



First-line treatment selection and early monitoring patterns in chronic phase-chronic myeloid leukemia in routine clinical practice: SIMPLICITY

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Funding information

Bristol-Myers Squibb (BMS). No financial support or compensation for publication was received by the authors of this manuscript. BMS funded medical writing services for this manuscript.

Abstract

Achieving successful outcomes in chronic phase-chronic myeloid leukemia (CP-CML) requires careful monitoring of cytogenetic/molecular responses (CyR/MR). SIMPLICITY (NCT01244750) is an observational study exploring tyrosine kinase inhibitor use and management patterns in patients with CP-CML receiving first-line imatinib ($n = 416$), dasatinib ($n = 418$) or nilotinib ($n = 408$) in the US and 6 European countries in routine clinical practice. Twelve-month follow-up data of 1242 prospective patients (enrolled October 01 2010-September 02 2015) are reported. 81% of patients had baseline comorbidities. Treatment selection was based on perceived efficacy over patient comorbidity profile. There was a predominance of imatinib-treated patients enrolled earlier in the study, with subsequent shift toward dasatinib- and nilotinib-treated patients by 2013/2014. Monitoring for either CyR/MR improved over time and was documented for 36%, 82%, and 95% of patients by 3, 6, and 12 months, respectively; 5% had no documentation of CyR/MR monitoring during the first year of therapy. Documentation of MR/CyR testing was higher in Europe than the US ($P < .001$) and at academic versus community practices ($P = .001$). Age < 65 years, patients being followed at sites within Europe, those followed at academic centers and patients no longer on first-line therapy were more likely to be monitored by 12 months. SIMPLICITY demonstrates that the NCCN and ELN recommendations on response monitoring have not been consistently translated into routine clinical practice. In the absence of appropriate monitoring practices, clinical response to TKI therapy cannot be established, any needed changes to treatment strategy will thus not be implemented, and long-term patient outcomes are likely to be impacted.

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1 | INTRODUCTION

Over the past 15 years the availability of tyrosine kinase inhibitors (TKIs) has transformed the natural history of chronic phase-chronic myeloid leukemia (CP-CML) from a terminal disease to treatable chronic illness.^{1,2} As a result, survival rates in patients with newly-diagnosed CP-CML approximate those in age-adjusted general populations.³⁻⁶

The European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) recommend imatinib (Gleevec®/Glivec®, Novartis), dasatinib (Sprycel®, Bristol-Myers Squibb) or nilotinib (Tasigna®, Novartis) as first-line therapy for CP-CML.^{7,8} All three agents, in research settings, enable CP-CML patients to achieve 1-year complete cytogenetic response (CCyR) rates of 69–80% and 5-year survival rates of 89–96%.⁹⁻¹³ Given availability of multiple first-line TKIs, patients and physicians have the opportunity to individualise initial treatment approaches by considering disease-, drug-, patient-, and physician-related factors, such as CML risk score, TKI safety profiles, patients' comorbidities, and economic considerations.¹⁴⁻¹⁶ However, it remains unclear how these factors influence TKI selection in routine clinical practice.

Once TKI therapy is initiated, careful monitoring of cytogenetic response (CyR) and molecular response (MR), using time-based “milestone” testing, is necessary to ensure optimal outcomes.^{8,17} Both the ELN and NCCN recommend, during the first year of TKI therapy, assessment of response every three months, with an emphasis on MR testing.^{7,8} Retrospective studies report improved overall survival among patients who achieve early MR, particularly at three and six months, further supporting the importance of response monitoring during the first year.^{18,19} Small studies conducted in routine clinical practice have reported, however, that patients may not be monitored as frequently as suggested.²⁰⁻²³

SIMPLICITY (NCT01244750) is an ongoing observational study of patients with CP-CML receiving first-line treatment with imatinib, dasatinib or nilotinib in the United States (US) and six European countries (Italy, Germany, Spain, France, the Netherlands and Russia). Its primary objective is to understand TKI use and management patterns in routine clinical practice. Preliminary monitoring patterns and predictors of monitoring have been reported previously.^{24,25} Here we report data in prospective patients with at least 12 months of follow-up (data cut: March 07 2017), focusing on baseline demographics, choice of first-line TKI and CyR/MR monitoring patterns.

2 | METHODS

SIMPLICITY includes three prospective cohorts of newly-diagnosed patients with CP-CML, ≥ 18 years at time of diagnosis, receiving first-line therapy with imatinib, dasatinib or nilotinib on or after October 01 2010 (Supporting Information Figure S1). Study sites include academic and private/community practices in France, Germany, Italy, the Netherlands, Russia, Spain and the US. Non-US sites were grouped and defined as “Europe”. Community practices were defined as small, private practices run by one or more independent physicians offering patient care on a local basis. Academic centers were defined as large,

hospital-based clinics or research units at universities, including centers of excellence, offering care on a regional/national basis. Enrollment began in each country after all three TKIs were approved and reimbursed in the first-line setting, except for France. The choice of TKI therapy was left to the discretion of the physician. Each cohort was closed when approximately 400 patients had been enrolled. Patients involved in ongoing CML clinical trials were excluded. The study protocol was approved by the relevant institutional review boards (IRBs) and patient consent obtained.

