Received: 24 November 2022 | Revised: 14 February 2023 | Accepted: 17 February 2023

DOI: 10.1002/cncr.34923

ORIGINAL ARTICLE

Determinants of frontline tyrosine kinase inhibitor choice for patients with chronic-phase chronic myeloid leukemia: A study from the Registro Italiano LMC and Campus CML

Mario Tiribelli MD[1,2] | Roberto Latagliata MD[3] | Massimo Breccia MD[4] | Isabella Capodanno MD[5] | Maria Cristina Miggiano MD[6] | Francesco Cavazzini MD[7] | Cristina Bucelli MD[8] | Immacolata Attolico MD[9] | Sabrina Leonetti Crescenzi MD[10] | Sabina Russo MD[11] | Mario Annunziata MD[12] | Federica Sorà MD[13] | Massimiliano Bonifacio MD[14] | Olga Mulas MD[15] | Giuseppina Loglisci MD[16] | Alessandro Maggi MD[17] | Gianni Binotto MD[18] | Elena Crisà MD[19] | Anna Rita Scortechini MD[20] | Anna Paola Leporace MD[21] | Rosaria Sancetta MD[22] | Pamela Murgano MD[23] | Elisabetta Abruzzese MD[24] | Fabio Stagno MD[25] | Davide Rapezzi MD[26] | Debora Luzi MD[27] | Iolanda Vincelli MD[28] | Monica Bocchia MD[29] | Carmen Fava MD[30] | Alessandra Malato MD[31] | Monica Crugnola MD[32] | Michele Pizzuti MD[33] | Francesca Lunghi MD[34] | Sara Galimberti MD[35] | Matteo Dalmazzo MD[36] | Renato Fanin MD[1,2] | Emilia Scalzulli MD[4] | Robin Foà MD[4] | Alessandra Iurlo MD[8] | Giuseppe Saglio MD[30] | Giorgina Specchia MD[9]

Correspondence
Mario Tiribelli, Division of Hematology and Bone Marrow Transplant, Azienda Sanitaria Universitaria Friuli Centrale, and Department of Medical Area, University of Udine, Ple S M della Misericordia 15, Udine 33100, Italy.
Email: mario.tiribelli@uniud.it

Abstract

Background: Imatinib, dasatinib, and nilotinib are tyrosine kinase inhibitors (TKIs) approved in Italy for frontline treatment of chronic-phase chronic myeloid leukemia (CP-CML). The choice of TKI is based on a combined evaluation of the patient's and the disease characteristics. The aim of this study was to analyze the use of frontline TKI therapy in an unselected cohort of Italian patients with CP-CML to correlate the choice with the patient's features.

Methods: A total of 1967 patients with CP-CML diagnosed between 2012 and 2019 at 36 centers throughout Italy were retrospectively evaluated; 1089 patients (55.4%) received imatinib and 878 patients (44.6%) received a second-generation (2G) TKI.

Results: Second-generation TKIs were chosen for most patients aged <45 years (69.2%), whereas imatinib was used in 76.7% of patients aged >65 years ($p < .001$). There was a predominant use of imatinib in intermediate/high European long–term survival risk patients (60.0%/66.0% vs. 49.7% in low-risk patients) and a limited use

of 2G-TKIs in patients with comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, previous neoplasms, ischemic heart disease, or stroke and in those with >3 concomitant drugs. We observed a greater use of imatinib (61.1%) in patients diagnosed in 2018–2019 compared to 2012–2017 (53.2%; $p = .002$). In multivariable analysis, factors correlated with imatinib use were age > 65 years, spleen size, the presence of comorbidities, and ≥3 concomitant medications.

Conclusions: This observational study of almost 2000 cases of CML shows that imatinib is the frontline drug of choice in 55% of Italian patients with CP-CML, with 2G-TKIs prevalently used in younger patients and in those with no concomitant clinical conditions. Introduction of the generic formulation in 2018 seems to have fostered imatinib use.

KEYWORDS
CML, frontline therapy, imatinib, second-generation TKI, TKI

INTRODUCTION

Frontline treatment of chronic myeloid leukemia (CML) in chronic phase (CP) is based on tyrosine kinase inhibitors (TKIs) in virtually all patients.[1] At present, three TKIs have been approved for frontline treatment in Italy: imatinib and the second-generation (2G) TKIs dasatinib and nilotinib. All three drugs are highly effective in newly diagnosed CP-CML, which grants a long-term overall survival (OS) that is now approaching that of the general population.[2,3] Second-generation TKIs have been associated with more rapid and deeper molecular responses compared to imatinib but without significant differences in OS.[4–6]

None of the published guidelines and recommendations[1,7,8] provide indications on which TKI should be used frontline, and the choice is based on a combined evaluation of the patient's and disease characteristics, notably age, the risk of progression as defined by Sokal or European long–term survival (ELTS) scores, the presence of comorbidities, and the use of concomitant medications. The preference of the treating physician's and patient's expectations, mostly in terms of a possible TKI discontinuation and in some cases economic considerations, particularly after the advent of generic imatinib, may also play a role in TKI selection.

