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Temporal trends in the proportion of “cure” in children, adolescents and young adults diagnosed with chronic myeloid leukemia in England: a population-based study

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Abbreviations used

AIC: Akaike Information Criteria

allo-HSCT: allogeneic hematopoietic stem cell transplant

CML: Chronic myeloid leukemia

CP: chronic phase

UK: United Kingdom

TKI: tyrosine kinase inhibitor

Abstract

Background

Survival probability in children, adolescents and young adults with chronic myeloid leukemia (CML) has dramatically improved during recent years. Tyrosine kinase inhibitors (TKI), targeted drugs developed for patients with CML, were introduced in 2001 in England. We here quantify the trends in the “cure” proportion according to the year of diagnosis.

Methods

We included all children, adolescents and young patients with CML (0 to 24 years) diagnosed in England during 1980-2005. We fitted mixture cure models to estimate the “cure” proportion and the median survival time among the “uncured” patients according to the year of diagnosis, adjusted for age at diagnosis.

Results

The “cure” proportion increased dramatically between 1980 and 2005, from under 10% to over 80%, while conversely, the median survival time of "uncured" patients decreased slightly between 1980 and 1999, with the trend from 2000 being uncertain.

Conclusions

The striking improvement of the “cure” fraction in young patients with CML since the early 1980’s, is concomitant with improvement of treatment, especially the allogeneic hematopoietic stem cell transplant and, later, the introduction of TKI. The trends over the last years 2000-2005 remain however uncertain and would benefit from further studies with more recent data and updated follow-up.

1 **Introduction**

2 Chronic myeloid leukemia (CML) in children and young people is a rare disease, representing only
3 2% of all leukemias in children diagnosed younger than 15 years and 9% of all leukemia in
4 adolescents at age 15 to 19 years.¹ The incidence is between 0.6 and 1.2 per million children per
5 year, very low in infancy and rising with age.² There are few clinical treatment guidelines for
6 pediatric CML, so treatment is often derived from practice standards used in adult patients.^{1,3}
7 Natural course of disease is biphasic, it begins with a chronic phase (CP) with a median duration
8 of four years, followed by acceleration phase lasting 6 to 18 months and finally transforming into
9 resistant, rapidly fatal blast phase with a median survival of 3 to 9 months. Natural course of disease
10 in children is comparable to that in adults.^{2,4}

11 The survival probability of children, adolescents and young adults diagnosed with CML showed a
12 dramatic improvement during the last 30 years due to introduction of new drugs. Before 1980,
13 CML was treated with “standard” chemotherapy. Busulfan, an alkylating agent active at the stem
14 cell level, and hydroxyurea, an inhibitor of the ribonucleotide reductase, were used as palliative
15 treatment to prolong CP.^{5,6} In the 1980s and 1990s, interferon alpha for chronic therapy and
16 allogeneic hematopoietic stem-cell transplant (allo-HSCT) as curative option became mainstay of
17 treatment.⁷ In 2001, tyrosine kinase inhibitor (TKI) imatinib was licensed as Glivec® in the United
18 Kingdom (UK), in clinical practice TKI became available for patients older 18 years by 1999 and
19 for younger patients by 2003. TKIs rapidly became the new gold standard treatment.^{1,8} In recent
20 years, second-generation TKIs, such as dasatinib, nilotinib and others followed.² TKI therapy
21 results in not only a hematological response, but also a complete cytogenetic response followed by
22 a status of minimal residual disease detectable only with highly sensitive methods like polymerase
23 chain reaction.⁸ This is paralleled by great improvements in survival. However, a life-long therapy
24 is required for most patients, while 10 to 15% of adult patients have successfully managed to stop