Testing for CyR is based either on chromosome banding analysis (CBA) or fluorescence in situ hybridization (FISH). CyR monitoring is categorized according to whether analysis was documented with a date present (with further categorization based on whether results are available or not) or not done (may include patients who were not tested due to progression). Testing with available results is classed as either “actionable” (for FISH data, if % Ph+ known and ≥ 200 evaluated nuclei; for bone marrow data, if % Ph+ known and ≥ 20 examined metaphases) or “not actionable” (includes all other available FISH and bone marrow data). Quantitative polymerase chain reaction (qPCR) used for MR was recorded whether or not it was reported using the international scale (IS). Frequency of testing for CyR or MR within 3, 6, and 12 months from initiation of first-line TKI includes patients with at least 3, 6, and 12 months of follow-up, respectively, and includes assessments performed between ≥ 30 days and each respective time-point. CyR and MR monitoring was analyzed for the total prospective population, and by year of TKI initiation, region (US or Europe) and practice type. In the US, CyR and MR monitoring was also analyzed according to the patient's insurance status (insured vs. noninsured).

Descriptive statistics are presented and *P* values were calculated using a chi-square test for categorical comparisons and Fisher's exact test in the case of small cell counts. For variables with skewed distribution (age), *P* values were calculated using the Wilcoxon two-sample test. No corrections were made for multiple comparisons. Multivariable logistic regression was performed to assess predictors of monitoring. Candidate predictors included age, sex, region, practice type, first-line TKI, Eastern Cooperative Oncology Group (ECOG) performance status, whether the patient was still on first-line TKI at the end of the monitoring period, whether the patient had Sokal or Hasford risk score, and year of first-line TKI initiation. Separate regressions were performed for three binary outcomes: testing for CyR and/or MR performed within (i) 3, (ii) 6, and (iii) 12 months of TKI initiation. A separate regression was also performed for the US to understand whether insurance status had any association with response monitoring. Multivariable models used backward elimination methods, removing variables that did not retain significance at the 0.05 level.

3 | RESULTS

3.1 | Study population

SIMPLICITY includes 241 sites (Europe; $n = 91$, US; $n = 150$). From 208 sites, 1242 patients were enrolled prospectively into the study between October 01 2010 and September 02 2015 (data download March 07 2017; Supporting Information Figure S1). Patients received

first-line imatinib ($n = 416$; median follow-up [interquartile range; IQR] 58.8 [48.7–60.0] months), dasatinib ($n = 418$; median follow-up [IQR] 45.9 [36.1–57.5] months) or nilotinib ($n = 408$; median follow-up [IQR] 46.7 [34.5–59.1] months).

There were more imatinib-treated patients enrolled earlier in the study (leading to earlier closure of this cohort [June 26, 2013]): 50.7% and 40.8% in 2010 and 2012, respectively. In contrast, 48.7% and 44.0% of patients in 2013 and 51.9% and 48.1% of patients in 2014 were treated with first-line dasatinib and nilotinib, respectively (Supporting Information Figure S2). The distribution of patients across the US and Europe, and between academic and private/community practices, is shown in Supporting Information Figure S3. 55% of the US sites were private/community practices compared with 41% of the sites in Europe.

Patient demographics are shown in Table 1. The overall median age (IQR; min, max) of patients at diagnosis was 56.6 (46.0–67.7; 17.7, 90.7) years. Median (IQR; min, max) age at time of initiation of first-line treatment was slightly higher in the imatinib group compared with the dasatinib and nilotinib groups: 59.7 years (47.3–70.2; 18.4, 89.6) vs. 56.3 (46.0–66.9; 19.1, 90.0) and 54.1 years (44.6–65.8; 17.7, 90.8), respectively ($P < .001$ for first vs. second generation TKI comparison). Demographics and clinical characteristics were similar for patients enrolled in the US versus Europe, and in academic centers versus community practices. Approximately a third of all patients had either a Sokal or Hasford score recorded. Median (IQR) age at first-line TKI was similar for patients who had a Sokal or Hasford score (56.3 years [45.3–68.2]) and those who did not (56.8 years [46.8–67.6]). Patients with a risk score have fewer median comorbidities (IQR) than those without (2.0 [0.0–3.0] vs. 3.0 [1.0–5.0], respectively). Additionally, a greater proportion of patients with a risk score are fully active (ECOG 0) than those without (40.7% vs. 32.0%, respectively).

