# Pattern of Use and Long-Term Safety of Tyrosine Kinase Inhibitors: A Decade of Real-World Management of Chronic Myeloid Leukemia

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# Pattern of Use and Long-Term Safety of Tyrosine Kinase Inhibitors: A Decade of Real-World Management of Chronic Myeloid Leukemia

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## Abstract

**Background and Objectives** First-line treatment of chronic phase (CP) chronic myeloid leukemia (CML) is based on the first-generation tyrosine kinase inhibitor (TKI) imatinib or the second-generation TKIs dasatinib or nilotinib. Thanks to the efficacy of TKIs, CML has switched from a fatal to a 'chronic' pathology, and data from clinical trials have become insufficient to drive physicians' prescription choices and address long-term treatment outcomes. On the brink of commercialization of generic imatinib, this study aims to evaluate the therapeutic pattern of CP-CML and the occurrence of adverse events (AEs) over a decade of local real clinical practice.

**Methods** A retrospective cohort study was performed on CP-CML patients followed up in the Local Health Unit of Treviso (Veneto Region, Italy) during the period 2005–2015. Data were captured from both administrative databases and physicians' patient diaries.

**Results** Of 81 CP-CML patients, 73 were treated with first-line imatinib; among the second-generation TKIs, only nilotinib was used ($n = 8$). Overall, 38% of imatinib-treated subjects needed to switch, mainly due to intolerance, whereas no switches occurred in the nilotinib cohort. Osteoarticular pain was the most common AE and was significantly more frequent in the imatinib cohort (68.49 vs. 25.00%, $p = 0.022$). Other common AEs were dermatologic manifestations, asthenia, and diarrhea.

**Conclusion** Although based on a small population, this study represents an unbiased reference on the long-term management of CML in an Italian clinical setting. Our results indicate a better profile of first-line nilotinib, both in terms of persistency and tolerability. AEs remain a major concern, highlighting the importance of close monitoring.

## Key Points

Progress in the treatment of chronic myeloid leukemia (CML) has been rapid, and increasing knowledge from routine clinical practice represents a key strategy in the lifelong fight against this disease.

This study represents an unbiased reference on the long-term management of CML in an Italian clinical setting, providing important real-world evidence on the therapeutic patterns and effectiveness of TKIs.

Our results suggest that nilotinib presents a better profile in terms of its efficacy and safety compared with imatinib, and highlight the importance of an accurate frontline treatment choice, reserving nilotinib for imatinib-intolerant or imatinib-resistant patients.

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## 1 Introduction

Chronic myeloid leukemia (CML) is a myelodysplastic neoplasm accounting for approximately 15% of all cases of leukemia in adults [1, 2]. The pathogenesis of CML is connected to the chromosomal translocation (9;22) (q3.3; q1.1), which leads to the formation of a fusion chromosome known as Philadelphia, carrying a hybrid BCR-ABL gene [3, 4]. This fusion gene encodes for a constitutively activated tyrosine kinase, which is involved in the malignant transformation of hematopoietic cells and progression of the pathology through three phases: chronic phase (CP), accelerated phase (AP), and blast crisis (BC) [5–7].

CML treatment is therefore mainly based on targeted tyrosine kinase inhibitors (TKIs) [8]. TKIs approved as first-line treatment are imatinib (a first-generation TKI) or second-generation TKIs such as dasatinib or nilotinib. Treatment choice is based on CML phase at entry, as well as patients' specific characteristics and risk of progression, estimated through the Sokal, Hasford, and EUTOS risk scores [8–11]. Overall, TKIs have proven high efficacy, accounting for an 8-year survival rate of approximately 87%, i.e. comparable with that of the general population [12]. As CML has progressively switched from a fatal to a 'chronic' pathology, standards for the management of CML have therefore moved from short-term survival to long-term outcomes, such as the achievement of early disease control and the reduction of persistent treatment intolerance [13]. In this context, data from randomized clinical trials (RCTs) have progressively become insufficient due to their relatively short follow-up times, as well as the significant differences in the enrolled cohorts compared with the real-life population [13–15]. Observational studies of real clinical practice could therefore be of great help for long-term monitoring of this pathology. In particular, at this time in which generic imatinib is entering the market, real-life studies could provide key data for a re-evaluation of the recommendations for clinicians' choice of first-line treatment.