To date, few data are available on frontline TKI use within an entire country and on the possible drivers of treatment choice. The aim of the present work was to analyze the use of frontline TKIs in a large, unselected cohort of Italian patients diagnosed with CP-CML after the approval of dasatinib and nilotinib and to correlate patients' features to drug choice.

MATERIALS AND METHODS

The Registro Italiano LMC (Italian CML Registry) is an initiative of the GIMEMA group to register in a dedicated web-based database (https://www.epiclin.it/lmc) all adult cases (aged >18 years) of CML diagnosed since 2012 at 68 hematology centers widespread throughout the entire Italian territory.[9] The "Campus CML" is an active research network of more than 50 Italian physicians involved in the management of CML throughout the country, with the aim of investigating different aspects of the disease.

The present work is a retrospective analysis of 1967 patients diagnosed with CML in CP at 36 centers between January 2012 and December 2019. All participating centers were recommended to include all cases referred to them during the study period to avoid as much as possible selection biases; the number of enrolled patients reflects the estimated incidence of CML in Italy.

The clinical features recorded were age, gender, standard laboratory data, spleen size, CML risk according to Sokal and ELTS scores,[10,11] concomitant diseases, and concurrent medications at the time of CML diagnosis.

The study was approved by the local ethics committees at the participating centers; all patients were registered after providing informed consent.

Statistical analysis

Continuous variables have been reported as median and interquartile range (IQR), and categorical variables have been reported as the count and relative frequency of each category. Comparisons of quantitative variables between groups of patients were performed by the Wilcoxon–Mann–Whitney test or Student *t*-test, and the association between categorical variables was tested by the Fisher exact test or χ^2 test as appropriate.

Statistical analyses were performed by using a standard statistical package (SPSS for Windows Version 25.0; Chicago, Illinois).

RESULTS

Baseline characteristics of the entire population

The main clinical features at diagnosis of the entire cohort are reported in Table 1. Median age at diagnosis was 59.3 years (IQR, 46.6–

TABLE 1 Clinical features of the whole cohort and corresponding frontline TKI treatment.

	All patients (*N* =1967)	Frontline imatinib (*n* =1089)	Frontline 2G-TKI (*n* =878)	*p*
Gender, male/female, No. (%)	1140/827 (58.0/42.0)	646/443 (59.3/40.7)	493/385 (56.1/43.9)	.166
Median age (IQR), years	59.3 (46.6–71.2)	66.3 (55.2–75.4)	50.6 (40.1–62.1)	<.001
Hb (IQR), g/dL	12.6 (10.9–14.0)	12.7 (11.2–14.0)	12.4 (10.5–14.1)	.038
WBC (IQR), $\times 10^9$/L	60.1 (29.6–139.0)	52.1 (26.8–105.2)	78.7 (34.3–176.3)	<.001
PLTS (IQR), $\times 10^9$/L	354 (243–552)	343 (239–547)	363 (249–570)	.047
Spleen, No. evaluable (%)	1900	1046	854	<.001
Not palpable	1027 (54.1)	636 (60.8)	391 (45.8)	
<5 cm below costal margin	541 (28.5)	298 (28.5)	243 (28.4)	
≥5 cm below costal margin	332 (17.4)	112 (10.7)	220 (25.8)	
Sokal score, No. evaluable (%)	1880	1034	846	.056
Low	731 (38.9)	364 (35.2)	367 (43.3)	
Intermediate	863 (45.9)	522 (50.5)	341 (40.4)	
High	286 (15.2)	148 (14.3)	138 (16.3)	
ELTS score, No. evaluable (%)	1835	1007	828	<.001
Low	1044 (56.9)	519 (51.6)	525 (63.4)	
Intermediate	573 (31.2)	344 (34.1)	229 (27.6)	
High	218 (11.9)	144 (14.3)	74 (9.0)	
Arterial hypertension, No. (%)	764 (38.9)	526 (48.3)	238 (27.1)	<.001
Diabetes, No. (%)	222 (11.3)	157 (14.4)	65 (7.4)	<.001
Previous neoplasm, No. (%)	266 (13.5)	193 (17.7)	73 (8.3)	<.001
COPD, No. (%)	152 (7.7)	109 (10.0)	43 (4.9)	<.001
Ischemic heart disease, No. (%)	137 (7.7)	119 (10.9)	18 (2.0)	<.001
Cerebrovascular events, No. (%)	51 (2.6)	47 (4.3)	4 (0.4)	<.001
Other vascular diseases, No. (%)	145 (7.4)	118 (10.8)	27 (3.0)	<.001
Concomitant drugs, No. evaluable (%)	1874	1009	865	<.001
0	713 (38.0)	252 (25.0)	461 (53.3)	
1–2	511 (27.3)	270 (26.8)	241 (27.8)	
3–5	405 (21.6)	286 (28.3)	119 (13.8)	
>5	245 (13.1)	201 (19.9)	44 (5.1)	

Abbreviations: 2G-TKI, second-generation tyrosine kinase inhibitor; COPD, chronic obstructive pulmonary disease; ELTS, European long–term survival; Hb, hemoglobin; IQR, interquartile range; PLTS, platelets; WBC, white blood cell.