In total, 1010 patients (81%) had baseline comorbidities, with a similar proportion reported in each TKI cohort (imatinib: 84%; dasatinib: 83%; nilotinib: 77%). The median (IQR) number of baseline comorbidities was 2.0 (1.0–4.0). A greater proportion of patients receiving nilotinib had no baseline comorbidities compared with other first-line TKIs (imatinib: 16%; dasatinib: 17%; nilotinib: 23%; $P = .029$). In each TKI cohort, a higher proportion of patients had ≥ 4 comorbidities (range: 30.4–32.2%), compared with 1, 2, or 3 baseline comorbidities (range: 13.0–18.5%). 45% of patients had CV comorbidities (imatinib: 50%; dasatinib: 46%; nilotinib: 41%), including hypertension (all TKIs: 36%; imatinib: 41%, dasatinib: 36%, nilotinib: 31%), hyperlipidemia (all TKIs: 20%; imatinib: 20%, dasatinib: 23%, nilotinib: 17%) and diabetes (all TKIs: 11%; imatinib: 14%, dasatinib: 11%, nilotinib: 9%). GI comorbidities were reported in 25% of patients (imatinib: 28%, dasatinib: 23%, nilotinib: 24%; 36% specified gastro-oesophageal reflux disease), and 18% had respiratory comorbidities (imatinib: 17%, dasatinib: 19%, nilotinib: 17%).

3.2 | Physicians' selection of first-line TKI

In 53% of patients, the primary reason cited by the treating physician for selecting first-line TKI was (perceived) "effectiveness". Other reasons that were primary drivers for treatment choice in SIMPLICITY patients included familiarity (11.2%), cost efficiency (10.2%), comorbidities (9.2%), and tolerability (6.4%). The median (IQR) number of

baseline comorbidities, in patients whose primary reason for physician selection of first-line TKI was comorbidities, was 3.0 (1.0–5.0); 58% of these patients had CV comorbidities.

3.3 | CyR and MR monitoring patterns

Among patients followed for at least 12 months, the median (IQR) time from initiation of first-line TKI to the end of follow-up was 52.4 (38.3–60.0) months. Median (IQR) follow-up times were shorter at European versus US sites (51.3 [38.2–59.5] versus 53.5 [38.3–60.0] months), owing to a lag in enrollment at European sites due to delayed site start-ups. Follow-up times were similar between academic centers and community practices (52.0 [38.2–60.0] and 52.8 [38.6–60.0] months, respectively).

Not all patients had documented CyR monitoring during the first 12 months of TKI therapy (Supporting Information Figure S4). Monitoring for either CyR/MR was documented for 36%, 82%, and 95% of patients by 3, 6, and 12 months (Table 2). Five percent of patients had no documentation of CyR/MR monitoring during the first year of TKI therapy. The median (IQR) number of CyR and/or MR tests documented by 12 months was 5.0 (3.0–6.0).

Testing was more frequently performed in Europe compared with the US; by 12 months, the proportion of patients tested for CyR/MR was 99% vs. 94% in Europe vs. the US, respectively; $P < .001$. A small proportion of patients had no documentation of CyR or MR monitoring during the first year of TKI therapy in Europe and the US (1% and 6% of patients, respectively). Similarly, testing was more frequently performed at academic centers than community practices. At 3 months, 40.1% of patients were tested for CyR/MR at academic centers compared with 31.3% at community practices. By 12 months, 97.3% at academic centers vs. 93.4% in community practices had documentation of CyR/MR testing ($P = .001$).

3.3.1 | CyR monitoring patterns

The proportion of patients with documentation of CyR monitoring increased with longer patient follow-up; at 3 months only 16% of patients had been tested for CyR, but this increased to 40% by 6 months and 55% by 12 months ($P < .001$). Of these, 92% (88% "actionable"; 12% "not actionable"), 90% (92% "actionable"; 8% "not actionable") and 89% (93% "actionable"; 7% "not actionable") of patients had CyR results available by 3, 6, and 12 months, respectively (Table 2).

A greater proportion of patients in Europe had documentation of CyR monitoring compared with the US by 3, 6 and 12 months, respectively (21% vs. 13%, 51% vs. 34% and 66% vs. 49%; $P < .001$ for each; Table 2). A greater proportion of patients had documented CyR monitoring at academic centers compared with community practices by 3, 6, and 12 months, respectively (20% vs. 12%, 50% vs. 28%, and 66% vs. 43%; $P < .001$ for each; Table 2). More patients attending academic centers in Europe had documentation of at least one CyR test, compared with US academic centers by 12 months (76% [95% with results available; 90% "actionable" and 10% "not actionable"] vs. 57% [89% with results available; 98% "actionable" and 2% "not actionable"]; $P < .001$). In the US, patterns of CyR monitoring between patients with and without insurance were similar (50.5% and 53.2%, respectively; $P = .76$).