On the brink of commercialization of generic imatinib, our observational study aims to take a snapshot of the pharmacological management of CP-CML over a decade of local real clinical practice, describing a real cohort of Italian cases in terms of therapeutic pattern and occurrence of adverse events (AEs).

## 2 Patients and Methods

A population-based retrospective cohort study was performed on all subjects affected by CP-CML and followed up at the Department of Haematology of the Local Health Unit n.2 of Treviso (Region of Veneto, Italy). Data were captured from administrative databases of drug dispensing by community and hospital pharmacies and reimbursed by the National Healthcare System (NHS). In order to have information that was as complete and accurate as possible, administrative data were integrated with those recorded in physicians' patient diaries, i.e. internal registries filled in by hematologists at the time of each physician visit. In respect to Italian rules on privacy, the original unique individual identification code (Regional Health Code [RHC]), univocally attributed to each beneficiary by the National Healthcare System, was replaced by an anonymous univocal alphanumeric identification code. The Ethics Committee of the Local Health Unit n.2 of Treviso (Regione Veneto, Comitato Etico per la Sperimentazione Clinica delle Province di Belluno e Treviso) notified the present study on 15 December 2016 (Studio n. XLV/RPA—AULSS 9—Studio Osservazionale—No Profit).

All patients with CP-CML during the period 1 January 2005 to 30 June 2015 were enrolled in our study. Among these patients, those treated with non-TKI drugs as frontline treatment were excluded. All patients were followed up from the date of diagnosis until the occurrence of the first event among (1) occurrence of hematopoietic stem cells transplantation (HSCT); (2) death; or (3) end of data availability (31 December 2015). The first date among these events was considered the exit date. Patients were characterized based on sex, age at diagnosis, risk scores of progression (Sokal, Hasford, EUTOS), type of BCR-ABL transcript, and comorbidities present at baseline.

First-line TKI treatment of CML was evaluated, considering information on the active principle, length of treatment, occurrence of therapeutic switches, and cause of the switch. The occurrence of any AE during first-line TKI treatment was assessed, considering adverse manifestations reported by hematologists in physicians' patient records (PPRs).

### 2.1 Statistical Analysis

Descriptive statistics were used to summarize the considered variables. Baseline patient characteristics, occurrence of therapeutic switches, and AEs were compared among subjects treated with different first-line TKIs. Continuous variables were reported as median and interquartile range (IQR) and were compared using the Kruskal–Wallis test. Percentages were compared using Fisher's exact test.

Missing data, the cause of which was the loss of some clinical examination records during the study period, were randomly distributed. In each analysis, subjects with no available data for the considered variable were excluded. Statistical significance was considered at $p$-values $< 0.05$. Statistical analysis was performed using software STATA version 14 (StataCorp LLC, College Station, TX, USA).

## 3 Results

A total cohort of 81 subjects with CP-CML between 2005 and 2015 was examined. For 74 of these patients, a first diagnosis of CML occurred during this period, whereas seven patients were diagnosed between 2001 and 2004. Overall, the median observation time was 5.93 years (IQR 3.64–9.25). Based on prescribed first-line TKI treatments, patients were divided into two groups: the imatinib cohort (73 subjects) and the nilotinib cohort (8 subjects). No CP-CML patient was prescribed dasatinib as frontline treatment. The baseline characteristics of the cohort are described in Table 1.

Patient sex was equally distributed, and the majority of subjects were diagnosed between 50 and 64 years of age and were assessed as being at low risk of progression, independently from the risk score used. All these characteristics were comparable in the imatinib versus nilotinib cohort. Considering the BCR-ABL transcript, the e14a2 or e13a2 transcripts were the most frequent (41.10 and 31.51%, respectively, among imatinib-treated subjects; 37.50% each among nilotinib-treated subjects); the less common e19a2 transcript was found in two subjects, both treated with imatinib.

