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Determinants of survival in patients with chronic myeloid leukaemia treated in the new era of oral therapy: findings from a UK population-based patient cohort

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Abstract

Objectives To examine contemporary survival patterns in the general population of patients diagnosed with chronic myeloid leukaemia (CML), and identify patient groups with less than optimal outcomes.

Design Prospective population-based cohort.

Setting UK's Haematological Malignancy Research Network (catchment population 3.6 million, with >2000 new haematological malignancies diagnosed annually).

Participants All patients newly diagnosed with chronic myeloid leukaemia, September 2004 to August 2011 and followed to 31st March 2013.

Main outcome measure Incidence and survival.

Results With a median diagnostic age of 59 years, the CML age standardized (European) incidence was 0.9 per 100,000 (95% Confidence Intervals 0.8 to 0.9), 5-year overall survival 78.9% (72.3 to 84.0), and 5-year relative survival 88.6% (81.0 to 93.3). The efficacy of treatment across all ages was clearly demonstrated; the relative survival curves for those under 60 years and over 60 years remaining closely aligned. Survival findings were similar for men and women, but varied with deprivation; the age and sex adjusted hazard ratio being 3.43 (1.89 to 6.22) for deprivation categories 4-5 (less affluent) versus 1-3 (more affluent). None of these differences were attributable to the biological features of the disease.

Conclusions When therapy is freely provided, population-based survival for CML is similar to that reported in clinical trials and age loses its prognostic significance. However, although most CML patients now experience close to normal life-spans, those living in more deprived areas tend to have poorer outcomes, despite receiving the same clinical care. A significant improvement in overall population outcomes could be achieved if these socioeconomic differences, which may reflect treatment compliance, could be eliminated.

Article summary

Focus

- Orally administered tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukaemia (CML); changing it from a fatal cancer in non-transplanted patients to a chronic condition with the potential for a normal life-span.
- Clinical trials suggest that the outcome for most CML patients treated with TKI therapy is excellent; yet survival rates in many populations, notably the US, are much lower than expected.
- This study examines outcomes in a contemporary UK population-based cohort.

Key messages

- When TKI therapy is freely provided, CML survival is similar to that reported for clinical trials and age is no longer prognostic.
- Given the life-long nature of TKI therapy, inequality of access because of cost is likely to be the main explanation for the marked disparity between CML survival in US registries and the results reported here.
- Despite universal health care coverage, socio-economic factors impact adversely on CML survival in the UK.
- With a median diagnostic age of 59 years, the return to a normal life-span has major cost implications for commissioners planning the future care of patients with CML.

Strengths & Limitations

- Data are from a comprehensive population-based cohort that includes all patients diagnosed in a defined geographic area.
- Complete follow-up is achieved via linkage to national health care systems.
- The relative rarity of CML limited our ability to examine for smaller sub-group effects in the present series.
- Whilst our findings for socio-economic status and may reflect differences in treatment compliance, this association needs to be confirmed in future studies.

Introduction

Introduced at the turn of the century, orally administered tyrosine kinase inhibitors (TKIs) have transformed the treatment of chronic myeloid leukaemia (CML), changing it from a comparatively rare but fatal cancer in non-transplanted patients to a long-term condition with a steadily increasing prevalence. TKI therapy is, however, life-long and expensive; the price of first-generation imatinib currently varying from around £21,000 per patient per year in the UK through to £57,000 in the US, with the newer TKIs being even more costly. Such costs have major, but poorly defined, implications for health economies around the world[1].

Given the potential for CML patients to achieve a near normal lifespan, contemporary clinical discussion tends to revolve around how the growing range of TKIs should be used, response monitored and resistance managed[2–6]. However, with reported survival rates from CML in some populations being poorer than that predicted from clinical trials, the extent to which findings from clinical trials can be extrapolated to the general patient population is also an issue of current debate[7–11]. In this context, the contrast between the 5-year survival of 89% reported for imatinib treated patients from the original clinical trial who were recruited in 2001 and followed until 2006[12] and the 2001-9 relative survival of 56.0% in United States' (US) Surveillance, Epidemiology and End Results (SEER) populations[13 14], seems particularly stark.

For CML, as with many other cancers, discrepancies between trial and population-based studies are commonly ascribed to systematic differences between the types of patients recruited into trials and those who are not; the former often tending to be comprised of younger patients with fewer co-morbidities and less advanced disease[7 9 15]. In addition, it is becoming ever more apparent that non-trial access to expensive drugs such as TKIs has a key role to play in countries without universal health care coverage[1 16–18]. Furthermore, even in countries like the UK where care is freely provided on the basis of clinical need, non-adherence to the daily oral regimen is becoming an increasingly recognized problem for the long-term management of CML[2 9 19–22].

Up-to-date population-based data on CML are limited; with much of the available information on CML survival in the general population predating the latest clinical trials, as well as introduction of the latest monitoring/management guidelines[2–5 23]. The population-based Haematological Malignancy Research Network (www.hmrn.org), which collects information to clinical trial standards on all new haematological malignancy diagnoses, was specifically established in 2004 to address issues such as this by providing 'real-time' data to inform clinical practice and research[24]. The present report provides contemporary data on CML

incidence and survival in the UK over the period 2004-13, and investigates whether there are any patient groups with less than optimal outcomes.

Methods

Data are from the UK's population-based Haematological Malignancy Research Network (www.hmrn.org). Full details of HMRN's structure, data collection methods and ethical approvals have been described elsewhere[24]. Briefly, as a matter of policy, all diagnoses and subsequent monitoring within the clinical network (>2,000 patients a year) are made using the latest World Health Organization (WHO) classification[25] at a single integrated haematopathology laboratory (www.hmds.info). All patients have full-treatment, response and outcome data collected to clinical trial standards. HMRN operates with Section 251 support under the NHS Act 2006; enabling the Health and Social Care Information Centre (HSCIC) to provide us with nationwide information on deaths, subsequent cancer registrations, and Hospital Episode Statistics (HES).

CML diagnosis was based on the demonstration of a BCR-ABL fusion transcript expressed by the Philadelphia (Ph) chromosome by RQ-PCR and/or the demonstration of t(9;22)(q34;q11) by conventional karyotyping or interphase FISH. The presence of additional karyotypic abnormalities was based on bone marrow metaphase analysis. As per standard practice, response to therapy was monitored using either molecular or cytogenetic tests or both; specifically, patients were monitored by quantitative PCR on peripheral blood, supplemented by bone marrow karyotyping when clinically indicated. ABL kinase mutational analysis was carried out when the transcript ratio increased over two sequential samples or on clinical demand.

Area-based population counts and measures of deprivation were sourced from UK national data[26 27]. With respect to the latter and in common with other reports,[27–29] the quintile distribution of the income domain of the index of deprivation (IMD; quintile one containing the most affluent fifth of England's lower super output areas and quintile five the least) is used as marker of socio-economic status[30]. Overall survival and loss of molecular response (MR) was calculated using standard time to event analyses and the program strel (v1.2.7) was used to estimate relative survival; age and sex-specific background mortality rates were obtained from national life tables[31]. All analyses were conducted in the statistical package Stata 12.

Results

Two-hundred and forty-two patients were diagnosed with CML in the study region over the seven year period September 2004 to August 2011; yielding a crude annual incidence rate of 0.97 per 100,000. The corresponding European and World age standardized incidence rates were 0.9 (95% Confidence Intervals 0.8 to 0.9) and 0.7 (0.6 to 0.7) per 100,000 respectively. As can be seen from Table 1 (column 1), 132 (54.6%) patients were diagnosed before their 60th birthday and 110 (45.4%) after; the median diagnostic age being 59.0 years (range 15.1 to 94.7). As expected, around 3 out of every 5 patients were male, and the area-based deprivation distribution of the cohort was broadly similar to that of the country as a whole (59.1% in quintiles 1-3 and 40.9% in quintiles 4-5).

Forty-seven (19.5%) patients died before the 1st April 2013; minimum follow-up 1.5 years and maximum 8.5 years. The crude survival curve across the full 8.5 year period is shown in Figure 1A, and the crude and relative survival curves over the first 6 years are compared in Figure 1B (data for the remaining 2.5 years follow-up are not shown because the small numbers of events prohibited relative survival estimation). The 5-year survival was 78.9% (72.3 to 84.0) and the relative survival, taking into account background mortality in the general population, was 88.6% (81.0 to 93.3). Two-hundred and thirty four (96.7%) of the 242 patients were treated with TKIs within the study region: 219 (93.6%) received first-line imatinib and the remainder receiving dasatinib as part of an on-going trial. Only 8 (3.3%) of the 242 patients were not treated with TKIs within the HMRN region: two died before treatment could be started, one refused treatment, one had a more serious competing comorbidity, two had supportive care only, and two moved and were treated in another part of the country. Since all patients diagnosed within HMRN are 'flagged' in the national scheme, we can confirm that these latter two patients were alive on 1st April 2013.

Patients with additional cytogenetic abnormalities at presentation had poorer outcomes than those who presented in chronic phase as Ph+ alone (Table 1). With respect to patient characteristics, compared to those who survived, those who died tended to be older and live in less affluent areas (Table 1): the adjusted hazard ratios for those ≥ 60 years compared to those < 60 years was 2.65 (1.42 to 4.96), and for less affluent areas (quintiles 4-5) compared to more affluent areas (quintiles 1-3) was 3.43 (1.89 to 6.22). In addition, females were marginally more likely to survive than males, although this was not statistically significant.

Whilst the age-specific crude survival curves continue to diverge with increasing time since diagnosis, the relative survival curves for the two age groups remain closely aligned: the 5-

year relative survival for those < 60 years and over ≥ 60 years being 89.9% (80.8 to 94.8) and 87.2% (69.8 to 94.9) respectively. This clearly demonstrates the efficacy of TKI treatment across all ages (Figure 2). Gender had little impact on outcome, and the overall and relative survival curves of men and women are similar; the 5-year relative survival for men and women being 90.1% (79.9 to 95.4) and 89.1% (71.9 to 96.1) respectively. By contrast, the deprivation-specific relative survival curves remain as disparate from each other as the overall survival curves (P=0.0014); the 5-year relative survival for the most affluent (categories 1-3) and the least affluent (categories 4-5) being 94.9% (82.3 to 98.6) and 79.5% (64.1 to 88.8) respectively.

As can be seen from Table 2, marginal deprivation differences were also evident for both molecular response achievement, defined here as one or more readings ≤ 0.1 BCR-ABL1 (major molecular response - MMR) or ≤ 1.0 BCR-ABL1 (molecular response - MR), and its retention. Overall, 71.4% of patients in deprivation category 1-3 and 59.6% in 4-5 achieved MMR, the corresponding frequencies for MR being 82.1% and 71.3% respectively. With respect to the time taken to achieve molecular response, the disparity between deprivation categories was evident from therapy outset, albeit non-statistically significantly so; the MMR cumulative frequencies being 16.4% and 21.2% (12 months), 32.9% and 36.2% (18 months) and 51.4% and 42.6% (24 months); the MR results were 45.7% and 38.3% (12 months), 66.4% and 54.6% (18 months) and 74.9% and 60.6% (24 months) respectively.