TABLE 1 Patient demographics according to first-line TKI therapy and for the total population

	First-Line TKI			All Patients
	Imatinib	Dasatinib	Nilotinib	
Cohort, N	416	418	408	1242
Sex, n (%)				
Male	236 (56.7)	222 (53.1)	221 (54.2)	679 (54.7)
Median (IQR) age at diagnosis (years)	59.6 (47.3–70.2)	56.2 (45.9–66.6)	54.0 (44.6–65.7)	56.6 (46.0–67.7)
Median (IQR) age at first-line TKI (years)	59.7 ^a (47.3–70.2)	56.3 (46.0–66.9)	54.1 (44.6–65.8)	56.6 (46.0–67.7)
Age at first-line TKI (years), n (%)				
<50	122 (29.3)	138 (33.0)	152 (37.3)	412 (33.2)
50–64	142 (34.1)	161 (38.5)	147 (36.0)	450 (36.2)
≥65	152 (36.5)	119 (28.5)	109 (26.7)	380 (30.6)
ECOG performance status, n (%) ^b				
N	314	335	335	984
0	122 (38.9)	147 (43.9)	165 (49.3)	434 (44.1)
1	80 (25.5)	72 (21.5)	74 (22.1)	226 (23.0)
2	12 (3.8)	8 (2.4)	8 (2.4)	28 (2.8)
3	1 (0.3)	3 (0.9)	0 (0.0)	4 (0.4)
4	2 (0.6)	0 (0.0)	1 (0.3)	3 (0.3)
Not Assessed	97 (30.9)	105 (31.3)	87 (26.0)	289 (29.4)
Sokal score at diagnosis ^c				
N	148	124	141	413
Low risk, n (%)	54 (13.0)	48 (11.5)	56 (13.7)	158 (12.7)
Intermediate risk, n (%)	67 (16.1)	42 (10.0)	47 (11.5)	156 (12.6)
High risk, n (%)	27 (6.5)	34 (8.1)	38 (9.3)	99 (8.0)
Missing, n (%)	268 (64.4)	294 (70.3)	267 (65.4)	829 (66.7)
Hasford score ^d at diagnosis				
N	140	118	132	390
Low risk, n (%)	75 (18.0)	69 (16.5)	75 (18.4)	219 (17.6)
Intermediate risk, n (%)	56 (13.5)	40 (9.6)	49 (12.0)	145 (11.7)
High risk, n (%)	9 (2.2)	9 (2.2)	8 (2.0)	26 (2.1)
Missing, n (%)	276 (66.3)	300 (71.8)	276 (67.6)	852 (68.6)
Race/ethnicity, n (%)				
White nonhispanic	298 (71.6)	281 (67.2)	276 (67.6)	855 (68.8)
Other/unknown	118 (28.4)	137 (32.8)	132 (32.4)	387 (31.2)
Region, n (%)				
Europe	172 (41.3)	115 (27.5)	144 (35.3)	431 (34.7)
United States	244 (58.7)	303 (72.5)	264 (64.7)	811 (65.3)
Practice type, n (%)				
Academic center	212 (51.0)	223 (53.3)	227 (55.6)	662 (53.3)
Private/community practices	204 (49.0)	195 (46.7)	181 (44.4)	580 (46.7)

^aP < .001.^b%s are calculated using the total number of patients for whom data on ECOG performance status are available as the denominator; data for 258 patients are missing.^cSokal score categories; low-risk: Sokal score <0.8; intermediate-risk: Sokal score 0.8–1.2; high-risk: >1.2.^dHasford score categories; low-risk: Hasford score ≤780; intermediate-risk: Hasford score >780–≤1480; high-risk: Hasford score >1480. ECOG performance status is defined as: 0, fully active; 1, restricted strenuous activity; 2, ambulatory and capable of all self-care, no work; 3, capable of only limited self-care; 4, completely disabled. TKI: tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range.

Overall, CyR testing was done by CBA and FISH separately in the first 12 months in 37% of patients. There is a greater emphasis at European sites to carry out CBA testing compared with US centers (55% vs. 28% of patients; Table 2).

3.3.2 | MR monitoring patterns

Of the patients followed, 32% had documentation of MR testing by 3 months; this increased to 74% by 6 months and 91% by 12 months (P < .0001) (Table 2). A greater proportion of patients in Europe were

TABLE 2 The number and % of patients followed for a minimum of 12 months tested for CyR (FISH, bone marrow, or both) or MR (including IS and non-IS) according to region