71.2), with 446 patients (22.7%) aged <45 years, 766 (38.9%) aged between 45 and 65 years, and 755 (38.4%) aged >65 years; 1140 patients (58.0%) were males.

Among 1881 evaluable patients, the CML risk according to the Sokal score was low in 731 patients (38.9%), intermediate in 864 (45.9%), and high in 286 (15.2%); among 1836 evaluable patients, 1044 (56.8%), 574 (31.3%), and 218 (11.9%) fell into low-, intermediate-, and high-risk categories, respectively, according to the novel ELTS score.

With regard to comorbidities, 1368 patients (69.5%) reported at least one active or previous disease at the time of CML diagnosis, the most common being arterial hypertension (n = 764; 38.9%), a previous neoplasm (n = 266; 13.5%), diabetes (n = 222; 11.3%), chronic bronchopulmonary diseases (n = 152; 7.7%), and a history of acute myocardial infarction (AMI)/ischemic heart disease (n = 137; 7.0%), stroke (n = 51; 2.6%), and other vascular diseases (n = 145; 7.4%). Among 1875 evaluable patients, 1161 (61.9%) were taking at least one concomitant medication, with 405 (21.6%) taking three to five drugs and 245 (13.1%) taking six or more drugs at the time of the TKI start.

There was a clear association between age and number of concomitant medications: among patients taking no drugs at the time

of starting the TKI, 45.8% were aged <45 years, 40.6% were aged 45–65 years, and only 13.6% were aged >65 years. For patients taking one or two concomitant medications the percentages of the three age classes were 12.5%, 48.0%, and 39.5%; in those taking three to five drugs the percentages of the three age classes were 1.8%, 32.7%, and 65.5%; and in those taking more than five drugs the percentages of the three age classes were 1.4%, 21.4%, and 77.1%, respectively.

Characteristics according to frontline TKIs

With regard to frontline therapy, 1089 patients (55.4%) received imatinib and 878 (44.6%) were treated with a 2G-TKI: 555 patients (28.2% of the entire cohort) received nilotinib and 319 (16.2% of the entire cohort) received dasatinib; only four patients were treated frontline with bosutinib in the context of a clinical trial. The main clinical features of patients at diagnosis according to the type of frontline TKI are reported in Table 1.

Among the 1089 patients treated frontline with imatinib, 941 (86.4%) received the standard dose (400 mg/day), whereas in 148 patients (13.6%) a reduced dose (<400 mg/day) was given. Among the 555 patients treated frontline with nilotinib, 22 (3.9%) were treated with a reduced dose (<600 mg/day), and 22 of the 319 patients (6.9%) received a reduced dose of dasatinib (<100 mg/day). Reasons for starting with a reduced dose were not available for single cases; however, the median age of patients receiving reduced doses was significantly higher than for patients starting at the standard dose: 77.5 years (IQR, 72.6–81.9) for imatinib, 74.1 years (IQR, 68.6–77.8) for dasatinib, and 53.1 years (IQR, 46.1–71.0) for nilotinib.

The main clinical features at diagnosis were evaluated by univariate analysis to find whether they played a role in the choice of frontline TKI treatment. According to age, 2G-TKIs were chosen for most patients aged <45 years (309 of 446; 69.2%), whereas imatinib was used in most patients aged >65 years (579 of 755; 76.7%) ($p < .001$); among patients aged 45–65 years, the use of imatinib or a 2G-TKI was similar (Figure 1).

There was a predominance of imatinib use in the intermediate but not in the low and high Sokal risk scores (49.8% low, 60.5% intermediate, and 51.4% high) and in intermediate/high ELTS risk scores (49.7% low, 60.0% intermediate, and 66.0% high).

A prevalent use of 2G-TKIs was also observed in patients presenting with higher white blood cell (WBC) counts (56.5% with WBC $\geq 100 \times 10^9$/L vs. 38.4% with WBC $< 100 \times 10^9$/L; $p < .001$), lower hemoglobin (Hb) levels (55.7% with Hb < 10 g/dL vs. 42.2% with Hb ≥ 10 g/dL; $p = .001$), and a bigger spleen enlargement (66.2% with a spleen >5 cm below the costal margin vs. 44.9% with a spleen of 1–5 cm vs. 38.0% with a nonpalpable spleen; $p < .001$) (Figure 2).