The hazard ratios for loss of response combined with deaths (Table 2) are, as expected, consistent with the findings for overall and relative survival (Fig 2 E and F); patients in deprivation categories 4-5 who achieved MMR were 1.71 (1.03 to 2.84) times more likely to lose their response or die, and the results were similar when the threshold was increased to include patients who achieved an MR (1.90, 1.03 to 3.49). It is also worth noting that according to the information recorded at death certification, all 9 deaths in deprivation categories 4-5 had CML cited as a contributing cause of death, compared to 4 of the 8 in deprivation categories 1-3.

The deprivation differences presented here could not be explained either by variations in the acquisition of additional cytogenetic anomalies or TKI resistance, both of which were rare in this population: 7 (3.4%) of the 209 Ph+ patients with no additional abnormalities at diagnosis (Table 1) acquired an additional anomaly during follow-up, and all were in deprivation category 1-3. With respect to the 10 (4.3 %) patients who developed TKI resistance, 4/140 were in deprivation category 1-3 and 6/94 in 4-5. None of the patients who acquired an additional cytogenetic anomaly developed TKI resistance.

Discussion

The outcome for CML patients treated mainly with imatinib in our UK population-based patient cohort is similar to that reported for clinical trials[12 32]; the 5-year relative survival estimates for men and women diagnosed 2004-11 and treated with TKIs over the period 2004-13 being 89.1% (79.9 to 95.4) and 90.1% (71.9 to 96.1) respectively. This suggests that the much poorer outcome recorded in the US reflects financial barriers to accessing TKI therapy. Furthermore, our data confirm the inferences from clinical trials that TKI treatment is equally effective at all ages, eliminating the impact of age in traditional prognostic scores[33 34]. Indeed the prospects for most patients are excellent, raising questions about the continuing relevance of such scoring systems. However, despite free access to TKI therapy, clinical outcomes appear significantly poorer in lower socio-economic groups in the UK; the age and sex adjusted hazard ratio for deprivation categories 4-5 (less affluent) compared to the more affluent being 3.43 (1.89 to 6.22). These differences were not attributable to differences in the biological features of the disease; and hence the most plausible explanation is that this may reflect differential compliance with treatment[2 3 20 21].

The ability to conduct comprehensive population-based analyses of the type presented here is a major strength of the UK's NHS. Predicated on these structures, our population-based patient cohort (www.hmrn.org) was initiated to serve both research and clinical needs, and as such the capture and follow-up of all patients diagnosed in our study area is a paramount objective[27]. A unique feature is that all diagnoses and subsequent monitoring of patients within the unified clinical network that spans the area is carried out by a single haematopathology laboratory. Additionally, the socio-demographic structure of our catchment population of approximately 3.6 million (around 6% of the UK's estimated total) is broadly representative of the national population in terms of age, sex, and deprivation; and increasingly our data are being extrapolated to the country as a whole[27 35–37].

Given the life-long nature of TKI therapy, inequality of access because of cost[1] is likely to be the main explanation for the marked disparity between CML survival in SEER registries and the results reported here and elsewhere in Europe[38–41]. In addition to financial constraints, closer inspection of the data suggests that other factors including diagnostic accuracy and coding misclassification could also be contributing to the differences observed; since with a median diagnostic age of 65 years, incidence across SEER registries is consistently higher

than elsewhere in the world, averaging around 1.8 per 100,000 and varying from about 1.4 per 100,000 in Hawaii through to 2.1 per 100,000 in Detroit[14]. By contrast, our age-standardized annual rate of 0.9 per 100,000 and median diagnostic of 59 years age are close to national and other European population-based estimates[38–41]. The accurate diagnosis of CML and its separation from other myeloproliferative disorders requires access to molecular diagnostic and cytogenetic analyses. Hence, while it is possible that the SEER variations are genuine, it is also possible that other haematological malignancies which are part of the differential diagnosis of CML, such as chronic myelomonocytic leukaemia (CMML), atypical CML and possibly myelodysplastic/myeloproliferative overlap syndromes, all of which have higher diagnostic ages and poorer survival, are being inadvertently included in the SEER CML dataset[27 39].

Our observations confirm that when TKI treatment is freely provided, survival for CML patients approaches that of unaffected individuals. Nevertheless, the requirement for daily oral therapy for this otherwise fatal disease has major, but poorly defined implications for health economies around the world[1]. In England and Wales, the National Institute for Health and Clinical Excellence (NICE) assess the clinical and cost effectiveness of new treatments prior to recommending their use across the NHS. In the original submission to NICE for imatinib approval, costs were estimated at approximately £16 - £20 million for the first 5-years of its introduction, but estimates beyond this time were not made due to lack of certainty about therapy uptake, long-term survival and consequent disease prevalence[42]. In the meantime, even more expensive second generation TKIs for CML, as well as new oral agents for more common haematological malignancies, are increasingly being adopted into clinical practice[43–45]. Obviously, ensuring optimum clinical outcome for the level of resources invested is a critical issue for clinicians and policy makers; and our findings suggest that more significant improvements in overall population outcomes could, perhaps, be achieved if socioeconomic differences, which may reflect variations in drug compliance, could be eliminated.

Whilst it is recognized that non-adherence to daily oral therapy can be a problem for long-term CML management even in populations with universal health care coverage[19–22], it has yet to be demonstrated that this is the reason for the socio-economic differences described here. Clearly, however, identification of the mechanisms underpinning the socio-economic survival differences within our population, and consequent design of appropriate interventions, could further improve survival. In this regard, recently developed serum imatinib assays[46] could, perhaps, be incorporated into future studies designed to investigate the reasons why some patients may not be taking their medication regularly.

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Supplementary information

Contributorship Statement

ER, AS, DH, RP, and AJ were responsible for the conception and design of the study. AS and DP managed and analysed the data. GS, RP, AJ and PE assisted in the acquisition of data and provided clinical advice regarding the analysis and interpretation of the data. All authors contributed to the final draft of the paper. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

All authors have completed the Unified Competing Interest form and declare that (1) none of them have support from any company for the submitted work; (2) None of them have relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) none of their spouses, partners, or children have financial relationships that may be relevant to the submitted work; and (4) none of them have any non-financial interests that may be relevant to the submitted work.

Details of contributors and guarantors:

ER, AS, DH, RP, and AJ were responsible for the conception and design of the study. AS and DP managed and analysed the data. GS, RP, AJ and PE assisted in the acquisition of data and provided clinical advice regarding the analysis and interpretation of the data. All authors contributed to the final draft of the paper. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

ER and AS are study guarantors.

Ethics approval

The Haematological Malignancy Research Network has ethical approval (REC 04/01205/69) from Leeds West Research Ethics Committee, R&D approval from each NHS Trust and exemption from Section 251 (formally Section 60) of the Health & Social Care Act (2001) (PIAG 1-05(h)/2007).

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Data sharing

No additional data are available.

Table 1: Characteristics of 242 patients with chronic myeloid leukaemia (CML) diagnosed September 2004 to August 2011, distributed by vital status on 1st April 2013

	Diagnosed Sept 2004 to Aug 2011 Total (N=242) No (%)	Status 1st April 2013		Hazard Ratios (95% CI)	
		Alive (N=195) No (%)	Dead (N=47) No (%)	Unadjusted	Adjusted*
Age at diagnosis, years					
< 60	132 (54.6)	116 (59.8)	16 (34.0)	1.00	1.00
≥ 60	110 (45.4)	79 (40.2)	31 (66.0)	2.59 (1.39 to 4.83)	2.65 (1.42 to 4.96)
Sex					
Male	145 (60.0)	115 (59.0)	30 (63.8)	1.00	1.00
Female	97 (40.0)	80 (41.0)	17 (36.2)	0.84 (0.46 to 1.52)	0.67 (0.37 to 1.23)
Deprivation quintile					
1-3	143 (59.1)	124 (63.9)	19 (40.4)	1.00	1.00
4-5 (less affluent)	98 (40.9)	70 (36.1)	28 (59.6)	2.60 (1.45 to 4.66)	3.43 (1.89 to 6.22)
Phase at presentation					
Chronic	235 (97.1)	192 (81.7)	43 (18.3)	1.00	1.00
Accelerated/blast crisis	7 (2.9)	3 (42.9)	4 (57.1)	7.46 (2.61 to 21.28)	22.93 (7.24 to 72.61)
Baseline cytogenetics					
Ph+ve only	209 (86.4)	173 (82.8)	36 (17.2)	1.00	1.00
Variant Ph+ve	18 (7.4)	15 (83.3)	3 (16.7)	0.89 (0.27 to 2.88)	1.12 (0.34 to 3.68)
Additional abnormality	12 (5.0)	6 (50.0)	6 (50.0)	3.96 (1.66 to 9.42)	4.94 (2.03 to12.00)
Amplified Ph+ve	3 (1.2)	1 (33.3)	2 (66.7)	6.82 (1.63 to 28.46)	13.61 (3.09 to 60.00)

*Adjusted for all other characteristic in the Table except the one of interest and cytogenetics

Table 2: Acquisition and loss of molecular response; patients diagnosed September 2004 to August 2011 and followed until 1st April 2013

		Achieved response/TKI treated (%)	Loss of response/ achieved response (%)	Deaths/achieved response (%)	Loss of response plus deaths[#]/achieved response (%)	Hazard Ratio* (95% CI) for loss of response plus deaths	
						Unadjusted	Adjusted*
Major molecular response (MMR = ≤0.1%)							
Deprivation quintile	1-3	100/140 (71.4)	28/100 (28.0)	8/100 (8.0)	35/100 (35.0)	1.0	1.0
	4-5 (less affluent)	56/94 (59.6)	20/56 (35.7)	8/56 (14.3)	27/56 (48.2)	1.68 (1.03 to 2.78)	1.71 (1.03 to 2.84)
Molecular response (MR = ≤1.0%)							
Deprivation quintile	1-3	115/140 (82.1)	15/115 (13.0)	8~/115 (7.0)	22/115 (19.1)	1.0	1.0
	4-5 (less affluent)	67/94 (71.3)	13/67 (19.4)	9~/67 (13.4)	21/67 (31.3)	1.78 (0.98 to 3.24)	1.90 (1.03 to 3.49)

[#] 3 deaths occurred in patients with a recorded loss of response

* Adjusted for age and sex

~ 4/8 deaths in deprivation categories 1-3 and 9/9 deaths in deprivation categories 4-5 were CML related (death certificates)

[Fig1A]

[Fig1B]

[Fig2]