	Monitoring patterns								
	During first 3 months of first-line TKI therapy			During first 6 months of first-line TKI therapy			During first 12 months of first-line TKI therapy		
	All (N = 1233)	Eu (n = 428)	US (n = 805)	All (N = 1224)	Eu (n = 422)	US (n = 802)	All (N = 1195)	Eu (n = 416)	US (n = 779)
CyR Monitoring patterns									
Done, date present, n (%)	197 (16)	91 (21)	106 (13)	485 (40)	215 (51)	270 (34)	656 (55)	274 (66)	382 (49)
Done/recorded with results available ^a	182 (92)	83 (91)	99 (93)	435 (90)	198 (92)	237 (88)	584 (89)	255 (93)	329 (86)
“Actionable” ^b	161 (88)	65 (78)	96 (97)	401 (92)	170 (86)	231 (98)	541 (93)	223 (88)	318 (97)
“Not actionable” ^c	21 (12)	18 (22)	3 (3)	34 (8)	28 (14)	6 (3)	43 (7)	32 (13)	11 (3)
Bone marrow karyotyping or FISH									
FISH, n (%)	139 (11)	49 (11)	90 (11)	330 (27)	112 (27)	218 (27)	447 (37)	148 (36)	299 (38)
Bone marrow karyotyping, n (%)	103 (8)	69 (16)	34 (4)	286 (23)	173 (41)	113 (14)	441 (37)	227 (55)	214 (28)
Done/recorded with no results available	15 (8)	8 (9)	7 (7)	50 (10)	17 (8)	33 (12)	72 (11)	19 (7)	53 (14)
Number of cytogenetic (bone marrow karyotyping or FISH) tests performed, n (%)^d									
0	1036 (84)	337 (79)	699 (87)	739 (60)	207 (49)	532 (66)	539 (45)	142 (34)	397 (51)
1	142 (72)	60 (66)	82 (77)	271 (56)	118 (55)	153 (57)	226 (35)	89 (33)	137 (36)
2	50 (25)	26 (29)	24 (23)	173 (36)	74 (34)	99 (37)	218 (33)	95 (35)	123 (32)
3	1 (1)	1 (1)	0 (0)	24 (5)	10 (5)	14 (5)	115 (18)	44 (16)	71 (19)
4+	4 (2)	4 (4)	0 (0)	17 (4)	13 (6)	4 (2)	97 (15)	46 (17)	51 (13)
MR Monitoring patterns									
Done, date present, n (%)	389 (32)	148 (35)	241 (30)	910 (74)	353 (84)	557 (69)	1087 (91)	406 (98)	681 (87)
Done/recorded with results on IS, n (%)	285 (73)	125 (85)	160 (66)	672 (74)	303 (86)	369 (66)	857 (79)	365 (90)	492 (72)
Done/recorded with results not on IS ^f , n (%)	99 (25)	20 (14)	79 (33)	218 (24)	40 (11)	178 (32)	214 (20)	34 (8)	180 (26)
Number of molecular tests performed on the IS or not, n (%)									
1	333 (87)	124 (86)	209 (87)	585 (66)	230 (67)	355 (65)	226 (21)	63 (16)	163 (24)
2	47 (12)	18 (12)	29 (12)	234 (26)	84 (25)	150 (27)	344 (32)	151 (38)	193 (29)
3	4 (1)	3 (2)	1 (0)	39 (4)	16 (5)	23 (4)	258 (24)	85 (21)	173 (26)
4+	0 (0)	0 (0)	0 (0)	32 (4)	13 (4)	19 (4)	243 (23)	100 (25)	143 (21)
Done/not recorded	5 (1)	3 (2)	2 (1)	20 (2)	10 (3)	10 (2)	16 (2)	7 (2)	9 (1)
Not done/recorded, n (%)	844 (68)	280 (65)	564 (70)	314 (26)	69 (16)	245 (31)	108 (9)	10 (2)	98 (13)
CyR or MR monitoring patterns									
Total tested, n (%)	444 (36)	162 (38)	282 (35)	1002 (82)	368 (87)	634 (79)	1141 (95)	411 (99)	730 (94)
Total not tested, n (%) ^e	789 (64)	266 (62)	523 (65)	222 (18)	54 (13)	168 (21)	54 (5)	5 (1)	49 (6)
Median (IQR) number of tests by 12 months	-	-	-	-	-	-	5 (3-6)	5 (4-6)	5 (3-6)

^aThe denominator is the total number of patients with a CyR test done with date present.

^bIncludes available FISH data if % Ph+ known and ≥ 200 evaluated nuclei or available bone marrow data if % Ph+ known and ≥ 20 examined metaphases; the denominator is the total number of patients with a CyR test done/recorded with results available.

^cIncludes all other available FISH and bone marrow data; the denominator is the total number of patients with a CyR test done/recorded with results available.

^dThe denominator is the total number of patients with CyR test done and a date present.

^eThe proportion of MR tests not on the IS includes “no” and “unknown”.

^fThe proportion of patients not tested includes those with no date reported. May include MR, FISH, or bone marrow data with missing testing dates. May include patients who were not tested due to progression.