Comorbidities present at diagnosis were equally distributed among the two treatment cohorts. Most patients were affected by hypertension (45.21 and 50% in the imatinib and nilotinib cohorts, respectively), while other cardiovascular diseases and osteoarticular pathologies also affected a significant percentage of patients. Twenty patients had a history of malignancies, with a similar proportion in both treatment cohorts (24.66 and 25.00% of imatinib- and nilotinib-treated subjects, respectively).

Over a comparable treatment duration (4.55 years [IQR 1.39–7.89] vs. 3.59 years [IQR 2.23–4.76], $p = 0.402$), imatinib was associated with a significantly higher occurrence of switches (28 vs. 0 cases, 38 vs. 0%) compared with nilotinib (Fig. 1). The median time to switch was 533 days (IQR 235–1530). Switches from imatinib were mainly related to treatment intolerance (20 cases), whereas the remaining eight cases were attributable to resistance.

Among subjects switching from imatinib, dasatinib was the most common second-line treatment ($n = 15$), whereas nilotinib was prescribed in 11 patients. One patient switched to non-TKI treatment and another patient switched to non-treatment, both due to severe intolerance to TKI therapy. Twelve of 28 patients needed to re-switch from a second- to third-line treatment.

Dasatinib and nilotinib were prescribed as third-line treatment in three patients each, whereas two patients were prescribed the third-generation TKI ponatinib. Of note, another three patients discontinued treatment. In particular, two patients discontinued because of severe intolerance, whereas one subject discontinued treatment following the achievement of treatment response after an overall period of 3.75 years (data not shown).

AEs occurring during first-line treatment with imatinib versus nilotinib are reported in Table 2. Osteoarticular pain was the most common AE, and was significantly more frequent among imatinib-treated patients (50 vs. 2 patients, 68.49 vs. 25.00%, $p = 0.022$). The median time to first report of osteoarticular pain was 48.5 days (IQR 14–116) and 169.5 days (19–320) for the imatinib and nilotinib cohorts, respectively. Other common AEs were dermatologic manifestations, asthenia, diarrhea, epigastric pain, fever, and infections or virus reactivation. Occurrence of all these AEs was more frequently reported in the imatinib cohort, although without statistical significance. AEs with lower latency from the beginning of treatment were fever (21 days [IQR 7–113] and 22 days for imatinib and nilotinib, respectively), and dermatologic manifestations (45 days [IQR 24–135] and 4 days [1–30] for imatinib and nilotinib, respectively, $p = 0.029$), whereas long latency was found for epigastric manifestations.

Serious AEs occurred in 10 subjects taking imatinib versus one subject taking nilotinib. Considering serious AEs that occurred during imatinib treatment, the development of unrelated CML malignancies was found in four patients, of whom one developed colon cancer, one was diagnosed with gastric cancer, one was diagnosed with prostate cancer, and another was diagnosed with uterine cancer. In addition, four patients in the imatinib cohort experienced stroke events and one had acute myocardial infarction. Pleural effusion and heart failure were reported in two patients, respectively. Among the nilotinib-treated subjects, only one experienced serious AEs, in particular pleural effusion, heart failure, and pericarditis.

No differences emerged in terms of sex and median age among subjects experiencing the reported AEs in the imatinib versus nilotinib groups.

## 4 Discussion

This observational study considered the long-term management of CML with TKIs in an real-world setting in Italy. Although very limited in size, the examined cohort was typical of patients seen in the real world, in terms of both sex and age. A slightly higher prevalence was found among men compared with women, confirming data in the epidemiological literature [16, 17]. The median age at diagnosis was 61 years, i.e. 14–15 years older than patients enrolled in the nilotinib versus imatinib ENESTnd RCT, and 13–16 years older than patients in the dasatinib versus imatinib DASISION RCT [18, 19]. Furthermore, the present population