There was a decreasing use of 2G-TKIs with a higher number of concomitant drugs: 64.6% for patients not taking concomitant drugs, 47.1% with one or two drugs, 29.3% with three to five drugs, and 17.9% for more than five drugs ($p < .001$) (Figure 3). Concordantly, there was a significantly higher use of imatinib in patients with hypertension (68.8%), diabetes (70.7%), chronic obstructive pulmonary disease (71.7%), a previous neoplasm (72.5%), and a history of AMI/

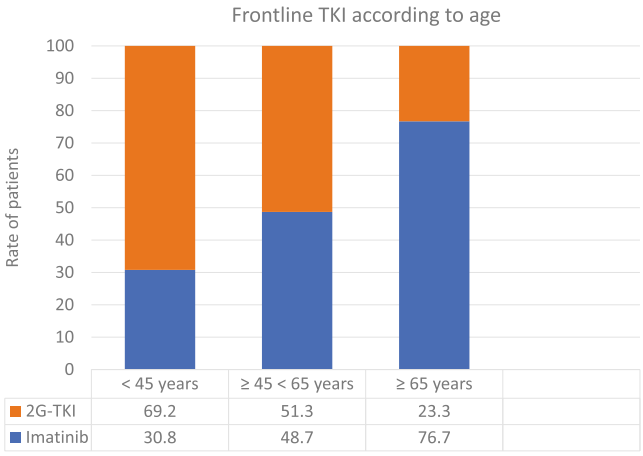

FIGURE 1 Distribution of frontline TKI according to age group. 2G-TKI indicates second-generation tyrosine kinase inhibitor.

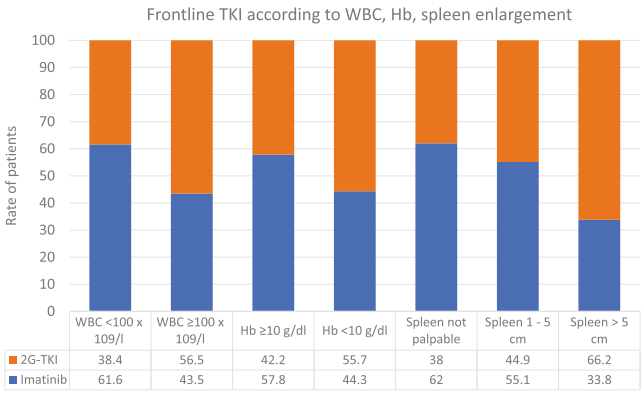

FIGURE 2 Distribution of frontline TKI according to clinical and laboratory features. 2G-TKI indicates second-generation tyrosine kinase inhibitor; Hb, hemoglobin; WBC, white blood cell.

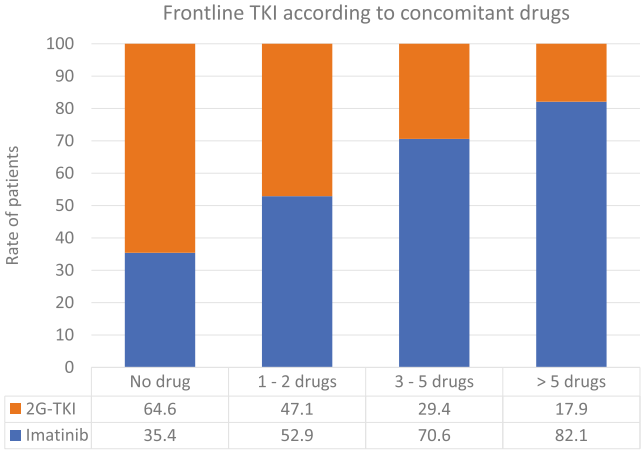

FIGURE 3 Distribution of frontline TKI according to the number of concomitant medications. 2G-TKI indicates second-generation tyrosine kinase inhibitor.

ischemic heart disease (86.8%) or stroke (92.1%) ($p < .001$ for all conditions) (Figure 4).

When the time frame of our analysis was divided into two periods, in accordance with the approval of generic imatinib in Italy (2017), we observed a greater use of imatinib (61.1%) in patients diagnosed in 2018–2019 compared to those of the 2012–2017 period (53.2%; $p = .002$). An increment of imatinib prescription after becoming generic was observed only in patients aged >45 years, whereas in patients aged <45 years there was no significant difference in imatinib use between the years 2012–2017 (31.7%) and 2018–2019 (27.7%; $p = .56$). In multivariable logistic regression analysis, the factors independently correlated with the choice of imatinib as frontline treatment were age >65 years, spleen enlargement <5 cm below the costal margin, the presence of comorbidities (second neoplasia, AMI/ischemic heart disease, and stroke), and the number of concomitant medications ≥3, as shown in Table 2.

DISCUSSION

With the availability of imatinib and 2G-TKIs in most countries, hematologists treating patients with CML have different options for frontline therapy, a situation sometimes referred to as an "embarrassment of riches." Because no clear benefit in OS has been reported by randomized clinical trials when imatinib was compared with 2G-TKIs,[4–6,12] possibly due to the efficacy of second-line treatment with a 2G-TKI after imatinib failure,[13] all published guidelines and recommendations substantially indicate any TKI as appropriate in the frontline setting. Thus, the choice is largely left to the treating clinicians, who must weigh the characteristics of the disease, the patient's features and preferences, and sometimes also personal experience with the different TKIs and economic issues.