25 TKI treatment following the achievement of a deep and long-lasting molecular responses. This
26 clearly demonstrated that a "functional" cure for CML is achievable.⁹
27 Medical cure at the individual level is defined when the original neoplasm has been completely
28 eradicated, and as pointed out by Zwaan and Sposto,¹⁰ "*there are no residual sequelae attributable*
29 *to having had the disease or being treated for it*". In this work, we investigated the population-
30 based level of "cure" (in contrast to the medical cure), *i.e.* it is defined at the group (and not
31 individual) level of a cohort of patients. Therefore, we used the words "cured" and "uncured" in
32 quotes, to make clear that this refers to *statistical cure*, which is computed and interpreted at the
33 population-level. One important aspect of all cure models is that, for the cure proportion to be
34 estimable, the survival curve must reach a plateau observed from the data.¹¹ In such case,
35 assumption of occurrence of cure is reasonable and using cure models would be adequate.^{12,13} As
36 well as quantifying the proportion of patients "cured", cure models also allow estimating the
37 median survival time of the "uncured" patients (*i.e.* the "fatal cases"), taking account of other
38 factors¹⁴, such as the year of diagnosis, age at diagnosis, etc. Cure models have been developed
39 and applied in different settings since the first publication by Boag.¹⁴⁻¹⁹
40 Using cure models in all children, adolescents and young adults diagnosed with CML in England,
41 we want to assess the trends in the probability to be "cured" (in a population-based meaning), with
42 a specific interest in the impact of the new therapy with TKIs, used since 2001. We also investigate
43 trends in the median survival time of the "uncured" patients.

44 **Material and Methods**

45 **Data**

46 The source for the study dataset was UK National Cancer Registry.²⁰ The subset analyzed were
47 children (0 to 14 years), adolescents (15 to 19 years) and young adults (20 to 24 years) diagnosed

48 with CML in England between 1980 and 2005. Their vital status was assessed on the 31st December
49 2015. So, we had a minimum of 10 years of potential follow-up for all patients. The time since
50 diagnosis was used as the time scale, and for the analyses, we restricted the follow-up to the first
51 15 years after diagnosis: patients alive at 15 years were censored.

52 **Descriptive analysis**

53 For descriptive purposes and for the univariable analysis, we categorized age at diagnosis in three
54 age-groups (< 5 years, 5 to 14 years and 15 to 24 years), and the year of diagnosis in five periods
55 (1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2005).

56 We plotted the survival probability according to calendar period of diagnosis using the non-
57 parametric Kaplan-Meier estimator. These plots allow for a visual assessment of the cure
58 assumption (plateau).¹¹

59 **Cure models**

60 Mixture cure models assume two subpopulations: a subpopulation considered as “cured” and a
61 subpopulation of fatal cases, e.g. “uncured”.²¹ In these models, we express the probability to be
62 alive at time t as the sum of (i) the probability to be cured and (ii) the probability to be uncured (*i.e.*
63 one minus the probability to be cured) times the probability to be alive at time t for the uncured,
64 which are the “fatal cases”, who died from any cause. Both the cure proportion and the survival
65 probability of the fatal cases could depend on covariables such as year of diagnosis or age at
66 diagnosis (multivariable model). From these expressions, we could derive the mortality rate, and
67 thus the full log-likelihood (see technical details in the appendix). We applied the mixture cure
68 models firstly in a univariable analysis on pre-defined subgroups, and secondly in a multivariable
69 analysis. In all analysis, we assumed a Weibull distribution for the survival function of the

70 "uncured", and we used a logistic parametrization for the proportion of cured to constrain the cured
71 fraction to fall in the range (0,1).¹² The formulae are provided in the appendix.

72 Univariable analyses

73 For the univariable analyses, a mixture cure model without any covariable was fitted in each
74 subgroup defined with the five periods of diagnosis defined above. We estimated the cure
75 proportion as well as the parameters of the Weibull distribution for the fatal cases (*i.e.* the
76 "uncured" group). The estimated parameters of the Weibull distribution for the fatal cases were
77 used to calculate the median survival time of the "uncured". We checked the quality of fit by
78 comparing the non-parametric observed survival estimated for each period of diagnosis with the
79 survival predicted using the estimated parameters from the fitted cure model.

80 Multivariable analyses

81 In the multivariable analyses, we assumed by default a non-linear effect of age at diagnosis both
82 on the (logit of the) cure proportion and on the (log of the) scale parameter of the Weibull
83 distribution: we used a quadratic regression spline with one knot located at 15 years. Regarding the
84 effect of year of diagnosis, we fitted 4 different mixture cure models assuming either a linear or a
85 non-linear effect of the year of diagnosis on either the (logit of the) cure proportion or on the (log
86 of the) scale parameter of the survival distribution of the fatal cases, or on both. For the non-linear
87 effect of year of diagnosis, we used a quadratic spline with one knot located at 1990 (the median
88 of the observed distribution of year of diagnosis among the observed events). The mathematical
89 details of the different models parametrizations are provided in the appendix. We used the Akaike
90 Information Criterion (AIC) to select the final model. From the final model, we derived the
91 temporal trends of the "cure" proportion and the median survival time of the "uncured" for specific