**Table 1** Baseline characteristics stratified according to frontline treatment

| Characteristics | Frontline imatinib | Frontline nilotinib | *p* Value |
|---|---|---|---|
| Total no. of patients | 73 | 8 | |
| Sex | | | |
| Male | 38 (52.05) | 5 (62.50) | 0.717 |
| Female | 35 (47.95) | 3 (37.50) | |
| Age at diagnosis, years | | | |
| Median [IQR] | 62 [51–69] | 60 [53–66] | 0.596 |
| < 50 | 14 (19.18) | 2 (25.00) | 1.000 |
| 50–64 | 31 (42.47) | 4 (50.00) | |
| 65–79 | 21 (28.77) | 2 (25.00) | |
| > 79 | 7 (9.59) | 0 | |
| *Risk score of progression* | | | |
| Sokal score | | | |
| Low | 26 (35.62) | 2 (25.00) | 0.610 |
| Intermediate | 15 (20.55) | 2 (25.00) | |
| High | 8 (10.96) | 2 (25.00) | |
| NA | 24 (32.88) | 2 (25.00) | |
| Hasford score | | | |
| Low | 13 (17.81) | 1 (12.50) | 0.486 |
| Intermediate | 5 (6.85) | 0 | |
| High | 2 (2.74) | 1 (12.50) | |
| n.a. | 53 (72.60) | 6 (75.00) | |
| EUTOS score | | | |
| Low | 21 (28.77) | 0 | 0.090 |
| High | 2 (2.74) | 1 (12.50) | |
| NA | 50 (68.49) | 7 (87.50) | |
| Type of BCR-ABL transcript | | | |
| e14a2 | 30 (41.10) | 3 (37.50) | 1.000 |
| e13a2 | 23 (31.51) | 3 (37.50) | |
| Both e14a2 and e13a2 | 2 (2.74) | 0 | |
| e19a2 | 2 (2.74) | 0 | |
| NA | 16 (21.92) | 2 (25.00) | |
| Comorbidities | | | |
| Chronic gastrointestinal disorders | 12 (16.44) | 2 (25.00) | 0.621 |
| Chronic kidney disorders | 7 (9.59) | 0 | – |
| Diabetes | 8 (10.96) | 0 | – |
| Hypertension | 33 (45.21) | 4 (50.00) | 1.000 |
| Mental disorders | 13 (17.81) | 1 (12.50) | 1.000 |
| Osteoarticular pathologies | 15 (20.55) | 1 (12.50) | 1.000 |
| Other cardiovascular diseases | 18 (24.66) | 2 (25.00) | 1.000 |
| Previous cancer | 18 (24.66) | 2 (25.00) | 1.000 |

Data are expressed as *n* (%) unless otherwise specified

*IQR* interquartile range, *NA* not available

also included patients aged ≥ 80 years at the time of CML onset, who are usually excluded from RCTs and whose management can be particularly critical. The discrepancy in terms of age between real-life and RCT populations has been previously discussed [13, 14]. Moreover, such RCTs might be poor predictors of response in real-world populations [13, 15, 20].

Most patients were considered at low risk of progression, independently from the risk score used. Of note, the Sokal score, although developed before the advent of TKIs, was the most frequently reported in PPRs, confirming how

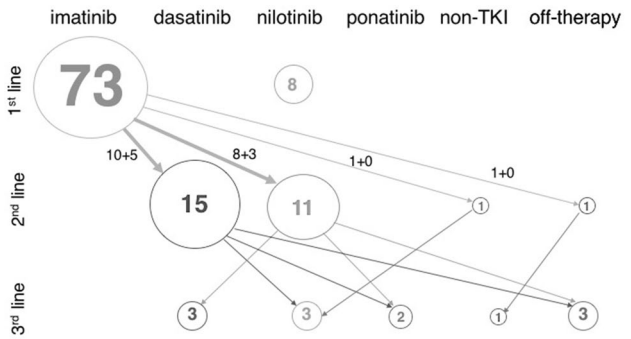


**Fig. 1** Occurrence of switches among the different therapies, and number of switches to second-line treatment attributable to intolerance and resistance (number for intolerance + number for resistance). *TKI* tyrosine kinase inhibitor

this score is still routinely used in clinical practice and is still considered an extremely predictive tool for treatment response and patient survival [21].