The major limits of the present study are its retrospective nature and the lack of decision tracking about the selection of a specific TKI for each individual patient. Nonetheless, our analysis included almost 2000 patients newly diagnosed with CML treated in many hematology units, both in academic and tertiary hospitals, widespread throughout the entire Italian territory. To the best of our knowledge, this is the largest real-life cohort in which determinants for frontline TKI choice have been addressed. Moreover, the choice of imatinib or a 2G-TKI was not biased by competing clinical trials because the only protocol active during the study period was the GIMEMA SUSTRENIM trial that randomized patients with CML 1:1 to frontline treatment with nilotinib or imatinib followed by a switch to nilotinib in case of a nonoptimal response.[14]

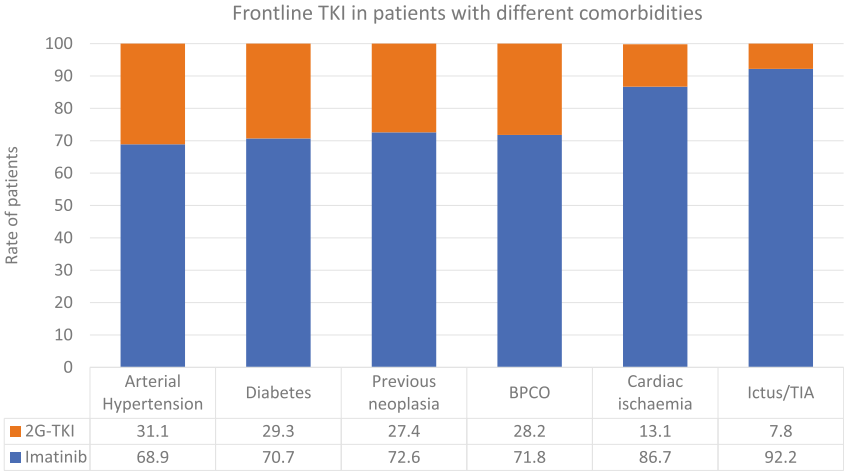

FIGURE 4 Distribution of frontline TKI according to selected concomitant diseases. 2G-TKI indicates second-generation tyrosine kinase inhibitor; BPCO, broncopulmonary chronic obstruction; TIA, transient ischemic attack.

TABLE 2 Independent clinical features associated with the choice of frontline imatinib by multivariate logistic regression.

	Odds ratio	95% confidence interval	*p*
Age > 65 years	3.008	2.378–3.805	<.001
Spleen enlargement < 5 cm	2.139	1.627–2.812	<.001
Concomitant medications ≥ 3	1.929	1.499–2.483	<.001
Previous neoplasia	1.640	1.181–2.278	.003
AMI/ischemic heart disease	2.756	1.571–4.836	<.001
Stroke/TIA	4.170	1.432–12.143	.009

Abbreviations: AMI, acute myocardial infarction; TIA, transient ischemic attack.

The results of this observational study demonstrate that approximately 55% of Italian patients newly diagnosed with CP-CML in the last decade received imatinib as a frontline therapy. In a retrospective French study on 507 patients diagnosed with CML between 2006 and 2016, 388 (76.5%) received imatinib and 114 (22.5%) received nilotinib or dasatinib as frontline treatment.[15] Similar figures emerged from the real-life study conducted between 2015 and 2017 in 257 patients treated at 21 tertiary centers and general hospitals in the United Kingdom, where imatinib was the frontline TKI in most patients (79%).[16] The reasons for the TKI choice were recorded for fewer than half of the patients and seemed to be a result of physicians' preference for a "standard" approach.

We found that the use of a 2G-TKI was prevalent in younger patients and in those with no concomitant clinical conditions. The former result is probably related to the higher rates of deep molecular responses (DMRs) associated with the use of 2G-TKIs compared to imatinib. In the ENESTnd study, the cumulative rate of molecular response 4.5 (MR4.5) at 5 years with nilotinib 300 mg twice daily was 54% compared to 31% with imatinib 400 mg daily.[17] With dasatinib 100 mg daily the cumulative 5-year MR4.5 rate was 42%, compared to 33% for imatinib 400 mg daily.[5] Because a DMR is a prerequisite for treatment discontinuation, the so-called treatment-free remission (TFR), it is arguable that the possibility of stopping a TKI was particularly appealing for younger patients. This has been highlighted in the survey that led to the formulation of a consensus paper from the GIMEMA CML Working Party aimed at identifying the treatment policies that could increase the possibility of a TFR.[18] There was a high concordance among Italian CML experts that 2G-TKIs should be preferred in all patients under the age of 40 years and in non–low risk patients aged 41–65 years, and data from the present study seem to confirm that in clinical practice these suggestions have been applied. A subanalysis among 266 Italian patients with CML enrolled in the SIMPLICITY trial reported that patients receiving frontline dasatinib ($n = 56$) had a relatively high median age, approximately 62 years.[19] Although we do not have the exact number of patients registered in both SIMPLICITY and the present study, we can estimate that patients enrolled in both analyses represent no more than 5% of the total population we studied; the median age of dasatinib-treated patients in SIMPLICITY was higher although not directly comparable to our experience because we cumulatively reported patients treated with 2G-TKIs. Approximately 10% of our patients (192 of 1967) started TKIs at a lower dose, mostly imatinib >400 mg/day (148 of 1089; 13.6%); patients receiving low doses were elderly, which thus points to age as a major determinant in this decision.