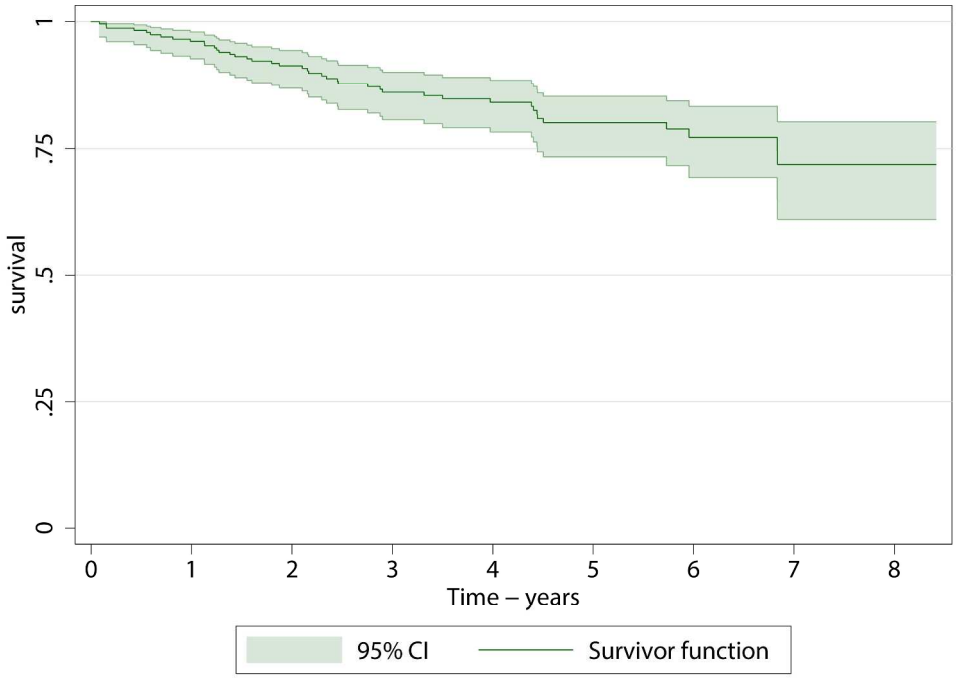
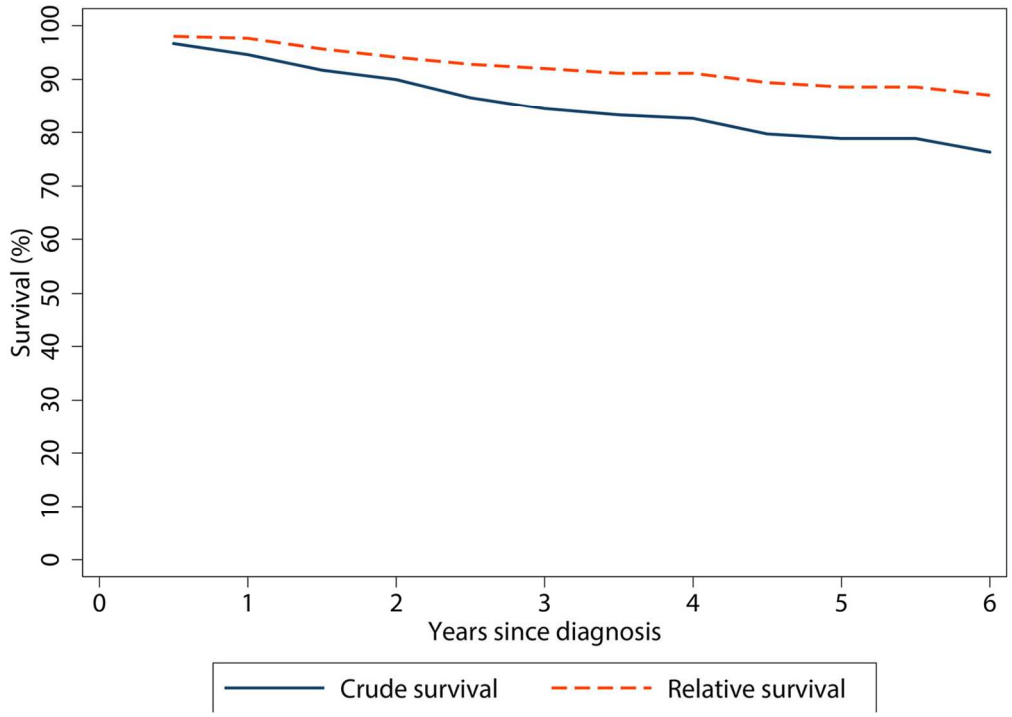


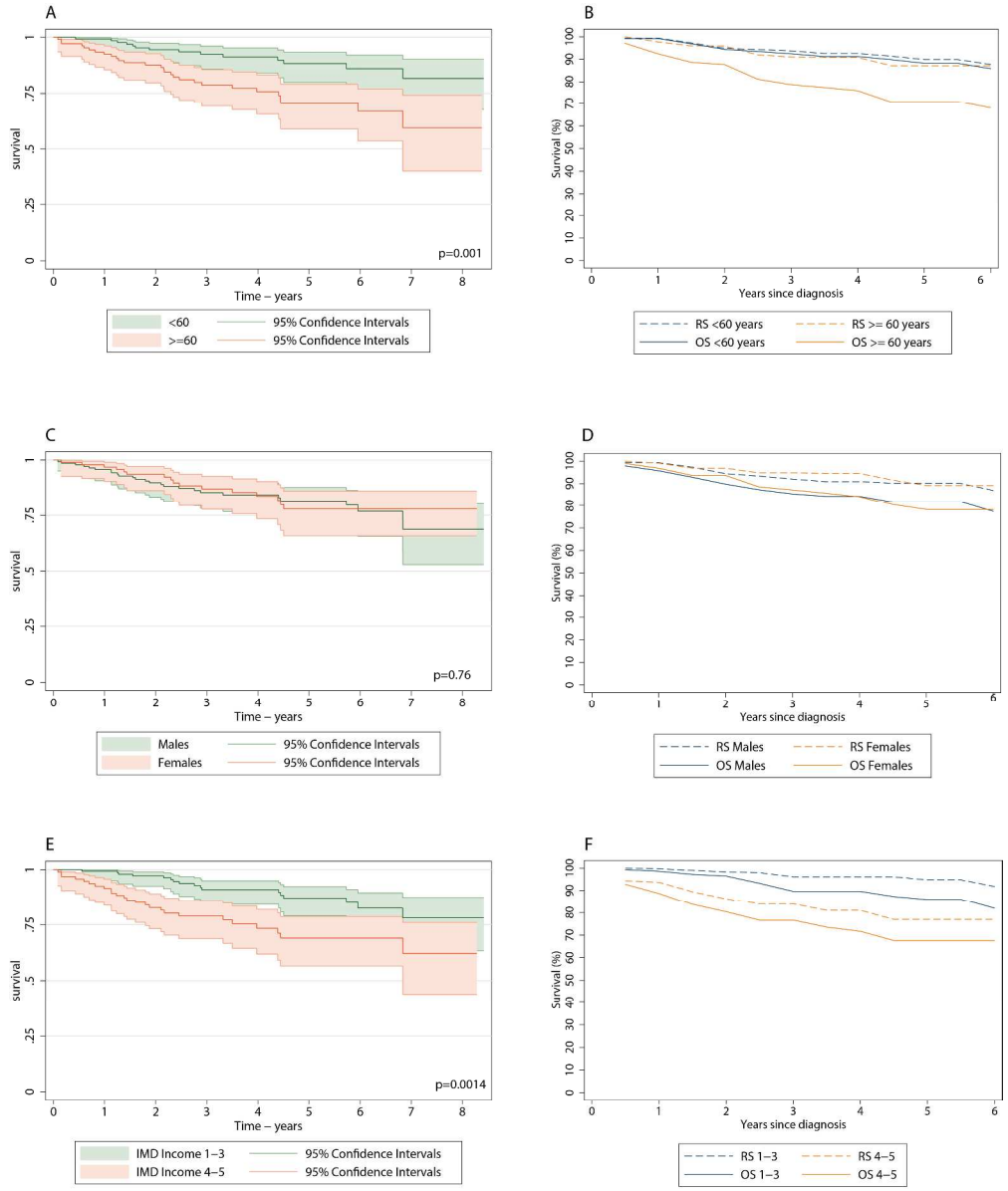
Figure 1: Crude survival of the 242 patients diagnosed with CML in HMRN 2004 to 2011 (deaths 2004 to 2013)

300x218mm (299 x 299 DPI)



Relative survival of the 242 patients diagnosed with CML in HMRN 2004 to 2011 (deaths 2004 to 2013)

535x378mm (72 x 72 DPI)



Crude (A, C, E) and relative survival (B, D, F) of the 234 patients diagnosed within HMRN 2004 to 2011 (deaths 2004 to 20 13) who were treated with tyrosine kinase inhibitors by age at diagnosis (A, B), Sex (C, D) and deprivation (E, F)
393x474mm (299 x 299 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	UK population-based patient cohort
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Please see abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Population-based data on outcomes for chronic myeloid leukaemia in a country where access to treatment is universal have not previously been reported.
Objectives	3	State specific objectives, including any prespecified hypotheses	To examine contemporary survival patterns in the general population of patients diagnosed with CML, and identify patient groups with less than optimal outcomes.
Methods			
Study design	4	Present key elements of study design early in the paper	Population-based cohort
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Location –Haematological Malignancy Research Network Recruitment - September 2004 to August 2011 Follow-up – April 2013 Data collection – medical records
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	All patients newly diagnosed since September, 2004.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Incidence and survival.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Index of Deprivation (IMD)
Bias	9	Describe any efforts to address potential sources of bias	Loss to follow-up. All patients are 'flagged' in the national death certification scheme so we are able to

			follow-up patients if they are treated outside of the study region.
Study size	10	Explain how the study size was arrived at	The study included all eligible cases.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Index of Deprivation (IMD), the categories defined in the national dataset were used.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Time to event analyses
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This is detailed in the results section page 6, 2nd paragraph.
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Please see Table 1 for socio-demographic characteristics and potential confounding variables.
		(b) Indicate number of participants with missing data for each variable of interest	None
		(c) Summarise follow-up time (eg, average and total amount)	1.5 years to 8.5 years
Outcome data	15*	Report numbers of outcome events or summary measures over time	These are detailed in tables 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1, confounders adjusted for a detailed in the footnote.
		(*b*) Report category boundaries when continuous variables were categorized	These are reported in the tables and result section.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	These are detailed in paragraph 1 of the discussion, page

			8.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations of the study are discussed in Paragraph 5.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	These are included in the discussion specifically paragraph 1,3, 4,5
Generalisability	21	Discuss the generalisability (external validity) of the study results	These are discussed in paragraph 2 of the discussion, page 8.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Leukaemia and Lymphoma Research funded the study and the Haematological Malignancy Research Network.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Determinants of survival in patients with chronic myeloid leukaemia treated in the new era of oral therapy: findings from a UK population-based patient cohort

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Determinants of survival in patients with chronic myeloid leukaemia treated in the new era of oral therapy: findings from a UK population-based patient cohort

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Abstract: 261

Abstract

Objectives To examine contemporary survival patterns in the general population of patients diagnosed with chronic myeloid leukaemia (CML), and identify patient groups with less than optimal outcomes.

Design Prospective population-based cohort.

Setting UK's Haematological Malignancy Research Network (catchment population 3.6 million, with >2000 new haematological malignancies diagnosed annually).

Participants All patients newly diagnosed with chronic myeloid leukaemia, September 2004 to August 2011 and followed to 31st March 2013.

Main outcome measure Incidence and survival.

Results With a median diagnostic age of 59 years, the CML age standardized (European) incidence was 0.9 per 100,000 (95% Confidence Intervals 0.8 to 0.9), 5-year overall survival 78.9% (72.3 to 84.0), and 5-year relative survival 88.6% (81.0 to 93.3). The efficacy of treatment across all ages was clearly demonstrated; the relative survival curves for those under 60 years and over 60 years remaining closely aligned. Survival findings were similar for men and women, but varied with deprivation; the age and sex adjusted hazard ratio being 3.43 (1.89 to 6.22) for deprivation categories 4-5 (less affluent) versus 1-3 (more affluent). None of these differences were attributable to the biological features of the disease.