Although mostly being identified as low-risk, the majority of patients were clinically compromised by other comorbidities. In particular, cerebrovascular/cardiovascular pathologies occurred in more than half of the cohort, and one in four subjects had a history of other malignancies. Of note, patients with severe or uncontrolled cardiovascular diseases were excluded from the ENEST, ENESTnd, and DASISION trials [22], and little is known on the best management of CML for patients with previous malignancies. In light of this, this study provides important information on the pharmacological management of CML in real clinical practice.

Our results clearly show a central role of imatinib as first-line treatment for CP patients, compared with a marginal number of patients prescribed second-generation TKIs. Baseline patient characteristics and CML-related characteristics were comparable among CP-CML subjects treated with frontline imatinib versus nilotinib, indicating that the choice of frontline treatment was not influenced by these factors.

Of note, nilotinib was the only second-generation TKI prescribed as first-line treatment for CP-CML, although the indications for its use are comparable with those of dasatinib. Furthermore, there are no specific recommendations on the choice between the two molecules [8]. The dominance of nilotinib could be motivated by its lower cost per day of treatment compared with dasatinib (€165.33 vs. €220.90 per day).

This pattern regarding choice of first-line treatments for CP patients is adherent to international guidelines, i.e. recommend second-generation TKIs in patients diagnosed with AP or BC, while leaving physicians to choose between first- and second-generation TKIs in low-risk CP patients [8].

Only one of 81 CP-CML patients remained stable after discontinuing TKI therapy following the achievement of a stable response to imatinib treatment. No cases of treatment discontinuation and subsequent relapse were reported. This result suggests that, to date, long-term management of CML in clinical practice is mainly based on stable prosecution of TKI treatment, in accordance with European LeukemiaNet (ELN) recommendations [8]. With regard to stable discontinuation, evidence derived from stopping studies is gaining increasing attention in clinical practice, given its crucial impact on patients' quality of life, reduction of AEs, and on the economic burden of pathology for the NHS [23].

Moreover, our study found a difference in the occurrence of therapeutic switches between these two TKIs. In fact, we found no switches in patients treated with frontline nilotinib, compared with 28 of 73 imatinib-treated patients who switched to a second-line treatment. This result must be taken carefully, given the very small and unbalanced number of patients in the imatinib versus nilotinib group, and the different market availability of the two TKIs over the observed period (imatinib was available in the entire period, whereas nilotinib entered the Italian market in 2007). In fact, the median duration of treatment was 1 year shorter for nilotinib compared with imatinib, although there was no statistical significance (4.55 years [IQR 1.39–7.89] vs. 3.59 years [IQR 2.23–4.76], $p = 0.402$). Nevertheless, two recent national and international observational studies by Castagnetti et al. and Machado-Alba and Machado-Duque [24, 25] found similar results, reporting a significantly higher proportion of switches in patients treated with imatinib compared with second-generation TKIs, mainly due to resistance. On the other hand, in our study most switches from imatinib were due to severe treatment intolerance.

Indeed, our results clearly highlight that AEs remain a critical concern during the management of CML. Sixty-one percent of examined patients experienced osteoarticular pain following the commencement of CML treatment, with a significantly higher frequency among imatinib-treated subjects. The association of imatinib and muscle cramps is well known in the literature [26], and, although not serious, this AE can severely compromise a patient's quality of life, leading to poor compliance to treatment and the need for treatment changes. Other frequent AEs included dermatological manifestations, asthenia, diarrhea, and epigastric pain. Nevertheless, the association of these AEs with ongoing TKI treatment was difficult to assess, particularly in light of the long latency observed for some AEs.