CyR: cytogenetic response; FISH: fluorescence in situ hybridization; IQR: interquartile range; IS: international scale; MR: molecular response; TKI: tyrosine kinase inhibitor.

monitored for MR by 12 months compared with the US (98% vs. 87%; $P < .001$). This was also true for the comparison between academic centers and community practices (94% vs. 87%, respectively; $P < .001$). Monitoring of MR in community practices occurred more frequently in Europe compared with the US by 12 months (97% vs. 84%, respectively; $P < .001$). In the US, similar proportions of patients had documentation of MR monitoring irrespective of insurance status; 88% and 83%, respectively ($P = .35$).

Among patients tested for MR by 12 months, 23% did not have standardised MR assessments. More patients in Europe had documentation of MR testing performed using the IS, within the first 12 months of TKI therapy, compared with the US (90% vs. 72%; $P < .001$). Use of standardised testing was similar across practice types, with the exception of European versus US academic centers (93% vs. 68%, respectively; $P < .001$).

Throughout the study, both the ELN and NCCN recommended MR monitoring every 3 months during the first year of TKI therapy.

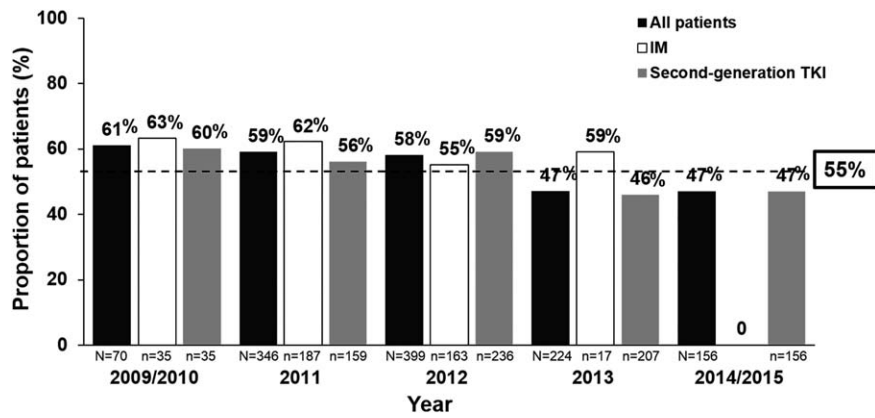


FIGURE 1 The proportion (%) of SIMPLICITY patients with CyR monitoring for the overall population, and for those patients receiving IM and second-generation TKIs, over the years of enrollment into the study. Both FISH and BM cytogenetic tests were included as long as a date was present. Patients had to be followed for ≥ 12 months. Includes assessments performed after index TKI start date, between 30 days and 12 months later. Dotted line corresponds to the proportion of patients with CyR monitoring during the first 12 months across the entire study period. BM: bone marrow; CyR: cytogenetic response; FISH: fluorescence in situ hybridization; IM: imatinib; TKI: tyrosine kinase inhibitor. N indicates the number of patients per cohort

Overall, based on MR results on the IS or not, 47% of patients underwent ≥ 3 molecular tests consistent with recommendations in the first year (47% US and 46% Europe) (Table 2); 50% were monitored in line with recommendations at academic centers (54% US and 45% Europe) and 43% in community centers (41% US and 50% Europe) (Table 2).

3.4 | CyR and MR monitoring by year of first-line TKI initiation in SIMPLICITY

Reviewing monitoring patterns over the duration of the study thus far, between 2009 and 2015, the proportion of patients with documentation of CyR monitoring during the first 12 months decreased (Figure 1). During 2009/2010, 61% of all patients had documentation of CyR within the year; this fell to 47% in 2014/2015. The proportion of patients who initiated first-line imatinib during 2009/2010 and had documentation of CyR monitoring within the first 12 months after initiation was 63%, which fell to 59% in 2013. The proportion of patients who initiated a

second generation first-line TKI during 2009/2010 and had documentation of CyR monitoring within the first 12 months after initiation was 60%; this fell to 46% in 2013. A somewhat higher proportion of patients who initiated Imatinib in 2009/2010 had CyR monitoring compared with second generation TKIs; this was relatively consistent through 2013 (Figure 1).

Furthermore, reviewing monitoring patterns over the duration of the study thus far also revealed a shift in MR monitoring practices over time, between 2009 and 2015. The proportion of patients who had MR monitoring (whether on IS or not) during the first 12 months following initiation of first-line TKI increased slightly (Supporting Information Figure S5). Analysis comparing MR monitoring patterns between imatinib and second-generation TKIs found no notable differences. During 2009/2010, 87% of all patients who had been followed for ≥ 12 months had documentation of MR within the year and this rose to 97% in 2014/2015. The same was true for patients who had MR monitoring on IS: 69% in 2009/2010 and 86% in 2014/2015 (Figure 2).