92 ages at diagnosis (6 months, and 5, 15 and 24 years). We derived Wald-type 95% confidence
93 intervals, using the multivariate delta method^{22,23} for deriving the standard errors of the “cure”
94 proportion and the median survival time of the “uncured”. To assess the fit of the final model, we
95 compared the survival as predicted from the final cure model for a given age a and a year of
96 diagnosis y to a non-parametric survival estimate obtained using the subgroups of patients aged
97 between $[a-2; a+2]$ and diagnosed in the period $[y-2; y+2]$. We also performed such comparison
98 for the survival of the “uncured” only (see appendix for technical details).
99 All the analyses were performed using the R software (version 3.4.1).

100 **Results**

101 **Demographic characteristics**

102 Overall 538 patients aged 0 to 24 years were diagnosed with CML between 1980 and 2005 in
103 England, and we observed 305 deaths (57%) (Table 1). Among the observed cases, 63% were in
104 the age group 15-24 years old. The observed survival probabilities were extremely different
105 according to the period of diagnosis, ranging from around 10% at 15 years for patients diagnosed
106 between 1980 and 1984 compared to around 70% for patients diagnosed between 2000 and 2005
107 (Figure 1). The survival for CML improved remarkably from 1995-1999 to 2000-2005.

108 **Mixture cure models**

109 Univariable analyses

110 From the univariable analyses, we observed a dramatic increase of the “cure” proportion, from 9%
111 in 1980-1984 (95% Confidence Interval [4%;22%]) to 71% (95% CI [62%; 79%]) in 2000-2005.
112 The median survival time for the "uncured" group ranged between 1.52 years (95% CI [0.97; 2.06])
113 and 2.72 years (95% CI [1.61; 3.84]), without a clear temporal trend pattern (Table 2). Figure 2

114 shows a comparison of the trends of the “cure” proportion with the median survival time of the
115 “uncured”. The trends showed an improvement of the “cure” proportion throughout 1980-2005.
116 The pattern for the median survival time among the “uncured” was not so clear, with a decrease
117 between 1985-1989 and 1995-1999, and a slight increase more recently (1995-1999 to 2000-2005).
118 When assessing the fit of the univariable cure models, we obtained very comparable estimates for
119 each period of diagnosis (Figure S1 in Appendix).

120 Multivariable analyses

121 The model with the lowest AIC (final model) was the model assuming a linear effect of the year of
122 diagnosis on the survival of the “uncured” and a non-linear effect of the year of diagnosis on the
123 “cure” proportion. From this model, we predicted the temporal trends of the “cure” proportion and
124 the median survival time among the “uncured” for different ages at diagnosis: 6 months, 5 years,
125 15 years and 24 years (Table 3 and Figure 3). From 1980 to 2005, we observed a slight decrease in
126 median survival time of the “uncured” patients, going from 1 year in 1980 to half a year in 2005
127 for infants diagnosed at 6 months, while it decreased from 4 to 2 years in patients aged 15 years
128 old. Conversely, we observed a dramatic improvement from 1980 to 2005 of the “cure” proportion,
129 rising to about 80% in 2005 for different ages at diagnosis (Table 3, Figure 3). When assessing the
130 fit of the multivariable cure model, we observed good agreement between the 2 overall survival
131 estimates (non-parametric *vs.* model-based) for each age/year combination (Figure S2 in
132 Appendix), as well as between the 2 survival estimates of the “uncured” (Figure S3 in Appendix).

133 Discussion

134 Cancer registry data provide a unique opportunity to assess “cure” at the population level and over
135 a long period. Here, we used cure models in pediatric and young adult patients with CML in

136 England, using data from the national population-based cancer registry to assess the temporal
137 trends over a 26-year period of observation in the “cure” proportion. We had a potential follow-up
138 time of at least 10 years for all patients diagnosed up to 2005. We also provided temporal trends of
139 the median survival time for the “uncured” (the “fatal cases”). From 1980 to 2005, we estimated a
140 spectacular increase in the proportion of patients “cure”, up to around 80% for patients diagnosed
141 in 2005 for all age groups. The results about “cure” proportion were consistent in the univariable
142 and the multivariable analyses. They were also in line with the results from the international
143 registry for pediatric patients with CML.²⁴