This study reports on the necessity of monitoring a patient's overall clinical condition and developing a strategy to better manage AEs. From this perspective, the ELN recently published recommendations for the management and avoidance of AEs in the treatment of CML [27]. According to the ELN, efforts should be made to predict

**Table 2** Evaluation of the most common adverse events overall, and occurring during first-line TKI treatment

| Adverse effects | Imatinib [*N* (%, out of 73)] | Nilotinib [*N* (%, out of 8)] | *p*-value |
|---|---|---|---|
| *Most common AEs* | | | |
| Osteoarticular pain | 50 (68.49) | 2 (25.00) | 0.022* |
| Latency, days | 48.5 [14–116] | 169.5 [19–320] | 0.739 |
| Median age, years [IQR] | 59.5 [50–68] | 60 [60–60] | 0.962 |
| Male (%) | 24 (48.00) | 2 (100.00) | – |
| Dermatologic manifestations | 49 (67.12) | 3 (37.50) | 0.127 |
| Latency, days | 45 [24–135] | 4 [1–30] | 0.029* |
| Median age, years [IQR] | 61 [52–70] | 64 [49–68] | 0.875 |
| Male (%) | 26 (53.06) | 1 (33.33) | 0.603 |
| Asthenia | 29 (39.73) | 2 (25.00) | 0.704 |
| Latency, days | 60 [27–330] | 132.5 [7–258] | 0.601 |
| Median age, years [IQR] | 61 [50–68] | 47.5 [39–56] | 0.296 |
| Male (%) | 12 (41.38) | 2 (100.00) | – |
| Diarrhea | 21 (28.77) | 2 (25.00) | 1.000 |
| Latency, days | 168 [29–545] | 563 [30–1095] | 0.785 |
| Median age, years [IQR] | 56 [51–69] | 64.5 [60–69] | 0.478 |
| Male (%) | 12 (57.14) | 1 (50.00) | 1.000 |
| Epigastric pain | 19 (26.03) | 2 (25.00) | 1.000 |
| Latency, days | 365 [93–1825] | 585 [15–1155] | 0.407 |
| Median age, years [IQR] | 54 [38–64] | 64 [60–68] | 0.231 |
| Male (%) | 13 (68.42) | 2 (100.00) | – |
| Fever | 12 (16.44) | 1 (12.50) | 1.000 |
| Latency, days | 21 [7–113] | 22 | 1.000 |
| Median age, years [IQR] | 51.5 [49.5–60] | 39 | 0.109 |
| Male (%) | 6 (50.00) | 1 (100.00) | – |
| Infections or viral reactivation | 12 (16.44) | 1 (12.50) | 1.000 |
| Latency, days | 240 [60–370] | 725 | 0.206 |
| Median age, years [IQR] | 61.5 [50–68.5] | 68 | 0.422 |
| Male (%) | 7 (58.33) | 1 (100.00) | – |
| *Most serious AEs* | | | |
| Stroke | 4 (5.48) | 0 | – |
| Latency, days | 1186 [652–2333] | – | – |
| Median age, years [IQR] | 73.5 [67–79] | – | – |
| Male (%) | 3 (75.00) | – | – |
| Malignancies | 4 (5.48) | 0 | – |
| Latency, days | 660 [210–1460] | – | – |
| Median age, years [IQR] | 61.5 [45.5–66] | – | – |
| Male (%) | 2 (50.00) | – | – |
| Pleural effusion | 2 (2.74) | 1 (12.50) | 0.271 |
| Latency, days | 1504 [1095–1912] | 148 | 0.221 |
| Median age, years [IQR] | 75.5 [70–81] | 49 | 0.221 |
| Male (%) | 1 (50.00) | 0 | |
| Heart failure | 2 (2.74) | 1 (12.50) | 0.271 |
| Latency, days | 1504 [1095–1912] | 148 | 0.221 |
| Median age, years [IQR] | 75.5 [70–81] | 49 | 0.221 |
| Male (%) | 1 (50.00) | 0 | |
| Acute myocardial infarction | 1 (1.37) | 0 | – |
| Latency, days | 1826 | – | – |
| Median age, years | 50 | – | – |

**Table 2** (continued)

| Adverse effects | Imatinib [*N* (%, out of 73)] | Nilotinib [*N* (%, out of 8)] | *p*-value |
|---|---|---|---|
| Male (%) | 1 (100.00) | – | – |
| Pericarditis | 0 | 1 (12.50) | – |
| Latency, days | – | 240 | – |
| Median age, years | – | 49 | – |
| Male (%) | – | 0 | – |

Serious AEs occurred in 10 subjects receiving imatinib vs. one subject receiving nilotinib

*AE* adverse events, *TKI* tyrosine kinase inhibitor, *IQR* interquartile range

*$p < 0.05$

and manage AEs without reducing or interrupting CML treatment. Particular attention must be given to comorbidities and drug interactions, and to new events unrelated to TKIs that are inevitable during such a long-lasting treatment period [27]. In addition, wider studies on the development of secondary malignancies following CML treatment are needed.