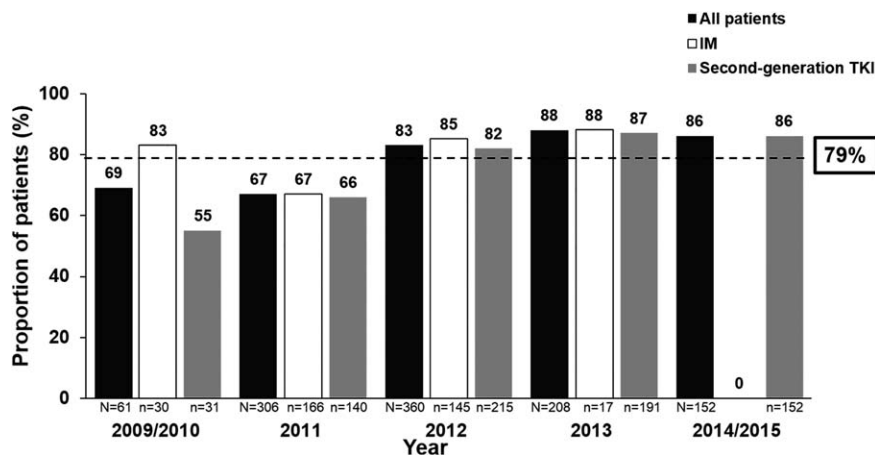


FIGURE 2 The proportion (%) of patients with MR monitoring for the overall population, and for those patients receiving IM and second-generation TKIs, over the years of enrollment into the study. MR monitoring patterns during the first 12 months of treatment according to the year of first-line TKI initiation – result on IS. IM: imatinib; IS: international scale; MR: molecular response; TKI: tyrosine kinase inhibitor. N indicates the number of patients per cohort

3.5 | Predictors of monitoring

In the 3- and 6-month multivariable logistic regression models, among the potential predictors considered, the only significant predictors of documented CyR/MR monitoring were whether a patient was followed at an academic center versus community practice (odds ratio [OR] for 3 month model = 1.45, $P = .002$; OR for 6 month model = 1.56, $P = .004$), year of index TKI initiation (2011 vs. 2014/2015 OR for 3 month model = 0.58, $P = .006$; 2011 vs. 2014/2015 OR for 6 month model = 0.45, $P = .005$; 2012 vs. 2014/2015 OR for 6 month model = 0.52, $P = .024$), and site location in Europe versus the US (OR for 6 month model = 1.53, $P = .017$). By 12 months, age <65 years (OR = 2.05, $P = .013$), European region (OR = 5.17, $P < 0.001$), no longer on first-line TKI (OR = 2.27, $P = .049$) and being followed at an academic center (OR = 1.90, $P = .037$) were all significant predictors of CyR/MR monitoring after backward selection. Risk score status, the year of first-line TKI initiation and insurance status in the US population were not found to be predictors of monitoring.

4 | DISCUSSION

While other demographic variables are similar, the median age of SIMPLICITY patients (56.6 years) is older than that of patients studied in the pivotal clinical trials of the TKIs under investigation (46.0–50.0 years) and three investigator-initiated RCTs evaluating use of imatinib (51.0–53.0 years).^{9,10,26–29} However, patient demographics, including the median age of SIMPLICITY patients, are similar to other observational studies and registries, including the European Treatment and Outcome Study (EUTOS) CML registry.³⁰ Given other observational studies advocate the use of imatinib in older patients,³¹ it is perhaps not surprising that the median age for patients on imatinib was slightly higher compared with that for patients on dasatinib or nilotinib ($P < 0.001$). It should be noted, however, that the IQR for age is large, reflecting the wide age range in our population. Age may have therefore been a factor determining treatment choice, but this was not captured as a reason for choice of first-line TKI in SIMPLICITY.

A higher proportion of patients had baseline comorbidities in SIMPLICITY (81%) than in EUTOS (55%) and other studies (36%).^{32,33} Nearly half of all SIMPLICITY patients have baseline CV comorbidities, which is important in light of the increasing awareness of late-emergent CV toxicities with TKIs. The comorbidity profiles of patients in each of the TKI cohorts were similar, although patients receiving nilotinib were somewhat more likely to have no baseline comorbidities and were less likely to have CV comorbidities. However, management practices and understanding of TKI safety profiles has evolved over the course of the study and thus, taken together with the low numbers of patients in each cohort, any between cohort differences should be interpreted cautiously. Given recent findings that baseline comorbidities may have a greater influence on survival than CML in the TKI era, individualisation of treatment choices is key to enhancing long-term tolerability and adherence.^{15,34}

We report the primary reason cited by the treating physician for selecting first-line TKI was (perceived) “effectiveness”. In clinical

practice, however, treatment choice is influenced by numerous factors, including those relating to the characteristics of the study center, patient characteristics, and preferences and expertise of the prescribing physician. Another factor that may influence TKI choice is Sokal or Hasford score. Calculation of these risk scores normally requires the measurement of numerous parameters, including the spleen size, that are not routinely assessed during normal clinical practice.³⁵ As such, only about one third of patients in this observational study had available risk scores. While there are some differences between SIMPLICITY patients with and without Sokal/Hasford risk scores, these risk scores were not significant predictors of response monitoring. Although the imatinib cohort was filled before either of the second-generation cohorts, it is important to note that enrollment into SIMPLICITY began in each country after all three TKIs were approved and thus the prescribing physician had the option to prescribe any of the TKIs. TKI selection in SIMPLICITY is thus driven by physician choice and perceptions of each agent rather than being a reflection of TKI availability.