144 For international comparison purposes, we did a PubMed search with terms (“cure models” AND
145 leukemia AND children) and we found only two epidemiological studies, which however focused
146 solely on childhood acute lymphoblastic leukemia.^{25,26} Other study in Great Britain assess “cure”
147 proportion in leukemia for children diagnosed up to 2000, but focused on other more common
148 subtypes, such as acute lymphoid and acute non-lymphoblastic leukemia.²⁷ Another recent study
149 from Trama *et al.* provided relative survival estimates and trends for adolescents and young adults
150 over 2000-2007 using data gathered from 27 European Countries, but they did not present survival
151 estimates for CML, or proportion of “cured”.²⁸ Our results complement previous studies by
152 quantifying the cure proportion and the median survival time of the uncured along with their trends
153 over 1980-2005, on the whole England population of children, adolescents and young adults
154 diagnosed with CML.

155 We observed a slight discrepancy between the univariable and the multivariable analyses regarding
156 the median survival time among the “uncured” over the period 2000-2005: the small increase in
157 median survival time for “uncured” estimated from the univariable analyses for the period 2000-
158 2005 compared to 1995-1999 was not clearly confirmed by the multivariable analysis, which
159 retained a slow decrease of the median survival time among the “uncured” throughout 1980-2005

160 with the final model. In the multivariable analysis, the model selection based on the AIC slightly
161 favored the model with a simple linear effect of the year of diagnosis on the survival for the
162 “uncured”. However, the AIC value of the model with a non-linear functional form for the year of
163 diagnosis on the survival for the “uncured” was quite similar to the AIC value of the retained model
164 (1912·64 vs. 1910·75 for the retained final model). The difference between the AIC values is less
165 than 2, meaning that both models could have been selected as the closest model to the true
166 generating model.²⁹ When we used this more complicated model (the model with the non-linear
167 effect of year of diagnosis on the “uncured” survival), we observed a slight increase in the median
168 survival time among the “uncured” between 2000 and 2005 (Figure S4 in the appendix). Thus, we
169 cannot conclude with certainty on the trend of the median survival time among the “uncured” over
170 the period 2000-2005; it will need to be confirmed in future studies with more recent data and
171 updated follow-up. This will increase the power, and thus the ability of the model to better identify
172 any potential increase in the median survival time among the “uncured”. From this more
173 complicated model, the trends and the values of the “cure” proportion were however quite similar
174 to the one provided by the final selected model, as was the trend of the median survival time among
175 the “uncured” over the period 1980-2000 (Figure S4 in the appendix). Therefore, these consistent
176 results reinforce the evidence of a (i) dramatic increase of the “cure” proportion from 1980 to 2005,
177 and (ii) a slight decrease of the median survival time among the uncured from 1980 to 2000. To
178 show the overall agreement between the 4 fitted models (with linear or non-linear effect of year of
179 diagnosis on the cure proportion and/or on the survival of the “uncured”), we provided a table in the
180 appendix (Table S1) with the model-based estimates of the cure proportion and the median survival
181 time of the “uncured” derived from each of the 4 fitted models, for 4 different values of age at
182 diagnosis and year of diagnosis.

183 We used a Weibull distribution for survival of the "uncured" in the cure model. Other methods
184 based on, for instance, the generalized modified Weibull distribution³⁰ or flexible parametric
185 models,³¹ could have provided more flexibility than the Weibull distribution. However, the visual
186 checks comparing the non-parametric survival estimates to the survival predicted from the mixture
187 cure models showed an adequate fit overall. We assumed an effect of variables only on the scale
188 parameter of the Weibull distribution, as modelling the influence of covariables on the shape
189 parameter is rarely necessary.^{12,32} This adequate fit was also confirmed by the comparison between
190 (i) the model-based survival estimates for the "uncured" and (ii) the non-parametric observed
191 survival estimates, once removed the component related to the "cure" (see the appendix for Figure
192 S3, and for the mathematical details).

193 It seems reasonable to assume that the large increase in the "cure" proportion depicted here between
194 periods 1995-1999 and 2000-2005 is related to the introduction and implementation of TKI
195 imatinib treatment in the National Health System of England, which occurred in 2001. Moreover,
196 because the CML is a rare disease in children and young adults, it seems reasonable to assume that
197 a substantial part of the incident cases studied here for England were included in adult clinical trials
198 and thus had benefited from the treatment before its official introduction.^{33,34} This could partly
199 explain the increase of the "cure" proportion before 2001. An additional explanation of the increase
200 in the "cure" proportion before 2001 might be related to the implementation of interferon alpha
201 and especially the use of allo-HSCT in the 1990s.³⁵ It must be taken into consideration that allo-
202 HSCT from matched siblings became a frequent treatment option for those 25% of patients having
203 a sibling donor in the early 1980's. From 1990 onwards, unrelated donors became available for the
204 majority (approximately 80%) of patients but the transplant related mortality was higher (more
205 than 20%) than with sibling donors.³⁶ The graphs in Figure 3 support the assumption that the broad
206 introduction of unrelated allo-HSCT from the early 1990's impacted the proportion of "cured"