This study has several limitations. The small size of the observed cohort represents a major limitation and, as a consequence, this study does not have the potency to establish the superiority of one treatment over other. Nevertheless, this small cohort represents the entire population affected by CP-CML and treated with TKIs in the study center between 2005 and 2015. In addition, the evaluation of demographic and disease-related characteristics revealed that this cohort was representative of the CML population, as described in both national and international literature [16, 17]. Second, the size of the imatinib and nilotinib groups was disproportionate. Third, despite baseline characteristic being comparable among CP patients treated with frontline imatinib and nilotinib, it was possible that unmeasured confounding by indication was present, i.e. treatment with nilotinib was mainly likely in patients with clinical characteristics that were different from imatinib-treated subjects. Fourth, this study covers a prolonged period (2005–2015), and aspects related to treatment might have changed over this time. In particular, while imatinib was available for the entire period, nilotinib only entered the Italian market in 2007. As a result, patient differences in the calendar year of inclusion in the cohort, and in the follow-up time, could have influenced our findings in terms of treatment persistency and occurrence of long-term AEs. In fact, it was likely patients receiving nilotinib had been more recently diagnosed and had a shorter follow-up, as was actually reported in our results, and, as a consequence, had a lower chance of having long-term AEs and switches. Fifth, underreporting and underestimation of milder AEs could be present, and the occurrence of AEs may have been influenced by the onset of relevant clinical conditions between the commencement of TKIs and the occurrence of AEs. Sixth, patients may be co-followed-up by different hospitals and physicians at the same time, therefore examined PPRs and local administrative databases might not be complete due to information recorded in other hospital districts. Finally, this study was not able to take into account the quality of life experienced by patients receiving different treatments, given that data on patients' perceptions and satisfaction with treatment were not recorded on the PPR. Considering that few data regarding patients' quality of life are available in the literature, and given the long-term duration of CML treatment, further research is worthy in this area.

Despite the above-mentioned limitations, this study represents an unbiased reference on the long-term management of CML in an Italian clinical setting, providing important real-world evidence on therapeutic patterns and effectiveness of TKIs.

## 5 Conclusions

Progress in the treatment of CML has been so rapid that any recommendations regarding the management of CML can quickly become obsolete [28]. Nevertheless, increasing knowledge from routine clinical practice represents a key strategy in the lifelong fight against this disease, which has now become chronic. Our results indicate a better profile of nilotinib as first-line therapy for CP-CML, both in terms of treatment persistency and tolerability. While this might be seen as an argument for using nilotinib as first-line therapy, it might also argue strongly for the continued use of imatinib as first-line therapy, reserving nilotinib for imatinib-intolerant or imatinib-resistant patients. This is particularly true as the first generic imatinib is about to be launched, thereby increasing the already high difference in costs for the NHS between imatinib and nilotinib. A full health economic evaluation is required to determine the most cost-effective care pathways using these expensive drugs.

## Compliance with Ethical Standards

**Funding** No funding was received for this study.

**Conflicts of Interest** Alessandra Bettiol, Ettore Marconi, Niccolò Lombardi, Giada Crescioli, Filippo Gherlinzoni, Thomas Walley, Alfredo Vannacci, Alessandro Chinellato and Pietro Giusti declare that they have no conflicts of interest.

**Ethical Approval** The Ethics Committee of the Local Health Unit n.2 of Treviso (Regione Veneto, Comitato Etico per la Sperimentazione Clinica delle Province di Belluno e Treviso) notified the present study on 15 December 2016 (Studio n. XLV/RPA—AULSS 9—Studio Osservazionale—No Profit).