Conclusions When therapy is freely provided, population-based survival for CML is similar to that reported in clinical trials and age loses its prognostic significance. However, although most CML patients now experience close to normal life-spans, those living in more deprived areas tend to have poorer outcomes, despite receiving the same clinical care. A significant improvement in overall population outcomes could be achieved if these socioeconomic differences, which may reflect treatment compliance, could be eliminated.

Article summary

Focus

- Orally administered tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukaemia (CML); changing it from a fatal cancer in non-transplanted patients to a chronic condition with the potential for a normal life-span.
- Clinical trials suggest that the outcome for most CML patients treated with TKI therapy is excellent; yet survival rates in many populations, notably the US, are much lower than expected.
- This study examines outcomes in a contemporary UK population-based cohort.

Key messages

- When TKI therapy is freely provided, CML survival is similar to that reported for clinical trials and age is no longer prognostic.
- Given the life-long nature of TKI therapy, inequality of access because of cost is likely to be the main explanation for the marked disparity between CML survival in US registries and the results reported here.
- Despite universal health care coverage, socio-economic factors impact adversely on CML survival in the UK.
- With a median diagnostic age of 59 years, the return to a normal life-span has major cost implications for commissioners planning the future care of patients with CML.

Strengths & Limitations

- Data are from a comprehensive population-based cohort that includes all patients diagnosed in a defined geographic area.
- Complete follow-up is achieved via linkage to national health care systems.
- The relative rarity of CML limited our ability to examine for smaller sub-group effects in the present series.
- Whilst our findings for socio-economic status may reflect differences in treatment compliance, this association needs to be confirmed in future studies.

Introduction

Introduced at the turn of the century, orally administered tyrosine kinase inhibitors (TKIs) have transformed the treatment of chronic myeloid leukaemia (CML), changing it from a comparatively rare but fatal cancer in non-transplanted patients to a long-term condition with a steadily increasing prevalence. TKI therapy is, however, life-long and expensive; the price of first-generation imatinib currently varying from around £21,000 per patient per year in the UK through to £57,000 in the US, with the newer TKIs being even more costly. Such costs have major, but poorly defined, implications for health economies around the world[1].

Given the potential for CML patients to achieve a near normal lifespan, contemporary clinical discussion tends to revolve around how the growing range of TKIs should be used, response monitored and resistance managed[2–6]. However, with reported survival rates from CML in some populations being poorer than that predicted from clinical trials, the extent to which findings from clinical trials can be extrapolated to the general patient population is also an issue of current debate[7–11]. In this context, the contrast between the 5-year survival of 89% reported for imatinib treated patients from the original clinical trial who were recruited in 2001 and followed until 2006[12] and the 2001-9 relative survival of 56.0% in United States' (US) Surveillance, Epidemiology and End Results (SEER) populations[13 14], seems particularly stark.

For CML, as with many other cancers, discrepancies between trial and population-based studies are commonly ascribed to systematic differences between the types of patients recruited into trials and those who are not; the former often tending to be comprised of younger patients with fewer co-morbidities and less advanced disease[7 9 15]. In addition, it is becoming ever more apparent that non-trial access to expensive drugs such as TKIs has a key role to play in countries without universal health care coverage[1 16–18]. Furthermore, even in countries like the UK where care is freely provided on the basis of clinical need, non-adherence to the daily oral regimen is becoming an increasingly recognized problem for the long-term management of CML[2 9 19–22].

Up-to-date population-based data on CML are limited; with much of the available information on CML survival in the general population predating the latest clinical trials, as well as introduction of the latest monitoring/management guidelines[2–5 23]. The population-based Haematological Malignancy Research Network (www.hmrn.org), which collects information to clinical trial standards on all new haematological malignancy diagnoses, was specifically established in 2004 to address issues such as this by providing 'real-time' data to inform

clinical practice and research[24]. The present report provides contemporary data on CML incidence and survival in the UK over the period 2004-13, and investigates whether there are any patient groups with less than optimal outcomes.

Methods

Data are from the UK's population-based Haematological Malignancy Research Network (www.hmrn.org). Full details of HMRN's structure, data collection methods and ethical approvals have been described elsewhere[24]. Briefly, *within the HMRN region, patient care is provided by a unified clinical network operating across 14 hospitals organized within five multi-disciplinary teams working to common guidelines covering investigation, treatment and follow-up (www.yorkshire-cancer-net.org.uk).* All diagnoses and subsequent monitoring within the clinical network (>2,000 patients a year) are made using the latest World Health Organization (WHO) classification[25] at a single integrated haematopathology laboratory (www.hmds.info). All patients have full-treatment, response and outcome data collected to clinical trial standards. HMRN operates with Section 251 support under the NHS Act 2006; enabling the Health and Social Care Information Centre (HSCIC) to provide us with nationwide information on deaths, subsequent cancer registrations, and Hospital Episode Statistics (HES).

CML diagnosis was based on the demonstration of a BCR-ABL fusion transcript expressed by the Philadelphia (Ph) chromosome by RQ-PCR and/or the demonstration of t(9;22)(q34;q11) by conventional karyotyping or interphase FISH. The presence of additional karyotypic abnormalities was based on bone marrow metaphase analysis. As per standard practice, response to therapy was monitored using either molecular or cytogenetic tests or both; specifically, patients were monitored by quantitative PCR on peripheral blood, supplemented by bone marrow karyotyping when clinically indicated. ABL kinase mutational analysis was carried out when the transcript ratio increased over two sequential samples or on clinical demand.

Area-based population counts and measures of deprivation were sourced from UK national data[26 27]. With respect to the latter and in common with other reports,[27–29] the quintile distribution of the income domain of the index of deprivation (IMD; quintile one containing the most affluent fifth of England's lower super output areas and quintile five the least) is used as marker of socio-economic status[30]. Overall survival and loss of molecular response (MR) was calculated using standard time to event analyses and the program strel (v1.2.7) was used to estimate relative survival; age and sex-specific background mortality rates were

obtained from national life tables[31]. All analyses were conducted in the statistical package Stata 12.

Results

Two-hundred and forty-two patients were diagnosed with CML in the study region over the seven year period September 2004 to August 2011; yielding a crude annual incidence rate of 0.97 per 100,000. The corresponding European and World age standardized incidence rates were 0.9 (95% Confidence Intervals 0.8 to 0.9) and 0.7 (0.6 to 0.7) per 100,000 respectively. As can be seen from Table 1 (column 1), 132 (54.6%) patients were diagnosed before their 60th birthday and 110 (45.4%) after; the median diagnostic age being 59.0 years (range 15.1 to 94.7). As expected, around 3 out of every 5 patients were male, and the area-based deprivation distribution of the cohort was broadly similar to that of the country as a whole (59.1% in quintiles 1-3 and 40.9% in quintiles 4-5).

Forty-seven (19.5%) patients died before the 1st April 2013; minimum follow-up 1.5 years and maximum 8.5 years. The crude survival curve across the full 8.5 year period is shown in Figure 1A, and the crude and relative survival curves over the first 6 years are compared in Figure 1B (data for the remaining 2.5 years follow-up are not shown because the small numbers of events prohibited relative survival estimation). The 5-year survival was 78.9% (72.3 to 84.0) and the relative survival, taking into account background mortality in the general population, was 88.6% (81.0 to 93.3). Two-hundred and thirty four (96.7%) of the 242 patients were treated with TKIs within the study region: 219 (93.6%) received first-line imatinib and the remainder receiving dasatinib as part of an on-going trial. Only 8 (3.3%) of the 242 patients were not treated with TKIs within the HMRN region: two died before treatment could be started, one refused treatment, one had a more serious competing comorbidity, two had supportive care only, and two moved and were treated in another part of the country. Since all patients diagnosed within HMRN are 'flagged' in the national scheme, we can confirm that these latter two patients were alive on 1st April 2013.

Patients with additional cytogenetic abnormalities at presentation had poorer outcomes than those who presented in chronic phase as Ph+ alone (Table 1). With respect to patient characteristics, compared to those who survived, those who died tended to be older and live in less affluent areas (Table 1): the adjusted hazard ratios for those ≥ 60 years compared to those < 60 years was 2.65 (1.42 to 4.96), and for less affluent areas (quintiles 4-5) compared to more affluent areas (quintiles 1-3) was 3.43 (1.89 to 6.22). In addition, females

were marginally more likely to survive than males, although this was not statistically significant.

Whilst the age-specific crude survival curves continue to diverge with increasing time since diagnosis, the relative survival curves for the two age groups remain closely aligned: the 5-year relative survival for those < 60 years and over ≥ 60 years being 89.9% (80.8 to 94.8) and 87.2% (69.8 to 94.9) respectively. This clearly demonstrates the efficacy of TKI treatment across all ages (Figure 2). Gender had little impact on outcome, and the overall and relative survival curves of men and women are similar; the 5-year relative survival for men and women being 90.1% (79.9 to 95.4) and 89.1% (71.9 to 96.1) respectively. By contrast, the deprivation-specific relative survival curves remain as disparate from each other as the overall survival curves (P=0.0014); the 5-year relative survival for the most affluent (categories 1-3) and the least affluent (categories 4-5) being 94.9% (82.3 to 98.6) and 79.5% (64.1 to 88.8) respectively. *Furthermore, the results were similar even when deprivation specific life tables were used to calculate relative survival.*

As can be seen from Table 2, marginal deprivation differences were also evident for both molecular response achievement, defined here as one or more readings ≤ 0.1 BCR-ABL1 (major molecular response - MMR) or ≤ 1.0 BCR-ABL1 (molecular response - MR), and its retention. Overall, 71.4% of patients in deprivation category 1-3 and 59.6% in 4-5 achieved MMR, the corresponding frequencies for MR being 82.1% and 71.3% respectively. With respect to the time taken to achieve molecular response, the disparity between deprivation categories was evident from therapy outset, albeit non-statistically significantly so; the MMR cumulative frequencies being 16.4% and 21.2% (12 months), 32.9% and 36.2% (18 months) and 51.4% and 42.6% (24 months); the MR results were 45.7% and 38.3% (12 months), 66.4% and 54.6% (18 months) and 74.9% and 60.6% (24 months) respectively.

The hazard ratios for loss of response combined with deaths (Table 2) are, as expected, consistent with the findings for overall and relative survival (Fig 2 E and F); patients in deprivation categories 4-5 who achieved MMR were 1.71 (1.03 to 2.84) times more likely to lose their response or die, and the results were similar when the threshold was increased to include patients who achieved an MR (1.90, 1.03 to 3.49). It is also worth noting that according to the information recorded at death certification, all 9 deaths in deprivation categories 4-5 had CML cited as a contributing cause of death, compared to 4 of the 8 in deprivation categories 1-3.