207 patients, and the median survival time of the “uncured”. We can hypothesize that patients, who
208 survived the therapy-related complications became long-term survivors, and the transplanted cases
209 who died from transplant-related toxicities had shorter median survival time. Conversely, the
210 apparent decrease in median survival time for “uncured” patients reported here could reflect a
211 selective effect of the new treatment on patients with better prognosis. In other words, if a new
212 treatment is selectively effective on patients with good prognosis, the “uncured” group will include
213 mostly patients with more aggressive malignancy: this would lead to an apparent decrease in the
214 median survival time of the “uncured” group, while the proportion of “cured” would increase.
215 Another explanation for the decrease in the median survival time of the “uncured” throughout
216 1980-2000 could be associated to the toxicity of the treatment, which would increase chances of
217 being cured, but at the expense of a higher toxicity and shorter survival time for the “uncured”:
218 patients treated with an intensive treatment with curative intent had a good chance of being cured,
219 but treatment failure may shorten patient’s life (because of side effects). The uncertainty (explained
220 in the beginning of the discussion) on the trend between 2000 and 2005 of the median survival time
221 of the “uncured” calls for cautious interpretation on that specific period.
222 Our results nonetheless support a remarkable change in the prognosis of young patients with CML,
223 with a population-level “cure” proportion around 80% for patients diagnosed in 2000-2005. In the
224 clinical and public health perspective however, this should be balanced with long-term side effects
225 of life-long TKI therapy, such as growth restriction¹, a particular concern in pre-pubertal children,
226 diminished quality of life and secondary malignancies,³⁷ especially in young patients, and further
227 information and specific follow-up of patients are warranted.¹⁰ The uncertainty around the trend in
228 median survival time for the “uncured” patients over 2000-2005 also warrants further consideration
229 and exploration using more recent data.

Contributors

Aurélien Belot and Daniel Drozdov designed the study, performed the statistical analysis and drafted the article.

Kayo Nakata did the data preparation and critically revised the article.

Audrey Bonaventure and Meinolf Suttorp provided support in clinical questions, contributed to interpretation of findings and critically revised the article.

Conflict of interest statement

The authors declared no conflicts of interest.

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Ethical approvals

We obtained the ethical and statutory approvals required for this research (PIAG 1-05(c)/2007 and REC 13/LO/0610) from the “Confidentiality Advisory Group (CAG) part of the Health Research Authority (HRA)”. We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

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Legends of figures and tables

Figure 1 Overall survival estimates by period of diagnosis in children, adolescents and young adults diagnosed with chronic myeloid leukemia in England, 1980-2005

Figure 2 Median survival time among “uncured” patients (in years) according to the proportion of “cure” for different periods of diagnosis, estimated with the univariable mixture cure model, in children, adolescents and young adults diagnosed with chronic myeloid leukemia in England, 1980-2005

Figure 3 Temporal trends of (i) the “cure” proportion (solid line) and (ii) the median survival time (in years) among the “uncured” (dashed line) with their corresponding 95% confidence intervals, estimated with the multivariable mixture cure model (final model, see method) in patients with chronic myeloid leukemia in England aged 6 months at diagnosis (A), 5 years (B), 15 years (C) and 24 years (D), 1980-2005

Table 1 Characteristics of patients (0-24 years) diagnosed between 1980 and 2005 with chronic myeloid leukemia in England by sex, age group and period of diagnosis

Table 2 Results from the univariable mixture cure model: “cure” proportion and median survival time of the “uncured” (in years) with their 95% confidence intervals for each period of diagnosis, in children, adolescents and young adults diagnosed with chronic myeloid leukemia in England, 1980-2005

Table 3 Results from the multivariable mixture cure model (using the retained final model): “cure” proportion and median survival time of the “uncured” (in years) with their 95% confidence intervals for specific age at diagnosis and year of diagnosis, in children, adolescents and young adults diagnosed with chronic myeloid leukemia in England, 1980-2005