All concomitant conditions besides CML led to a preferential use of imatinib over 2G-TKIs. The estimated impact of any examined comorbidity ranged from a rate of increased imatinib use approximately 15%–25% for arterial hypertension and diabetes (70% imatinib compared to 47% and 54% in patients without hypertension or diabetes, respectively) to over 30% for previous AMI/heart ischemic disease (86% vs. 54%) and over 40% for patients with a history of stroke (97% vs. 55%). It is well known that nilotinib has been associated with an increased risk of peripheral arterial thrombosis and diabetes and dasatinib has been associated with different pleuropulmonary diseases,[20] and that the presence of comorbidities, such as arterial hypertension, may also enhance the risk of developing specific toxicities during TKI therapy. In a study from The University of Texas MD Anderson Cancer Center in 531 patients with CML treated with different TKIs, 237 patients (45%) developed cardiovascular events and, among them, hypertension was seen in 175 (74%).[21] A real-life Swedish study on 1238 TKI-treated patients diagnosed with CP-CML between 2002 and 2017 showed an increased incidence ratio (IRR) of morbidity compared to matched healthy controls, with a significantly higher risk in patients treated with nilotinib or dasatinib, mainly for acute myocardial infarction (IRR, 2.9 for nilotinib), chronic ischemic heart disease (IRR, 2.2 for nilotinib), pleural effusion (IRR, 11.6 for dasatinib), and upper respiratory infections (IRR, 3.0 for dasatinib).[22]

Quite unexpectedly, we observed a greater use of imatinib among patients with high-risk CML, although it is known that 2G-TKIs are associated with a lower rate of progression in this subset.[4] The counterintuitive finding of imatinib prevalence might be explained by the older age of high-risk patients because age is a parameter included in both the Sokal and ELTS scores. The number of subjects with high Sokal risk was 42 of 420 (10%) in evaluable patients aged <45 years compared to 158 of 721 (21.9%) in evaluable patients aged >65 years (21.9%), which highlights the relevance of the parameter age in the risk calculation. Among the 42 high-risk patients aged <45 years, nine received frontline imatinib and 33 received frontline 2G-TKIs. Furthermore, the increased rate of 2G-TKI use in patients with more "aggressive" features at baseline, such as bigger spleen enlargement, higher WBC counts, and lower Hb levels, points to the attention of responsible physicians to signs of high-risk disease.

Lastly, the introduction of the generic formulation in 2018 seems to have fostered the use of imatinib because no significant difference in efficacy or toxicity has been reported with the switch from the branded preparation to generic imatinib[23–25] with a consistent economic advantage. We feel that financial issues could have had a role in this trend, but they are coupled with increasing evidence of similar overall survival with imatinib and 2G-TKIs and with different goals of the treatment (e.g., TFR in younger patients and disease control in elderly ones).

In conclusion, the present availability of three different TKI drugs (imatinib, dasatinib, and nilotinib) makes the choice of frontline treatment of patients newly diagnosed with CML a tailored decision for each single case. In the real-life setting, this points to the physicians' judgment and to the consequent need for their continual training and comparison of data and experiences. In the present work, we have not focused on the efficacy or tolerability of the treatments because the main goal was describing possible patrons when choosing among the different TKIs available; nonetheless, given the importance of correlating present data with clinical outcomes, we are planning further analyses of this large data set of patients with CML.

AFFILIATIONS

[1]Division of Hematology and Bone Marrow Transplant, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy

[2]Department of Medical Area, University of Udine, Udine, Italy

[3]Hematology Unit, Ospedale Belcolle, Viterbo, Italy

[4]Hematology, Department of Precision and Translational Medicine, "Sapienza" University, Rome, Italy

[5]Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy

[6]Hematology Department, San Bortolo Hospital, Vicenza, Italy

[7]Hematology Unit, University of Ferrara, Ferrara, Italy

[8]Division of Hematology, Foundation IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy

[9]Hematology Section, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

[10]Hematology, San Giovanni Hospital, Rome, Italy

[11]Hematology, University of Messina, Messina, Italy

[12]Hematology Unit, Presidio Ospedaliero Moscati, Aversa, Italy

[13]Institute of Hematology, Fondazione Policlinico Universitario A. Gemelli IRCCS, and Department of Radiological and Hematological Sciences, Cattolica University, Rome, Italy

[14]Section of Hematology, Department of Medicine, University of Verona, Verona, Italy

[15]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

[16]Hematology, Vito Fazzi Hospital, Lecce, Italy

[17]Hematology, Ospedale San Giuseppe Moscati, Taranto, Italy

[18]Hematology and Clinical Immunology, Department of Medicine, University of Padua, Padua, Italy

[19]Hematology, Ospedale Maggiore della Carità di Novara, University of Eastern Piedmont, Novara, Italy

[20]Hematology Unit, Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona, Italy

[21]Hematology Unit, Azienda Ospedaliero Universitaria Sant'Andrea, Rome, Italy

[22]Hematology Unit, Dell'Angelo Hospital, Venezia-Mestre, Italy

[23]Division of Hematology, Sant'Elia Hospital, Caltanissetta, Italy

[24]Division of Hematology, S. Eugenio Hospital, Rome, Italy

[25]Hematology Section and Bone Marrow Transplant Unit, Rodolico Hospital, Azienda Ospedaliero Universitaria Policlinico "Rodolico-San Marco", Catania, Italy