**Informed Consent** Formal consent is not required for this type of study.

## References


1. Faderl S, Kantarjian HM, Talpaz M. Chronic myelogenous leukemia: update on biology and treatment. Oncology. 1999;13(2):169–80.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
3. Nowell PCHD. A minute chromosome in human chronic granulocytic leukemia. Science. 1960;132:1497.
4. Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature. 1973;243(5405):290–3.
5. Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science. 1990;247(4944):824–30.
6. Quintas-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment. Mayo Clin Proc. 2006;81(7):973–88.
7. Chereda B, Melo JV. Natural course and biology of CML. Ann Hematol. 2015;94(Suppl 2):S107–21.
8. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872–84.
9. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood. 1984;63(4):789–99.
10. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst. 1998;90(11):850–8.
11. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood. 2011;118(3):686–92.
12. Kantarjian H, O'Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, Shan J, et al. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood. 2012;119(9):1981–7.
13. Mauro MJ, Davis C, Zyczynski T, Khoury HJ. The role of observational studies in optimizing the clinical management of chronic myeloid leukemia. Ther Adv Hematol. 2015;6(1):3–14.
14. Rohrbacher M, Berger U, Hochhaus A, Metzgeroth G, Adam K, Lahaye T, et al. Clinical trials underestimate the age of chronic myeloid leukemia (CML) patients. Incidence and median age of Ph/BCR-ABL-positive CML and other chronic myeloproliferative disorders in a representative area in Germany. Leukemia. 2009;23(3):602–4.
15. Latagliata R, Breccia M, Carmosino I, Cannella L, De Cuia R, Diverio D, et al. "Real-life" results of front-line treatment with Imatinib in older patients (≥ 65 years) with newly diagnosed chronic myelogenous leukemia. Leuk Res. 2010;34(11):1472–5.
16. Berger U, Maywald O, Pfirrmann M, Lahaye T, Hochhaus A, Reiter A, et al. Gender aspects in chronic myeloid leukemia: long-term results from randomized studies. Leukemia. 2005;19(6):984–9.
17. Hoglund M, Sandin F, Simonsson B. Epidemiology of chronic myeloid leukaemia: an update. Ann Hematol. 2015;94(Suppl 2):S241–7.
18. Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer. 2010;116(16):3852–61.
19. Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011;12(9):841–51.
20. Michallet M, Tulliez M, Corm S, Gardembas M, Huguet F, Oukessou A, et al. Management of chronic myeloid leukaemia in clinical practice in France: results of the French subset of patients from the UNIC study. Curr Med Res Opin. 2010;26(2):307–17.
21. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. Blood. 2012;120(7):1390–7.
22. Novartis pharmaceuticals. A Study of Imatinib Versus Nilotinib in Adult Patients With Newly Diagnosed Philadelphia Chromosome Positive (Ph +) Chronic Myelogenous Leukemia in Chronic Phase (CML-CP) (ENESTnd). Available at: https://clinicaltrials.gov/ct2/show/NCT00471497. Accessed 15 March 2017.
23. Saussele S, Richter J, Hochhaus A, Mahon FX. The concept of treatment-free remission in chronic myeloid leukemia. Leukemia. 2016;30(8):1638–47.
24. Castagnetti F, Di Raimondo F, De Vivo A, Spitaleri A, Gugliotta G, Fabbiano F, et al. A population-based study of chronic myeloid leukemia patients treated with imatinib in first line. Am J Hematol. 2017;92(1):82–7.
25. Machado-Alba JE, Machado-Duque ME. Use patterns of first-line inhibitors of tyrosine kinase and time to change to second-line therapy in chronic myeloid leukemia. Int J Clin Pharm. 2017;39(4):851–9.
26. Mughal TI, Radich JP, Deininger MW, Apperley JF, Hughes TP, Harrison CJ, et al. Chronic myeloid leukemia: reminiscences and dreams. Haematologica. 2016;101(5):541–58.
27. Steegmann JL, Baccarani M, Breccia M, Casado LF, Garcia-Gutierrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016;30(8):1648–71.
28. Baccarani M, Castagnetti F, Gugliotta G, Rosti G. A review of the European LeukemiaNet recommendations for the management of CML. Ann Hematol. 2015;94(Suppl 2):S141–7.