The deprivation differences presented here could not be explained either by variations in the acquisition of additional cytogenetic anomalies or TKI resistance, both of which were rare in this population: 7 (3.4%) of the 209 Ph+ patients with no additional abnormalities at diagnosis (Table 1) acquired an additional anomaly during follow-up, and all were in deprivation category 1-3. With respect to the 10 (4.3 %) patients who developed TKI resistance, 4/140 were in deprivation category 1-3 and 6/94 in 4-5. None of the patients who acquired an additional cytogenetic anomaly developed TKI resistance.

Discussion

The outcome for CML patients treated mainly with imatinib in our UK population-based patient cohort is similar to that reported for clinical trials[12 32]; the 5-year relative survival estimates for men and women diagnosed 2004-11 and treated with TKIs over the period 2004-13 being 89.1% (79.9 to 95.4) and 90.1% (71.9 to 96.1) respectively. This suggests that the much poorer outcome recorded in the US reflects financial barriers to accessing TKI therapy. Furthermore, our data confirm the inferences from clinical trials that TKI treatment is equally effective at all ages, eliminating the impact of age in traditional prognostic scores[33 34]. Indeed the prospects for most patients are excellent, raising questions about the continuing relevance of such scoring systems. However, despite free access to TKI therapy, clinical outcomes appear significantly poorer in lower socio-economic groups in the UK; the age and sex adjusted hazard ratio for deprivation categories 4-5 (less affluent) compared to the more affluent being 3.43 (1.89 to 6.22). These differences were not attributable to differences in the biological features of the disease; and hence the most plausible explanation is that this may reflect differential compliance with treatment[2 3 20 21].

The ability to conduct comprehensive population-based analyses of the type presented here is a major strength of the UK's NHS. Predicated on these structures, our population-based patient cohort (www.hmrn.org) was initiated to serve both research and clinical needs, and as such the capture and follow-up of all patients diagnosed in our study area is a paramount objective[27]. A unique feature is that all diagnoses and subsequent monitoring of patients within the unified clinical network that spans the area is carried out by a single haematopathology laboratory. Additionally, the socio-demographic structure of our catchment population of approximately 3.6 million (around 6% of the UK's estimated total) is broadly representative of the national population in terms of age, sex, and deprivation; and increasingly our data are being extrapolated to the country as a whole[27 35–37].

Given the life-long nature of TKI therapy, inequality of access because of cost[1] is likely to be the main explanation for the marked disparity between CML survival in SEER registries and the results reported here and elsewhere in Europe[38–41]. In addition to financial constraints, closer inspection of the data suggests that other factors including diagnostic accuracy and coding misclassification could also be contributing to the differences observed; since with a median diagnostic age of 65 years, incidence across SEER registries is consistently higher than elsewhere in the world, averaging around 1.8 per 100,000 and varying from about 1.4 per 100,000 in Hawaii through to 2.1 per 100,000 in Detroit[14]. By contrast, our age-standardized annual rate of 0.9 per 100,000 and median diagnostic of 59 years age are close to national and other European population-based estimates[38–41]. The accurate diagnosis of CML and its separation from other myeloproliferative disorders requires access to molecular diagnostic and cytogenetic analyses. Hence, while it is possible that the SEER variations are genuine, it is also possible that other haematological malignancies which are part of the differential diagnosis of CML, such as chronic myelomonocytic leukaemia (CMML), atypical CML and possibly myelodysplastic/myeloproliferative overlap syndromes, all of which have higher diagnostic ages and poorer survival, are being inadvertently included in the SEER CML dataset[27 39].

Our observations confirm that when TKI treatment is freely provided, survival for CML patients approaches that of unaffected individuals. Nevertheless, the requirement for daily oral therapy for this otherwise fatal disease has major, but poorly defined implications for health economies around the world[1]. In England and Wales, the National Institute for Health and Clinical Excellence (NICE) assess the clinical and cost effectiveness of new treatments prior to recommending their use across the NHS. In the original submission to NICE for imatinib approval, costs were estimated at approximately £16 - £20 million for the first 5-years of its introduction, but estimates beyond this time were not made due to lack of certainty about therapy uptake, long-term survival and consequent disease prevalence[42]. In the meantime, even more expensive second generation TKIs for CML, as well as new oral agents for more common haematological malignancies, are increasingly being adopted into clinical practice[43–45]. Obviously, ensuring optimum clinical outcome for the level of resources invested is a critical issue for clinicians and policy makers; and our findings suggest that more significant improvements in overall population outcomes could, perhaps, be achieved if socioeconomic differences, which may reflect variations in drug compliance, could be eliminated.

Whilst it is recognized that non-adherence to daily oral therapy can be a problem for long-term CML management even in populations with universal health care coverage[19–22], it has yet to be demonstrated that this is the reason for the socio-economic differences described here. *To investigate this further, additional longitudinal studies that incorporate the collection of appropriate monitoring data, as well as information on other life-style factors that could potentially contribute to outcome, will need to be carried out.* Clearly, however, identification of the mechanisms underpinning the socio-economic survival differences within our population, and consequent design of appropriate interventions, could further improve survival. In this regard, recently developed serum imatinib assays[46] could, perhaps, be incorporated into future studies designed to investigate the reasons why some patients may not be taking their medication regularly.

Supplementary information

Competing interests

All authors have completed the Unified Competing Interest form and declare that (1) none of them have support from any company for the submitted work; (2) None of them have relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) none of their spouses, partners, or children have financial relationships that may be relevant to the submitted work; and (4) none of them have any non-financial interests that may be relevant to the submitted work.

Details of contributors and guarantors:

ER, AS, DH, RP, and AJ were responsible for the conception and design of the study. AS and DP managed and analysed the data. GS, RP, AJ and PE assisted in the acquisition of data and provided clinical advice regarding the analysis and interpretation of the data. All authors contributed to the final draft of the paper. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

ER and AS are study guarantors.

Ethics approval

The Haematological Malignancy Research Network has ethical approval (REC 04/01205/69) from Leeds West Research Ethics Committee, R&D approval from each NHS Trust and exemption from Section 251 (formally Section 60) of the Health & Social Care Act (2001) (PIAG 1-05(h)/2007).

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Data sharing

No additional data are available.

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Table 1: Characteristics of 242 patients with chronic myeloid leukaemia (CML) diagnosed September 2004 to August 2011, distributed by vital status on 1st April 2013

	Diagnosed Sept 2004 to Aug 2011 Total (N=242) No (%)	Status 1st April 2013		Hazard Ratios (95% CI)	
		Alive (N=195) No (%)	Dead (N=47) No (%)	Unadjusted	Adjusted*
Age at diagnosis, years					
< 60	132 (54.6)	116 (59.8)	16 (34.0)	1.00	1.00
≥ 60	110 (45.4)	79 (40.2)	31 (66.0)	2.59 (1.39 to 4.83)	2.65 (1.42 to 4.96)
Sex					
Male	145 (60.0)	115 (59.0)	30 (63.8)	1.00	1.00
Female	97 (40.0)	80 (41.0)	17 (36.2)	0.84 (0.46 to 1.52)	0.67 (0.37 to 1.23)
Deprivation quintile					
1-3	143 (59.1)	124 (63.9)	19 (40.4)	1.00	1.00
4-5 (less affluent)	98 (40.9)	70 (36.1)	28 (59.6)	2.60 (1.45 to 4.66)	3.43 (1.89 to 6.22)
Phase at presentation					
Chronic	235 (97.1)	192 (81.7)	43 (18.3)	1.00	1.00
Accelerated/blast crisis	7 (2.9)	3 (42.9)	4 (57.1)	7.46 (2.61 to 21.28)	22.93 (7.24 to 72.61)
Baseline cytogenetics					
Ph+ve only	209 (86.4)	173 (82.8)	36 (17.2)	1.00	1.00
Variant Ph+ve	18 (7.4)	15 (83.3)	3 (16.7)	0.89 (0.27 to 2.88)	1.12 (0.34 to 3.68)
Additional abnormality	12 (5.0)	6 (50.0)	6 (50.0)	3.96 (1.66 to 9.42)	4.94 (2.03 to12.00)
Amplified Ph+ve	3 (1.2)	1 (33.3)	2 (66.7)	6.82 (1.63 to 28.46)	13.61 (3.09 to 60.00)

*Adjusted for all other characteristic in the Table except the one of interest and cytogenetics

Table 2: Acquisition and loss of molecular response; patients diagnosed September 2004 to August 2011 and followed until 1st April 2013

		Achieved response/TKI treated (%)	Loss of response/ achieved response (%)	Deaths/achieved response (%)	Loss of response plus deaths[#]/achieved response (%)	Hazard Ratio* (95% CI) for loss of response plus deaths	
						Unadjusted	Adjusted*
Major molecular response (MMR = ≤0.1%)							
Deprivation quintile	1-3	100/140 (71.4)	28/100 (28.0)	8/100 (8.0)	35/100 (35.0)	1.0	1.0
	4-5 (less affluent)	56/94 (59.6)	20/56 (35.7)	8/56 (14.3)	27/56 (48.2)	1.68 (1.03 to 2.78)	1.71 (1.03 to 2.84)
Molecular response (MR = ≤1.0%)							
Deprivation quintile	1-3	115/140 (82.1)	15/115 (13.0)	8~/115 (7.0)	22/115 (19.1)	1.0	1.0
	4-5 (less affluent)	67/94 (71.3)	13/67 (19.4)	9~/67 (13.4)	21/67 (31.3)	1.78 (0.98 to 3.24)	1.90 (1.03 to 3.49)

[#] 3 deaths occurred in patients with a recorded loss of response

* Adjusted for age and sex

~ 4/8 deaths in deprivation categories 1-3 and 9/9 deaths in deprivation categories 4-5 were CML related (death certificates)

[Fig1A]

[Fig1B]

[Fig2]

Determinants of survival in patients with chronic myeloid leukaemia treated in the new era of oral therapy: findings from a UK population-based patient cohort

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Abstract

Objectives To examine contemporary survival patterns in the general population of patients diagnosed with chronic myeloid leukaemia (CML), and identify patient groups with less than optimal outcomes.

Design Prospective population-based cohort.

Setting UK's Haematological Malignancy Research Network (catchment population 3.6 million, with >2000 new haematological malignancies diagnosed annually).

Participants All patients newly diagnosed with chronic myeloid leukaemia, September 2004 to August 2011 and followed to 31st March 2013.

Main outcome measure Incidence and survival.

Results With a median diagnostic age of 59 years, the CML age standardized (European) incidence was 0.9 per 100,000 (95% Confidence Intervals 0.8 to 0.9), 5-year overall survival 78.9% (72.3 to 84.0), and 5-year relative survival 88.6% (81.0 to 93.3). The efficacy of treatment across all ages was clearly demonstrated; the relative survival curves for those under 60 years and over 60 years remaining closely aligned. Survival findings were similar for men and women, but varied with deprivation; the age and sex adjusted hazard ratio being 3.43 (1.89 to 6.22) for deprivation categories 4-5 (less affluent) versus 1-3 (more affluent). None of these differences were attributable to the biological features of the disease.

Conclusions When therapy is freely provided, population-based survival for CML is similar to that reported in clinical trials and age loses its prognostic significance. However, although most CML patients now experience close to normal life-spans, those living in more deprived areas tend to have poorer outcomes, despite receiving the same clinical care. A significant improvement in overall population outcomes could be achieved if these socioeconomic differences, which may reflect treatment compliance, could be eliminated.