[26]Hematology, Azienda Ospedaliera Santa Croce e Carle, Cuneo, Italy

[27]Onco-Hematology Department, Azienda Ospedaliera Santa Maria, Terni, Italy

[28]Hematology, Bianchi-Melacrino-Morelli Hospital, Reggio Calabria, Italy

[29]Hematology, Azienda Ospedaliero Universitaria Senese, Siena, Italy

[30]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

[31]Hematology, Cervello Hospital, Palermo, Italy

[32]Hematology and Stem Cell Transplant Unit, Azienda Ospedaliero Universitaria, Parma, Italy

[33]Hematology, San Carlo Hospital, Potenza, Italy

[34]Hematology, San Raffaele Hospital, Milan, Italy

[35]Hematology, University of Pisa, Pisa, Italy

[36]Division of Hematology and Internal Medicine, "San Luigi Gonzaga" University Hospital, Turin, Italy

AUTHOR CONTRIBUTIONS

Mario Tiribelli: Study design, analysis, data interpretation, and writing–original draft. **Roberto Latagliata**: Study design, analysis, data interpretation, and writing–original draft. **Massimo Breccia**: Writing–review and editing. **Isabella Capodanno**: Data collection. **Maria Cristina Miggiano**: Data collection. **Francesco Cavazzini**: Data collection. **Cristina Bucelli**: Data collection. **Immacolata Attolico**: Data collection. **Sabrina Leonetti Crescenzi**: Data collection. **Sabina Russo**: Data collection. **Mario Annunziata**: Data collection. **Federica Sorà**: Data collection. **Massimiliano Bonifacio**: Data collection. **Olga Mulas**: Data collection. **Giuseppina Loglisci**: Data collection. **Alessandro Maggi**: Data collection. **Gianni Binotto**: Data collection. **Elena Crisà**: Data collection. **Anna Rita Scortechini**: Data collection. **Anna Paola Leporace**: Data collection. **Rosaria Sancetta**: Data collection. **Pamela Murgano**: Data collection. **Elisabetta Abruzzese**: Data collection. **Fabio Stagno**: Data collection. **Davide Rapezzi**: Data collection. **Debora Luzi**: Data collection. **Iolanda Vincelli**: Data collection. **Monica Bocchia**: Data collection. **Carmen Fava**: Data collection. **Alessandra Malato**: Data collection. **Monica Crugnola**: Data collection. **Michele Pizzuti**: Data collection. **Francesca Lunghi**: Data collection. **Sara Galimberti**: Data collection. **Matteo Dalmazzo**: Data collection. **Renato Fanin**: Writing–review and editing. **Emilia Scalzulli**: Data collection. **Robin Foà**: Writing–review and editing. **Alessandra Iurlo**: Writing–review and editing. **Giuseppe Saglio**: Writing–review and editing. **Giorgina Specchia**: Writing–review and editing.

CONFLICT OF INTEREST STATEMENT

Mario Tiribelli has been a consultant for Bristol-Myers Squibb, Incyte, and Novartis. Massimo Breccia has been an expert witness for Incyte, Pfizer, and Novartis. Cristina Bucelli has been a consultant for the Novartis Foundation for Sustainable Development. Elena Crisà has been a consultant for IRCCS Candiolo. Anna Rita Scortechini has been a consultant for 3B Medical. Anna Paola Leporace has been a consultant for Azienda Ospedaliera Sant'Andrea di Roma. Elisabetta Abruzzese has been a consultant for Instituto Científico Pfizer, Bristol-Myers Squibb, Incyte, and Novartis. Fabio Stagno has been a consultant for Novartis, Incyte, and Pfizer. Davide Rapezzi has received travel support from Novartis and Incyte. Monica Bocchia has been a consultant for Novartis and Incyte. Monica Crugnola has been a consultant for Novartis. Robin Foà has been an expert witness for Amgen and Novartis. The other authors declare no conflicts of interest.

ORCID

Mario Tiribelli https://orcid.org/0000-0001-9449-2621
Roberto Latagliata https://orcid.org/0000-0002-7741-862X
Massimo Breccia https://orcid.org/0000-0003-1163-6162
Massimiliano Bonifacio https://orcid.org/0000-0003-0716-1686
Elisabetta Abruzzese https://orcid.org/0000-0001-5228-6491
Alessandra Iurlo https://orcid.org/0000-0002-4401-0812

