients treated with imatinib.1 The improved life expectancy of adults with CML treated with imatinib currently approaches 90% at 10 years.1,20,21 Although children have more aggressive features at presentation compared to adults, probabilities of overall survival remain high and comparable in children, in adolescents and in young adults treated with imatinib.10,11,12 The high probability of progression for children allocated to the high-risk group could favor risk-adapted treatment with the use of second-generation tyrosine kinase inhibitors as first-line therapy in these patients.

The estimated 5-year overall survival rate reported in our non-selected cohort of children compares favorably with results reported in adults treated in trials with imatinib.21-23.25,26 Although children have more aggressive features than reported in adults with CML 10-12. Because the improvement in the survival of patients with CML after introduction of imatinib has resulted in an increased life expectancy, about half of adult patients now die of causes unrelated of CML. The main non-related CML deaths reported in adults in the tyrosine kinase inhibitor era are those due to secondary malignancies and cardiovascular events.6,24 Thus CML-related death could represent a better assessment of treatment efficacy. In the present study, the 5-year survival rate accounting for competing events of 97% corresponded to a 3% probability of death because of CML which is rather similar to the 4% probability reported in adults.4 However, in contrast to the adult study, the follow up was not censored at transplantation in the present study, consequently deaths from HSCT are competing events. The non-related CML deaths notified in the present study were due to post-transplant complications and were more common than CML as a cause of death. Thus HSCT should be reserved for cases of treatment failure in children in chronic phase, as proposed in the recommendation of the International Berlin-Frankfurt-Munster study group.20

The ELTS score discriminates the probability of dying of CML better than do the Sokal, Euro and EUTOS scores in adults with CML. In the present study none of these scores was able to discriminate risk groups with significant differences in survival based on CML deaths only. The low number of events (only 5 CML-related deaths) is one of the possible explanations for these findings. Moreover, because of the low number of comorbidities in the pediatric population, the risk of dying due to competing events is restricted to the complications of HSCT.

In this pediatric cohort, the ELTS score demonstrated better differentiation of progression-free survival than did the Sokal (in patients less than 45 years old) and Euro scores in children and adolescents with CML in chronic phase treated with imatinib. We therefore propose that the ELTS score should be considered in therapeutic algorithms and clinical trials in children and adolescents.

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References

1. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in good-risk chronic granulocytic leukemia. Blood. 1984;63(4):789-799.
2. Hasford J, Flümann M, Hehlman R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alpha. J Natl Cancer Inst. 1996;98(11):850–857.
3. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2010 patients with CML on imatinib treatment: the EUTOS score. Blood. 2011;118(5):686–692.
4. Sokal JE, Baccarani M, Tura S, et al. Prognostic discrimination among younger patients with chronic granulocytic leukemia: relevance to bone marrow transplantation. Blood. 1989;66(6):1552-1557.
5. Gurea Salas D, Glauche I, Tauer JT, et al. Can prognostic scoring systems for chronic myeloid leukemia as established in adults be applied to pediatric patients? Ann Hematol. 2015;94(10):1363-1371.
6. Flümann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016;30(1):48-56.
7. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Blood. 2013;122(6):872-884.
8. Guilhot J, Baccarani M, Clark RE, et al. Definitions, methodological and statistical issues for phase 3 clinical trials in chronic myeloid leukemia: a proposal by the European LeukemiaNet. Blood. 2012;119(25):5963-5971.
9. Gray RJ. A class of k-samples tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16(3):1141-1154.
10. Castagnetti F, Gugliotta G, Baccarani M, et al. Differences among young adults, adults and elderly chronic myeloid leukemia patients. Ann Oncol. 2015;26(1):185-192.
11. Kalmanti L, Saussele S, Lauseker M, et al. Younger patients with chronic myeloid leukemia do well in spite of poor prognostic indicators: results from the randomized CML study IV. Ann Hematol. 2014;93(1):71–80.
12. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European countries. Leukemia. 2015;29(6):1336–1345.
13. Oyekunde AA, Osho PO, Aneke JC, et al. The predictive value of the Sokal and Hasford scoring systems in chronic myeloid leukemia in the imatinib era. J Hemat Malign. 2012;2(2):25-32.
14. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34(24):2851-2857.
15. Hehlmann R, Müller MC, Lauseker M, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-Study IV. J Clin Oncol. 2014;32(5):415-423.
16. Milot F, Baruchel A, Guilhot J, et al. Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: results of the French national phase IV trial. J Clin Oncol. 2011;29(20):2827-2832.
17. Milot F, Guilhot J, Baruchel A, et al. Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study. Blood. 2014;124(15):2408-2410.
18. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-α in newly diagnosed chronic myeloid leukemia. J Clin Oncol. 2011;29(12):1634-1642.
19. Hoffmann VS, Baccarani M, Hasford J, et al. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. Leukemia. 2017;31(5):593–601.
20. De la Fuente J, Baruchel A, Biondi A, et al. How I manage CML in children - guidelines for the management of chronic myeloid leukemia in children and young people up to the age of 18 years. Br J Haematol. 2014;167(1):53-47.
21. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol. 2016;34(20):2333-2340.
22. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib versus imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30(5):1044–1054.
23. Pemmaraju N, Kantarjian H, Shan J, et al. Analysis of outcomes in adolescents and young adults with chronic myelogenous leukemia treated with upfront tyrosine kinase inhibitor therapy. Haematologica. 2012;97(7):1029–1035.
24. Saki K, Strom S, O’Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. Lancet Haematol. 2015;2(5):e166-e193.