Article summary

Focus

- Orally administered tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukaemia (CML); changing it from a fatal cancer in non-transplanted patients to a chronic condition with the potential for a normal life-span.
- Clinical trials suggest that the outcome for most CML patients treated with TKI therapy is excellent; yet survival rates in many populations, notably the US, are much lower than expected.
- This study examines outcomes in a contemporary UK population-based cohort.

Key messages

- When TKI therapy is freely provided, CML survival is similar to that reported for clinical trials and age is no longer prognostic.
- Given the life-long nature of TKI therapy, inequality of access because of cost is likely to be the main explanation for the marked disparity between CML survival in US registries and the results reported here.
- Despite universal health care coverage, socio-economic factors impact adversely on CML survival in the UK.
- With a median diagnostic age of 59 years, the return to a normal life-span has major cost implications for commissioners planning the future care of patients with CML.

Strengths & Limitations

- Data are from a comprehensive population-based cohort that includes all patients diagnosed in a defined geographic area.
- Complete follow-up is achieved via linkage to national health care systems.
- The relative rarity of CML limited our ability to examine for smaller sub-group effects in the present series.
- Whilst our findings for socio-economic status may reflect differences in treatment compliance, this association needs to be confirmed in future studies.

Introduction

Introduced at the turn of the century, orally administered tyrosine kinase inhibitors (TKIs) have transformed the treatment of chronic myeloid leukaemia (CML), changing it from a comparatively rare but fatal cancer in non-transplanted patients to a long-term condition with a steadily increasing prevalence. TKI therapy is, however, life-long and expensive; the price of first-generation imatinib currently varying from around £21,000 per patient per year in the UK through to £57,000 in the US, with the newer TKIs being even more costly. Such costs have major, but poorly defined, implications for health economies around the world[1].

Given the potential for CML patients to achieve a near normal lifespan, contemporary clinical discussion tends to revolve around how the growing range of TKIs should be used, response monitored and resistance managed[2–6]. However, with reported survival rates from CML in some populations being poorer than that predicted from clinical trials, the extent to which findings from clinical trials can be extrapolated to the general patient population is also an issue of current debate[7–11]. In this context, the contrast between the 5-year survival of 89% reported for imatinib treated patients from the original clinical trial who were recruited in 2001 and followed until 2006[12] and the 2001-9 relative survival of 56.0% in United States' (US) Surveillance, Epidemiology and End Results (SEER) populations[13 14], seems particularly stark.

For CML, as with many other cancers, discrepancies between trial and population-based studies are commonly ascribed to systematic differences between the types of patients recruited into trials and those who are not; the former often tending to be comprised of younger patients with fewer co-morbidities and less advanced disease[7 9 15]. In addition, it is becoming ever more apparent that non-trial access to expensive drugs such as TKIs has a key role to play in countries without universal health care coverage[1 16–18]. Furthermore, even in countries like the UK where care is freely provided on the basis of clinical need, non-adherence to the daily oral regimen is becoming an increasingly recognized problem for the long-term management of CML[2 9 19–22].

Up-to-date population-based data on CML are limited; with much of the available information on CML survival in the general population predating the latest clinical trials, as well as introduction of the latest monitoring/management guidelines[2–5 23]. The population-based Haematological Malignancy Research Network (www.hmrn.org), which collects information to clinical trial standards on all new haematological malignancy diagnoses, was specifically established in 2004 to address issues such as this by providing 'real-time' data to inform clinical practice and research[24]. The present report provides contemporary data on CML

incidence and survival in the UK over the period 2004-13, and investigates whether there are any patient groups with less than optimal outcomes.

Methods

Data are from the UK's population-based Haematological Malignancy Research Network (www.hmrn.org). Full details of HMRN's structure, data collection methods and ethical approvals have been described elsewhere[24]. Briefly, *within the HMRN region, patient care is provided by a unified clinical network operating across 14 hospitals organized within five multi-disciplinary teams working to common guidelines covering investigation, treatment and follow-up (www.yorkshire-cancer-net.org.uk).* All diagnoses and subsequent monitoring within the clinical network (>2,000 patients a year) are made using the latest World Health Organization (WHO) classification[25] at a single integrated haematopathology laboratory (www.hmds.info). All patients have full-treatment, response and outcome data collected to clinical trial standards. HMRN operates with Section 251 support under the NHS Act 2006; enabling the Health and Social Care Information Centre (HSCIC) to provide us with nationwide information on deaths, subsequent cancer registrations, and Hospital Episode Statistics (HES).

CML diagnosis was based on the demonstration of a BCR-ABL fusion transcript expressed by the Philadelphia (Ph) chromosome by RQ-PCR and/or the demonstration of t(9;22)(q34;q11) by conventional karyotyping or interphase FISH. The presence of additional karyotypic abnormalities was based on bone marrow metaphase analysis. As per standard practice, response to therapy was monitored using either molecular or cytogenetic tests or both; specifically, patients were monitored by quantitative PCR on peripheral blood, supplemented by bone marrow karyotyping when clinically indicated. ABL kinase mutational analysis was carried out when the transcript ratio increased over two sequential samples or on clinical demand.

Area-based population counts and measures of deprivation were sourced from UK national data[26 27]. With respect to the latter and in common with other reports,[27–29] the quintile distribution of the income domain of the index of deprivation (IMD; quintile one containing the most affluent fifth of England's lower super output areas and quintile five the least) is used as marker of socio-economic status[30]. Overall survival and loss of molecular response (MR) was calculated using standard time to event analyses and the program strel (v1.2.7) was used to estimate relative survival; age and sex-specific background mortality rates were

obtained from national life tables[31]. All analyses were conducted in the statistical package Stata 12.

Results

Two-hundred and forty-two patients were diagnosed with CML in the study region over the seven year period September 2004 to August 2011; yielding a crude annual incidence rate of 0.97 per 100,000. The corresponding European and World age standardized incidence rates were 0.9 (95% Confidence Intervals 0.8 to 0.9) and 0.7 (0.6 to 0.7) per 100,000 respectively. As can be seen from Table 1 (column 1), 132 (54.6%) patients were diagnosed before their 60th birthday and 110 (45.4%) after; the median diagnostic age being 59.0 years (range 15.1 to 94.7). As expected, around 3 out of every 5 patients were male, and the area-based deprivation distribution of the cohort was broadly similar to that of the country as a whole (59.1% in quintiles 1-3 and 40.9% in quintiles 4-5).

Forty-seven (19.5%) patients died before the 1st April 2013; minimum follow-up 1.5 years and maximum 8.5 years. The crude survival curve across the full 8.5 year period is shown in Figure 1A, and the crude and relative survival curves over the first 6 years are compared in Figure 1B (data for the remaining 2.5 years follow-up are not shown because the small numbers of events prohibited relative survival estimation). The 5-year survival was 78.9% (72.3 to 84.0) and the relative survival, taking into account background mortality in the general population, was 88.6% (81.0 to 93.3). Two-hundred and thirty four (96.7%) of the 242 patients were treated with TKIs within the study region: 219 (93.6%) received first-line imatinib and the remainder receiving dasatinib as part of an on-going trial. Only 8 (3.3%) of the 242 patients were not treated with TKIs within the HMRN region: two died before treatment could be started, one refused treatment, one had a more serious competing comorbidity, two had supportive care only, and two moved and were treated in another part of the country. Since all patients diagnosed within HMRN are 'flagged' in the national scheme, we can confirm that these latter two patients were alive on 1st April 2013.

Patients with additional cytogenetic abnormalities at presentation had poorer outcomes than those who presented in chronic phase as Ph+ alone (Table 1). With respect to patient characteristics, compared to those who survived, those who died tended to be older and live in less affluent areas (Table 1): the adjusted hazard ratios for those ≥ 60 years compared to those < 60 years was 2.65 (1.42 to 4.96), and for less affluent areas (quintiles 4-5) compared to more affluent areas (quintiles 1-3) was 3.43 (1.89 to 6.22). In addition, females

were marginally more likely to survive than males, although this was not statistically significant.

Whilst the age-specific crude survival curves continue to diverge with increasing time since diagnosis, the relative survival curves for the two age groups remain closely aligned: the 5-year relative survival for those < 60 years and over ≥ 60 years being 89.9% (80.8 to 94.8) and 87.2% (69.8 to 94.9) respectively. This clearly demonstrates the efficacy of TKI treatment across all ages (Figure 2). Gender had little impact on outcome, and the overall and relative survival curves of men and women are similar; the 5-year relative survival for men and women being 90.1% (79.9 to 95.4) and 89.1% (71.9 to 96.1) respectively. By contrast, the deprivation-specific relative survival curves remain as disparate from each other as the overall survival curves (P=0.0014); the 5-year relative survival for the most affluent (categories 1-3) and the least affluent (categories 4-5) being 94.9% (82.3 to 98.6) and 79.5% (64.1 to 88.8) respectively. *Furthermore, the results were similar even when deprivation specific life tables were used to calculate relative survival.*

As can be seen from Table 2, marginal deprivation differences were also evident for both molecular response achievement, defined here as one or more readings ≤ 0.1 BCR-ABL1 (major molecular response - MMR) or ≤ 1.0 BCR-ABL1 (molecular response - MR), and its retention. Overall, 71.4% of patients in deprivation category 1-3 and 59.6% in 4-5 achieved MMR, the corresponding frequencies for MR being 82.1% and 71.3% respectively. With respect to the time taken to achieve molecular response, the disparity between deprivation categories was evident from therapy outset, albeit non-statistically significantly so; the MMR cumulative frequencies being 16.4% and 21.2% (12 months), 32.9% and 36.2% (18 months) and 51.4% and 42.6% (24 months); the MR results were 45.7% and 38.3% (12 months), 66.4% and 54.6% (18 months) and 74.9% and 60.6% (24 months) respectively.

The hazard ratios for loss of response combined with deaths (Table 2) are, as expected, consistent with the findings for overall and relative survival (Fig 2 E and F); patients in deprivation categories 4-5 who achieved MMR were 1.71 (1.03 to 2.84) times more likely to lose their response or die, and the results were similar when the threshold was increased to include patients who achieved an MR (1.90, 1.03 to 3.49). It is also worth noting that according to the information recorded at death certification, all 9 deaths in deprivation categories 4-5 had CML cited as a contributing cause of death, compared to 4 of the 8 in deprivation categories 1-3.

The deprivation differences presented here could not be explained either by variations in the acquisition of additional cytogenetic anomalies or TKI resistance, both of which were rare in this population: 7 (3.4%) of the 209 Ph+ patients with no additional abnormalities at diagnosis (Table 1) acquired an additional anomaly during follow-up, and all were in deprivation category 1-3. With respect to the 10 (4.3 %) patients who developed TKI resistance, 4/140 were in deprivation category 1-3 and 6/94 in 4-5. None of the patients who acquired an additional cytogenetic anomaly developed TKI resistance.

