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ABSTRACT

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: 92%-98%), 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).[1-3] While the Sokal score for patients less than 45 years

Table 1. Probabilities of progression-free survival and survival accounting for competing events in children with chronic myeloid leukemia treated with imatinib.

Prognostic score	Number of cases n (%)	Progression or death (% risk group)	5-year PFS estimate (95% CI)	*P*	CML deaths (% risk group)	Competing events (% risk group)	5-year survival estimate (95% CI) accounting for CML deaths	*P*
Sokal young score								
Low risk	54 (18%)	3 (5.5%)	93% (81-98)		0	2 (3.7%)	100%	
Intermediate risk	118 (38%)	6 (5%)	94% (87-97)	*P*=0.279	2 (1.7%)	2 (1.7%)	97% (92-100)	*P*=0.576
High risk	137 (44%)	14 (10.2%)	87% (79-92)		3 (2.2%)	3 (2.2%)	96% (89-100)	
Missing	41							
Euro score								
Low risk	165 (55%)	9 (5.5%)	94% (88-97)		2 (1.2%)	3 (1.8%)	98% (94-100)	
Intermediate risk	103 (34%)	9 (8.7%)	89% (79-94)	*P*=0.211	1 (1%)	4 (3.9%)	99% (93-100)	*P*=0.182
High risk	35 (12%)	5 (14.3%)	81% (60-92)		2 (5.7%)	0	87% (75-98)	
Missing	47							
EUTOS score								
Low risk	238 (78%)	13 (5.5%)	93% (88-96)		3 (1.3%)	4 (1.7%)	98% (93-99)	
High risk	68 (22%)	10 (14.7%)	81% (67-89)	*P*=0.009	2 (3%)	3 (4.4%)	94% (83-99)	*P*=0.340
Missing	44							
EUTOS Long-Term Survival score								
Low risk	199 (64%)	6 (3%)	96% (92-98)		1 (0.5%)	2 (1%)	99% (95-100)	
Intermediate risk	68 (22%)	6 (8.8%)	88% (76-95)	*P*<0.0001	2 (2.9%)	3 (4.4%)	96% (88-99)	*P*=0.107
High risk	42 (14%)	11 (26.2%)	67% (49-82)		2 (4.8%)	2 (4.8%)	89% (70-98)	
Missing	41							

CI: confidence interval; CML: chronic myeloid leukemia; PFS: progression-free survival. Because of some lacking data (spleen size n=31; platelet count n=1; eosinophil count n = 11; basophil count n=15 or blast and myeloblast percentage n=11) determination of at least one prognostic score was not possible in a total of 48 children (all scores and EUTOS Long-Term Survival score were missing in 38 and 41 of them, respectively). All patients with critical events (progression and/or deaths) were assessable for the calculation of the risk score.

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.[4] Limited data are available regarding the utility of the EUTOS score in the pediatric population.[5] 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 old), Euro, EUTOS and ELTS scores were performed using mathematical equations including the following parameters: sex, spleen size, hematocrit, platelets and blasts in blood for the Sokal score; age, spleen size, platelets, blasts, basophils and eosinophils in blood for the Euro score; spleen size and basophils in blood for the EUTOS score; and age, spleen size, platelets and blasts in blood for the ELTS score, as previously reported.[2-4,6] On the basis of the calculated scores, the children were categorized into low risk, intermediate risk or high risk groups for the Sokal (for patients less than 45 years), Euro and EUTOS scores and into 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/m^2 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

