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.

Introduction

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

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

TKI treatment following the achievement of a deep and long-lasting molecular responses. This clearly demonstrated that a "functional" cure for CML is achievable.[9]

Medical cure at the individual level is defined when the original neoplasm has been completely eradicated, and as pointed out by Zwaan and Sposto,[10] "*there are no residual sequelae attributable to having had the disease or being treated for it*". In this work, we investigated the population-based level of "cure" (in contrast to the medical cure), *i.e.* it is defined at the group (and not individual) level of a cohort of patients. Therefore, we used the words "cured" and "uncured" in quotes, to make clear that this refers to *statistical cure,* which is computed and interpreted at the population-level. One important aspect of all cure models is that, for the cure proportion to be estimable, the survival curve must reach a plateau observed from the data.[11] In such case, assumption of occurrence of cure is reasonable and using cure models would be adequate.[12,13] As well as quantifying the proportion of patients "cured", cure models also allow estimating the median survival time of the "uncured" patients (i.e. the "fatal cases"), taking account of other factors[14], such as the year of diagnosis, age at diagnosis, etc. Cure models have been developed and applied in different settings since the first publication by Boag.[14-19]

Using cure models in all children, adolescents and young adults diagnosed with CML in England, we want to assess the trends in the probability to be "cured" (in a population-based meaning), with a specific interest in the impact of the new therapy with TKIs, used since 2001. We also investigate trends in the median survival time of the "uncured" patients.

Material and Methods

Data

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

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

Descriptive analysis

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

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

Cure models

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

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

Univariable analyses

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

Multivariable analyses

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

ages at diagnosis (6 months, and 5, 15 and 24 years). We derived Wald-type 95% confidence intervals, using the multivariate delta method[22,23] for deriving the standard errors of the "cure" proportion and the median survival time of the "uncured". To assess the fit of the final model, we compared the survival as predicted from the final cure model for a given age *a* and a year of diagnosis *y* to a non-parametric survival estimate obtained using the subgroups of patients aged between [a-2; a+2] and diagnosed in the period [y-2; y+2]. We also performed such comparison for the survival of the "uncured" only (see appendix for technical details).

All the analyses were performed using the R software (version 3.4.1).

Results

Demographic characteristics

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

Mixture cure models

Univariable analyses

From the univariable analyses, we observed a dramatic increase of the "cure" proportion, from 9% in 1980-1984 (95% Confidence Interval [4%;22%]) to 71% (95% CI [62%; 79%]) in 2000-2005. The median survival time for the "uncured" group ranged between 1.52 years (95% CI [0·97; 2·06]) and 2.72 years (95% CI [1·61; 3·84]), without a clear temporal trend pattern (Table 2). Figure 2

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

Multivariable analyses

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

Discussion

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

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

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

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

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

We used a Weibull distribution for survival of the "uncured" in the cure model. Other methods based on, for instance, the generalized modified Weibull distribution[30] or flexible parametric models,[31] could have provided more flexibility than the Weibull distribution. However, the visual checks comparing the non-parametric survival estimates to the survival predicted from the mixture cure models showed an adequate fit overall. We assumed an effect of variables only on the scale parameter of the Weibull distribution, as modelling the influence of covariables on the shape parameter is rarely necessary.[12,32] This adequate fit was also confirmed by the comparison between (i) the model-based survival estimates for the "uncured" and (ii) the non-parametric observed survival estimates, once removed the component related to the "cure" (see the appendix for Figure S3, and for the mathematical details).

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

patients, and the median survival time of the "uncured". We can hypothesize that patients, who survived the therapy-related complications became long-term survivors, and the transplanted cases who died from transplant-related toxicities had shorter median survival time. Conversely, the apparent decrease in median survival time for "uncured" patients reported here could reflect a selective effect of the new treatment on patients with better prognosis. In other words, if a new treatment is selectively effective on patients with good prognosis, the "uncured" group will include mostly patients with more aggressive malignancy: this would lead to an apparent decrease in the median survival time of the "uncured" group, while the proportion of "cured" would increase. Another explanation for the decrease in the median survival time of the "uncured" throughout 1980-2000 could be associated to the toxicity of the treatment, which would increase chances of being cured, but at the expense of a higher toxicity and shorter survival time for the "uncured": patients treated with an intensive treatment with curative intent had a good chance of being cured, but treatment failure may shorten patient's life (because of side effects). The uncertainty (explained in the beginning of the discussion) on the trend between 2000 and 2005 of the median survival time of the "uncured" calls for cautious interpretation on that specific period.

Our results nonetheless support a remarkable change in the prognosis of young patients with CML, with a population-level "cure" proportion around 80% for patients diagnosed in 2000-2005. In the clinical and public health perspective however, this should be balanced with long-term side effects of life-long TKI therapy, such as growth restriction[1], a particular concern in pre-pubertal children, diminished quality of life and secondary malignancies,[37] especially in young patients, and further information and specific follow-up of patients are warranted.[10] The uncertainty around the trend in median survival time for the "uncured" patients over 2000-2005 also warrants further consideration 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