Discussion

The outcome for CML patients treated mainly with imatinib in our UK population-based patient cohort is similar to that reported for clinical trials[12 32]; the 5-year relative survival estimates for men and women diagnosed 2004-11 and treated with TKIs over the period 2004-13 being 89.1% (79.9 to 95.4) and 90.1% (71.9 to 96.1) respectively. This suggests that the much poorer outcome recorded in the US reflects financial barriers to accessing TKI therapy. Furthermore, our data confirm the inferences from clinical trials that TKI treatment is equally effective at all ages, eliminating the impact of age in traditional prognostic scores[33 34]. Indeed the prospects for most patients are excellent, raising questions about the continuing relevance of such scoring systems. However, despite free access to TKI therapy, clinical outcomes appear significantly poorer in lower socio-economic groups in the UK; the age and sex adjusted hazard ratio for deprivation categories 4-5 (less affluent) compared to the more affluent being 3.43 (1.89 to 6.22). These differences were not attributable to differences in the biological features of the disease; and hence the most plausible explanation is that this may reflect differential compliance with treatment[2 3 20 21].

The ability to conduct comprehensive population-based analyses of the type presented here is a major strength of the UK's NHS. Predicated on these structures, our population-based patient cohort (www.hmrn.org) was initiated to serve both research and clinical needs, and as such the capture and follow-up of all patients diagnosed in our study area is a paramount objective[27]. A unique feature is that all diagnoses and subsequent monitoring of patients within the unified clinical network that spans the area is carried out by a single haematopathology laboratory. Additionally, the socio-demographic structure of our catchment population of approximately 3.6 million (around 6% of the UK's estimated total) is broadly representative of the national population in terms of age, sex, and deprivation; and increasingly our data are being extrapolated to the country as a whole[27 35–37].

Given the life-long nature of TKI therapy, inequality of access because of cost[1] is likely to be the main explanation for the marked disparity between CML survival in SEER registries and the results reported here and elsewhere in Europe[38–41]. In addition to financial constraints, closer inspection of the data suggests that other factors including diagnostic accuracy and coding misclassification could also be contributing to the differences observed; since with a median diagnostic age of 65 years, incidence across SEER registries is consistently higher than elsewhere in the world, averaging around 1.8 per 100,000 and varying from about 1.4 per 100,000 in Hawaii through to 2.1 per 100,000 in Detroit[14]. By contrast, our age-standardized annual rate of 0.9 per 100,000 and median diagnostic of 59 years age are close to national and other European population-based estimates[38–41]. The accurate diagnosis of CML and its separation from other myeloproliferative disorders requires access to molecular diagnostic and cytogenetic analyses. Hence, while it is possible that the SEER variations are genuine, it is also possible that other haematological malignancies which are part of the differential diagnosis of CML, such as chronic myelomonocytic leukaemia (CMML), atypical CML and possibly myelodysplastic/myeloproliferative overlap syndromes, all of which have higher diagnostic ages and poorer survival, are being inadvertently included in the SEER CML dataset[27 39].

Our observations confirm that when TKI treatment is freely provided, survival for CML patients approaches that of unaffected individuals. Nevertheless, the requirement for daily oral therapy for this otherwise fatal disease has major, but poorly defined implications for health economies around the world[1]. In England and Wales, the National Institute for Health and Clinical Excellence (NICE) assess the clinical and cost effectiveness of new treatments prior to recommending their use across the NHS. In the original submission to NICE for imatinib approval, costs were estimated at approximately £16 - £20 million for the first 5-years of its introduction, but estimates beyond this time were not made due to lack of certainty about therapy uptake, long-term survival and consequent disease prevalence[42]. In the meantime, even more expensive second generation TKIs for CML, as well as new oral agents for more common haematological malignancies, are increasingly being adopted into clinical practice[43–45]. Obviously, ensuring optimum clinical outcome for the level of resources invested is a critical issue for clinicians and policy makers; and our findings suggest that more significant improvements in overall population outcomes could, perhaps, be achieved if socioeconomic differences, which may reflect variations in drug compliance, could be eliminated.

Whilst it is recognized that non-adherence to daily oral therapy can be a problem for long-term CML management even in populations with universal health care coverage[19–22], it has yet to be demonstrated that this is the reason for the socio-economic differences described here. *To investigate this further, additional longitudinal studies that incorporate the collection of appropriate monitoring data, as well as information on other life-style factors that could potentially contribute to outcome, will need to be carried out.* Clearly, however, identification of the mechanisms underpinning the socio-economic survival differences within our population, and consequent design of appropriate interventions, could further improve survival. In this regard, recently developed serum imatinib assays[46] could, perhaps, be incorporated into future studies designed to investigate the reasons why some patients may not be taking their medication regularly.

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Supplementary information

Competing interests

All authors have completed the Unified Competing Interest form and declare that (1) none of them have support from any company for the submitted work; (2) None of them have relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) none of their spouses, partners, or children have financial relationships that may be relevant to the submitted work; and (4) none of them have any non-financial interests that may be relevant to the submitted work.

Details of contributors and guarantors:

ER, AS, DH, RP, and AJ were responsible for the conception and design of the study. AS and DP managed and analysed the data. GS, RP, AJ and PE assisted in the acquisition of data and provided clinical advice regarding the analysis and interpretation of the data. All authors contributed to the final draft of the paper. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

ER and AS are study guarantors.

Ethics approval

The Haematological Malignancy Research Network has ethical approval (REC 04/01205/69) from Leeds West Research Ethics Committee, R&D approval from each NHS Trust and exemption from Section 251 (formally Section 60) of the Health & Social Care Act (2001) (PIAG 1-05(h)/2007).

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Data sharing

No additional data are available.

Table 1: Characteristics of 242 patients with chronic myeloid leukaemia (CML) diagnosed September 2004 to August 2011, distributed by vital status on 1st April 2013

	Diagnosed Sept 2004 to Aug 2011 Total (N=242) No (%)	Status 1st April 2013		Hazard Ratios (95% CI)	
		Alive (N=195) No (%)	Dead (N=47) No (%)	Unadjusted	Adjusted*
Age at diagnosis, years					
< 60	132 (54.6)	116 (59.8)	16 (34.0)	1.00	1.00
≥ 60	110 (45.4)	79 (40.2)	31 (66.0)	2.59 (1.39 to 4.83)	2.65 (1.42 to 4.96)
Sex					
Male	145 (60.0)	115 (59.0)	30 (63.8)	1.00	1.00
Female	97 (40.0)	80 (41.0)	17 (36.2)	0.84 (0.46 to 1.52)	0.67 (0.37 to 1.23)
Deprivation quintile					
1-3	143 (59.1)	124 (63.9)	19 (40.4)	1.00	1.00
4-5 (less affluent)	98 (40.9)	70 (36.1)	28 (59.6)	2.60 (1.45 to 4.66)	3.43 (1.89 to 6.22)
Phase at presentation					
Chronic	235 (97.1)	192 (81.7)	43 (18.3)	1.00	1.00
Accelerated/blast crisis	7 (2.9)	3 (42.9)	4 (57.1)	7.46 (2.61 to 21.28)	22.93 (7.24 to 72.61)
Baseline cytogenetics					
Ph+ve only	209 (86.4)	173 (82.8)	36 (17.2)	1.00	1.00
Variant Ph+ve	18 (7.4)	15 (83.3)	3 (16.7)	0.89 (0.27 to 2.88)	1.12 (0.34 to 3.68)
Additional abnormality	12 (5.0)	6 (50.0)	6 (50.0)	3.96 (1.66 to 9.42)	4.94 (2.03 to12.00)
Amplified Ph+ve	3 (1.2)	1 (33.3)	2 (66.7)	6.82 (1.63 to 28.46)	13.61 (3.09 to 60.00)

*Adjusted for all other characteristic in the Table except the one of interest and cytogenetics

Table 2: Acquisition and loss of molecular response; patients diagnosed September 2004 to August 2011 and followed until 1st April 2013

		Achieved response/TKI treated (%)	Loss of response/ achieved response (%)	Deaths/achieved response (%)	Loss of response plus deaths[#]/achieved response (%)	Hazard Ratio* (95% CI) for loss of response plus deaths	
						Unadjusted	Adjusted*
Major molecular response (MMR = ≤0.1%)							
Deprivation quintile	1-3	100/140 (71.4)	28/100 (28.0)	8/100 (8.0)	35/100 (35.0)	1.0	1.0
	4-5 (less affluent)	56/94 (59.6)	20/56 (35.7)	8/56 (14.3)	27/56 (48.2)	1.68 (1.03 to 2.78)	1.71 (1.03 to 2.84)
Molecular response (MR = ≤1.0%)							
Deprivation quintile	1-3	115/140 (82.1)	15/115 (13.0)	8~/115 (7.0)	22/115 (19.1)	1.0	1.0
	4-5 (less affluent)	67/94 (71.3)	13/67 (19.4)	9~/67 (13.4)	21/67 (31.3)	1.78 (0.98 to 3.24)	1.90 (1.03 to 3.49)

[#] 3 deaths occurred in patients with a recorded loss of response

* Adjusted for age and sex

~ 4/8 deaths in deprivation categories 1-3 and 9/9 deaths in deprivation categories 4-5 were CML related (death certificates)

[Fig1A]

[Fig1B]

[Fig2]

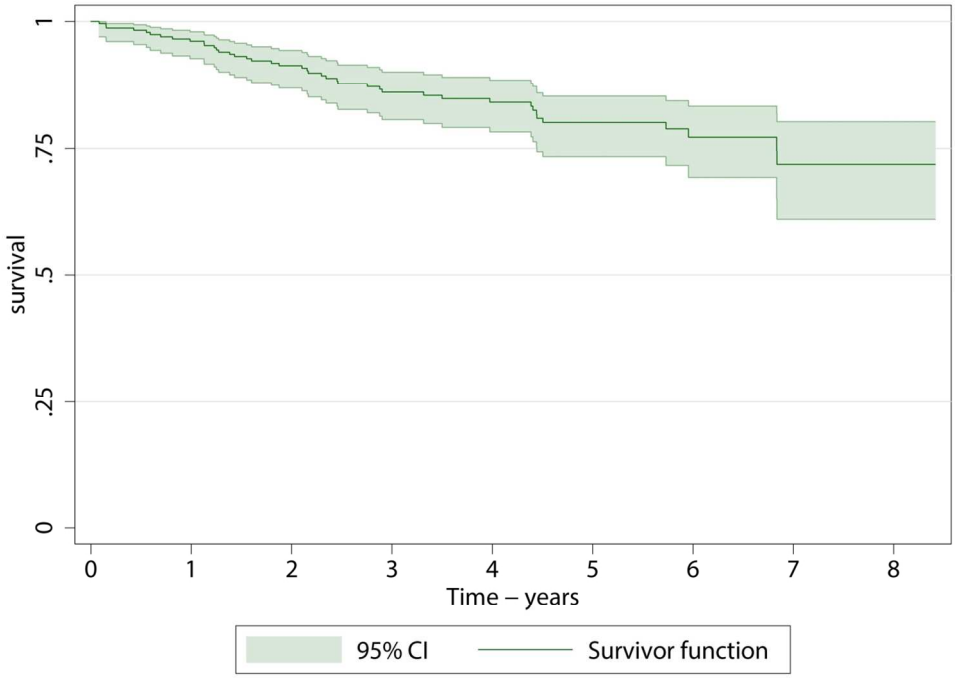

Figure 1: Crude survival of the 242 patients diagnosed with CML in HMRN 2004 to 2011 (deaths 2004 to 2013)