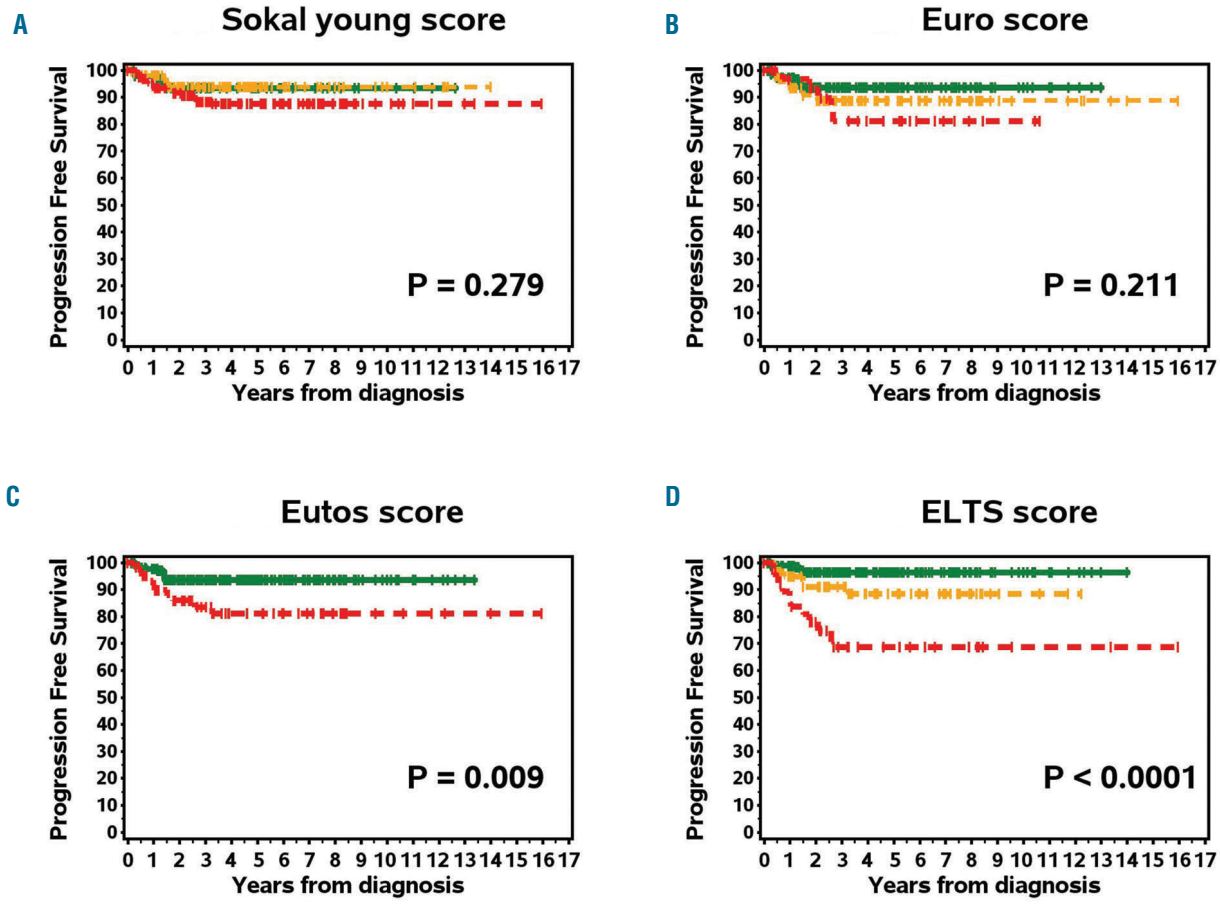

Figure 1. Progression-free survival stratified according to risk categorization by the four scores. (A) Sokal score, (B) Euro score, (C) EUTOS score, (D) EUTOS Long-Term Survival (ELTS) score. Green represent low risk patients, orange represent intermediate risk patients and red represents high-risk patients.

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 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.[1,2] 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.[4,13] Subsequently, the EUTOS scoring system was introduced in adult patients treated with imatinib.[3] The improved life expectancy of adults with CML treated with imatinib currently approaches that for the general population, with 41% to 44% of the deaths not directly related to CML but rather to comorbidities.[6,14,15] Based on the concept of competing risks, the ELTS score was recently developed in order to consider disease-specific death in adults with CML.[6] This new score differentiated the probability of dying of CML in the adult population better than did the Sokal, Euro and EUTOS scores.[6] The aim of the present study was to test the relevance of the ELTS score in a large cohort of children and adolescents with CML. In the present cohort of 350 children treated with imatinib for CML in first chronic phase, the ELTS score identified a lower proportion of high-risk children than the Sokal score, as observed in adults, while the proportions of the children allocated to low-risk (64%), intermediate-risk (22%) and high-risk (14%) groups by the ELTS score were similar to the proportions reported in adults.[6]

The 5-year progression-free survival rate of 92% for the entire cohort of children is consistent with previous reports in children and adults with CML in chronic phase treated with imatinib front line.[16-19] The recently developed ELTS score divided the children of the present study into three separate risk groups according to their progression-free survival with all risk groups differing significantly from each other. The ELTS score showed better differentiation of progression-free survival than the other scores in our cohort of children and could be used to predict the long-term outcome of children with CML in chronic phase. This finding suggests the establishment of new treatment policies with the incorporation of this score into the therapeutic algorithms of the current recommendations proposed for childhood CML.[20] 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.[21,22] 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.[10,11,23] Because the improvement in the survival of patients with CML after introduction of imatinib has resulted in 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.[6] 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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