REFERENCES

1. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966-984. doi:10.1038/s41375-020-0776-2
2. Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2016;34(24):2851-2857. doi:10.1200/jco.2015.66.2866
3. Maas CCHM, van Klaveren D, Ector GICG, et al. The evolution of the loss of life expectancy in patients with chronic myeloid leukaemia: a population-based study in the Netherlands, 1989–2018. *Br J Haematol*. 2022;196(5):1219-1224. doi:10.1111/bjh.17989
4. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia*. 2021;35(2):440-453. doi:10.1038/s41375-020-01111-2
5. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients trial. *J Clin Oncol*. 2016;34(20):2333-2340. doi:10.1200/jco.2015.64.8899
6. Vener C, Banzi R, Ambrogi F, et al. First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. *Blood Adv*. 2020;4(12):2723-2735. doi:10.1182/bloodadvances.2019001329
7. National Comprehensive Cancer Network. *Chronic Myeloid Leukemia. Version 3.2022*. National Comprehensive Cancer Network; 2022. NCCN Clinical Practice Guidelines in Oncology.
8. Smith G, Apperley J, Milojkovic D, et al. A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. *Br J Haematol*. 2020;191(2):171-193. doi:10.1111/bjh.16971
9. Specchia G, Pregno P, Breccia M, et al. Prognostic factors for overall survival in chronic myeloid leukemia patients: a multicentric cohort study by the Italian CML GIMEMA Network. *Front Oncol*. 2021;11:739171. doi:10.3389/fonc.2021.739171
10. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood*. 1984;63(4):789-799. doi:10.1182/blood.v63.4.789.789
11. Pfirrmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. *Leukemia*. 2020;34(8):2138-2149. doi:10.1038/s41375-020-0931-9
12. Brümmendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. *Br J Haematol*. 2015;168(1):69-81. doi:10.1111/bjh.13108
13. Tiribelli M, Bonifacio M, Binotto G, et al. Excellent outcomes of 2G-TKI therapy after imatinib failure in chronic phase CML patients. *Oncotarget*. 2018;9(18):14219-14227. doi:10.18632/oncotarget.24478
14. Pane F, Luciano L, Pugliese N, et al. International prospective study comparing nilotinib versus imatinib with early switch to nilotinib to obtain sustained treatment-free remission in patients with chronic myeloid leukemia. A GIMEMA and HOVON study. *Blood*. 2018;132(suppl 1):1750. doi:10.1182/blood-2018-99-118925
15. Canet J, Cony-Makhoul P, Orazio S, et al. Second- or third-generation tyrosine kinase inhibitors in first-line treatment of chronic myeloid leukemia in general population: is there a real benefit? *Cancer Med*. 2021;10(20):6959-6970. doi:10.1002/cam4.4186
16. Milojkovic D, Cross NCP, Ali S, et al. Real-world tyrosine kinase inhibitor treatment pathways, monitoring patterns and responses in patients with chronic myeloid leukaemia in the United Kingdom: the UK TARGET CML study. *Br J Haematol*. 2021;192(1):62-74. doi:10.1111/bjh.16733
17. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;30(5):1044-1054. doi:10.1038/leu.2016.5
18. Baccarani M, Abruzzese E, Accurso V, et al. Managing chronic myeloid leukemia for treatment-free remission: a proposal from the GIMEMA CML WP. *Blood Adv*. 2019;3(24):4280-4290. doi:10.1182/bloodadvances.2019000865
19. Abruzzese E, Bosi A, Breccia M, et al. Treatment patterns in patients with chronic-phase chronic myeloid leukaemia in routine clinical practice: the SIMPLICITY Italian population. *Mediterr J Hematol Infect Dis*. 2019;11(1):e2019025. doi:10.4084/mjhid.2019.025
20. Cortes J. How to manage CML patients with comorbidities. *Blood*. 2020;136(22):2507-2512. doi:10.1182/hematology.2020006911
21. Jain P, Kantarjian H, Boddu PC, et al. Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. *Blood Adv*. 2019;3(6):851-861. doi:10.1182/bloodadvances.2018025874
22. Dahlén T, Edgren G, Ljungman P, et al. Adverse outcomes in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: follow-up of patients diagnosed 2002–2017 in a complete coverage and nationwide agnostic register study. *Am J Hematol*. 2022;97(4):421-430. doi:10.1002/ajh.26463
23. Bonifacio M, Scaffidi L, Binotto G, et al. Safety and efficacy of switching from branded to generic imatinib in chronic phase chronic myeloid leukemia patients treated in Italy. *Leuk Res*. 2018;74:75-79. doi:10.1016/j.leukres.2018.09.018
24. Scalzulli E, Colafigli G, Latagliata R, et al. Switch from branded to generic imatinib: impact on molecular responses and safety in chronic-phase chronic myeloid leukemia patients. *Ann Hematol*. 2020;99(12):2773-2777. doi:10.1007/s00277-020-04096-1
25. Erçalışkan A, Seyhan Erdoğan D, Eşkazan AE. Current evidence on the efficacy and safety of generic imatinib in CML and the impact of generics on health care costs. *Blood Adv*. 2021;5(17):3344-3353. doi:10.1182/bloodadvances.2021004194

How to cite this article: Tiribelli M, Latagliata R, Breccia M, et al. Determinants of frontline tyrosine kinase inhibitor choice for patients with chronic-phase chronic myeloid leukemia: a study from the Registro Italiano LMC and Campus CML. *Cancer*. 2023;129(17):2637-2644. doi:10.1002/cncr.34923