123x90mm (300 x 300 DPI)

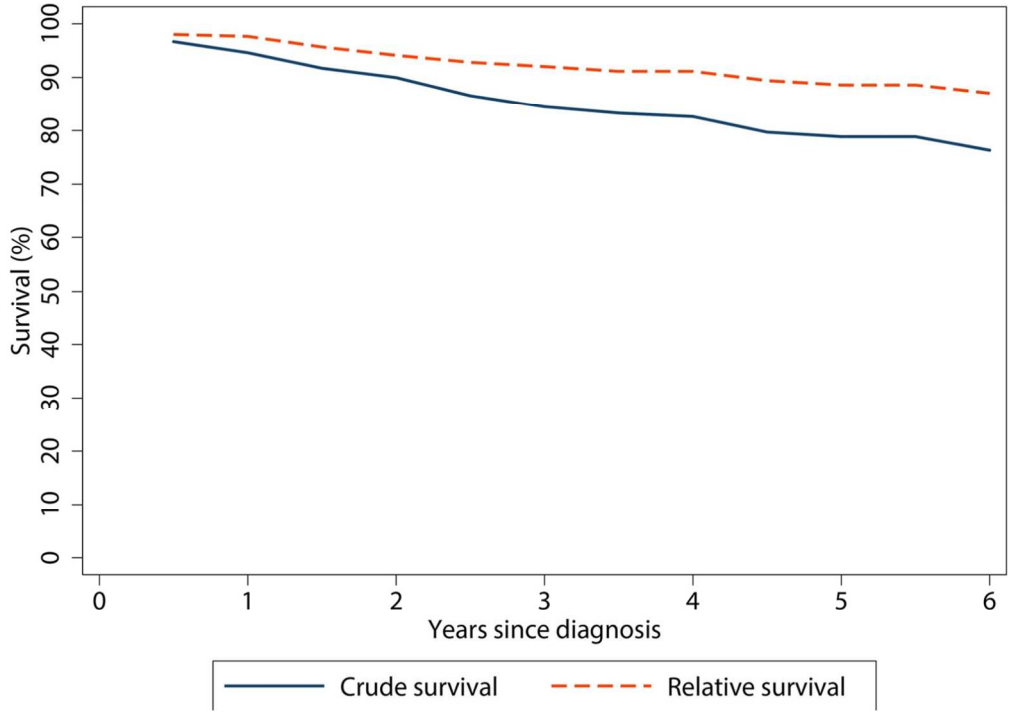

Figure 1B: Relative survival of the 242 patients diagnosed with CML in HMRN 2004 to 2011 (deaths 2004 to 2013)

127x90mm (300 x 300 DPI)

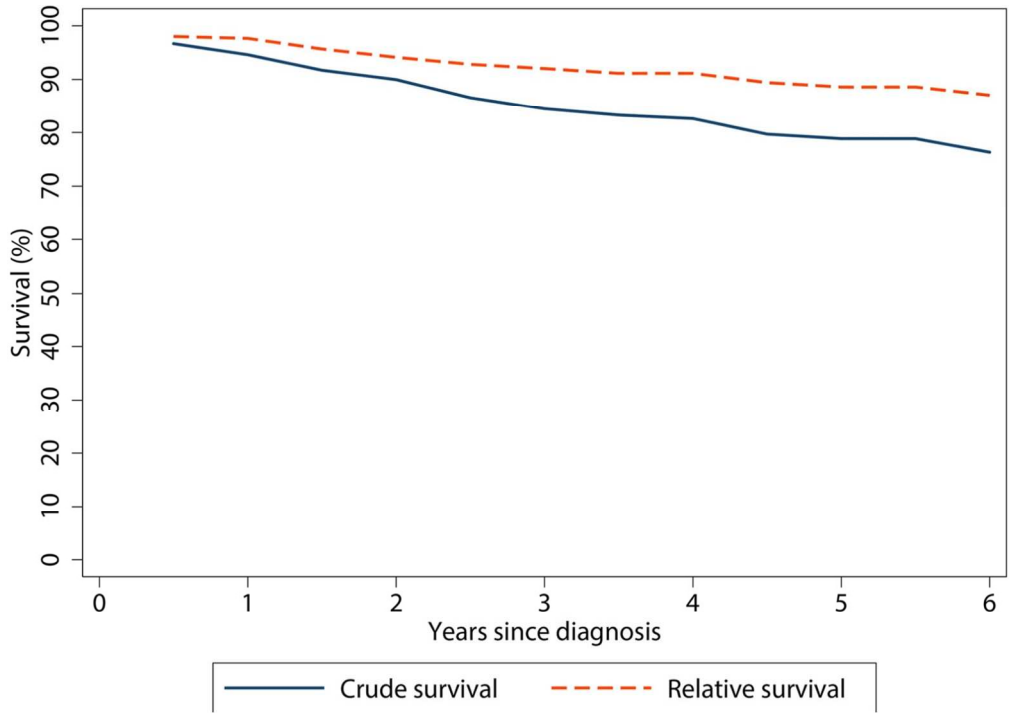

Figure 1B: Relative survival of the 242 patients diagnosed with CML in HMRN 2004 to 2011 (deaths 2004 to 2013)

127x90mm (300 x 300 DPI)

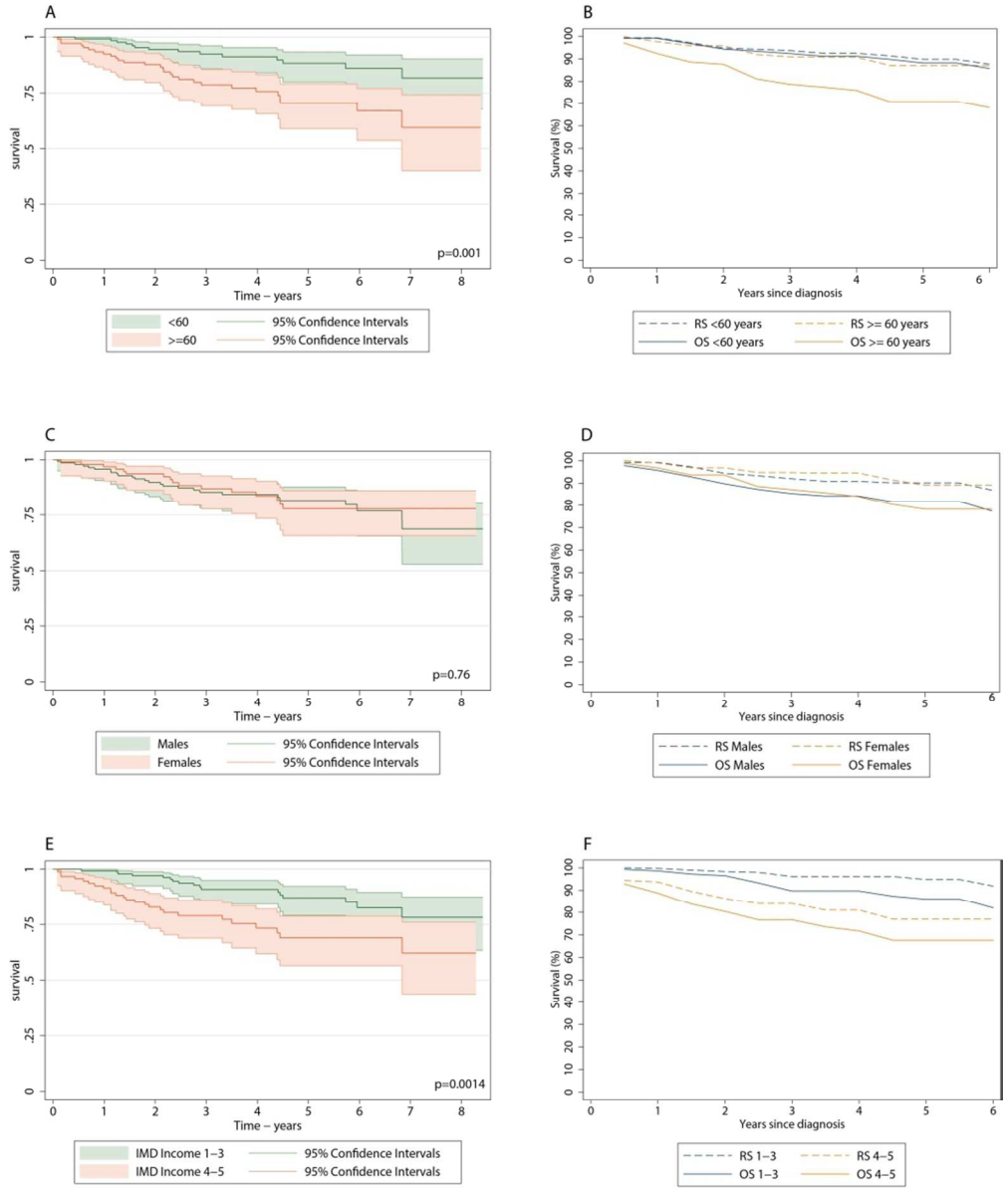

Figure 2: Crude (A, C, E) and relative survival (B, D, F) of the 234 patients diagnosed within HMRN 2004 to 2011 (deaths 2004 to 20 13) who were treated with tyrosine kinase inhibitors by age at diagnosis (A, B), Sex (C, D) and deprivation (E, F)
90x108mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	UK population-based patient cohort
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Please see abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Population-based data on outcomes for chronic myeloid leukaemia in a country where access to treatment is universal have not previously been reported.
Objectives	3	State specific objectives, including any prespecified hypotheses	To examine contemporary survival patterns in the general population of patients diagnosed with CML, and identify patient groups with less than optimal outcomes.
Methods			
Study design	4	Present key elements of study design early in the paper	Population-based cohort
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Location –Haematological Malignancy Research Network Recruitment - September 2004 to August 2011 Follow-up – April 2013 Data collection – medical records
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	All patients newly diagnosed since September, 2004.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Incidence and survival.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Index of Deprivation (IMD)
Bias	9	Describe any efforts to address potential sources of bias	Loss to follow-up. All patients are 'flagged' in the national death certification scheme so we are able to

			follow-up patients if they are treated outside of the study region.
Study size	10	Explain how the study size was arrived at	The study included all eligible cases.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Index of Deprivation (IMD), the categories defined in the national dataset were used.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Time to event analyses
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This is detailed in the results section page 6, 2nd paragraph.
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Please see Table 1 for socio-demographic characteristics and potential confounding variables.
		(b) Indicate number of participants with missing data for each variable of interest	None
		(c) Summarise follow-up time (eg, average and total amount)	1.5 years to 8.5 years
Outcome data	15*	Report numbers of outcome events or summary measures over time	These are detailed in tables 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1, confounders adjusted for a detailed in the footnote.
		(*b*) Report category boundaries when continuous variables were categorized	These are reported in the tables and result section.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	These are detailed in paragraph 1 of the discussion, page

			8.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations of the study are discussed in Paragraph 5.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	These are included in the discussion specifically paragraph 1,3, 4,5
Generalisability	21	Discuss the generalisability (external validity) of the study results	These are discussed in paragraph 2 of the discussion, page 8.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Leukaemia and Lymphoma Research funded the study and the Haematological Malignancy Research Network.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.