Early and routine monitoring of CyR and MR in CML patients is crucial to achieve long-term treatment goals.²⁰ Timely monitoring helps to ensure that milestone “warning” responses are rapidly identified and acted upon.^{7,8,36} SIMPLICITY has found that patients may not be monitored, by CyR or MR, as frequently as suggested in evidence-based management recommendations. These findings support data reported from other routine clinical practice studies.^{20,37,38} Indeed, case report data from 38 US oncologists showed only 46% of patients met recommendations of 3–4 tests per year.^{20,37} Furthermore, a retrospective review of the IMS LifeLink Health Plan Claims database and Truven Health Analytic MarketScan reported only 27% of the 1205 patients were monitored in accordance with recommendations.^{37,38} Ultimately, poor monitoring practices can result in higher overall patient costs, which is an important consideration.³⁹

Regarding monitoring patterns by region, practice type and insurance status, CyR and MR monitoring were more common in academic centers versus community practices, and in Europe versus the US. This may be reflective of the slight predominance of patients treated within academic centers vs. community practices (53% vs. 47%) in SIMPLICITY, and referral of CML patients to such centers in Europe. Regional differences in monitoring patterns support previous studies, demonstrating that European monitoring practices are more stringent than those in the US,⁴⁰ likely at least in part due to differences in healthcare infrastructure. Additionally, differences in monitoring patterns between practice types are likely to reflect differences in the standard of, and approach to, management across academic and community practices, and may reflect the stronger lead taken by academic centers in response monitoring. However, in both academic and community practices, only a third of patients were monitored for CyR/MR at 3 months, and thus patients at all types of centers are not being monitored in line with guideline recommendations. This highlights the need for further multi-faceted educational approaches to facilitate broader adoption of monitoring recommendations. However, a survey of oncologists in two US states noted significant barriers to guideline adoption, including lack

of interest in monitoring guideline educational programmes.³⁹ An observational study of 705 patients from 36 centers in France reported that MR monitoring in routine clinical practice is closely aligned with the updated recommendations. The authors of the study highlight the majority of patients were still receiving first-line treatment and were in optimal response.⁴¹ There were no reported differences in monitoring patterns according to insurance status, which suggests that lower rates of monitoring were not the result of issues with insurance. SIMPLICITY does not capture data capable of elucidating what these factors may be. The findings that age <65 years and those who had switched off their first-line treatment were predictors of monitoring by 12 months, suggest that older patients, as well as those who are kept on their first-line therapy, may be at greater risk of not being monitored adequately.

Monitoring patterns in the first 12 months of follow-up need to be interpreted in the context of both the shifting treatment landscape and changes in CyR/MR monitoring guideline recommendations. The evolution in practice over the course of SIMPLICITY thus far is shown in Supporting Information Figure S1. Three trends are worth mentioning. First, more patients receiving second-generation TKIs were enrolled in the later years of the enrollment window of 2009–2015 compared with those receiving first-line imatinib. As mentioned, enrollment into the imatinib cohort was completed first, by June 26, 2013, and therefore only patients treated with dasatinib or nilotinib could be enrolled into the study after this timepoint (cohorts were closed on August 28, 2014 and January 30 2015, respectively). Thus findings should be interpreted in the context of the different rates at which the individual TKI cohorts were filled over time. Furthermore, the comparatively smaller cohorts in Europe may partially reflect the noted lag in the timing of IRB approvals compared with the US, and the approval and reimbursement of the respective TKI agents within Europe. Second, at study initiation, there was a greater focus, from the ELN, on bone marrow CyR testing.^{42,43} Recommendations have since evolved, and results from SIMPLICITY may be influenced by these shifting practices. Analysis of frequency of CyR/MR monitoring according to year of initiation of first-line TKI shows that, for imatinib and second-generation TKIs, CyR monitoring decreases after 2012, but MR monitoring does not decrease over time. The results likely demonstrate a paradigm shift reflective of the updates made to clinical recommendations over the SIMPLICITY observation period (Figures 1 and 2). Third, growing awareness of the importance of standardised MR testing has led to the introduction and gradual adoption of IS testing in clinical practice, yet not all MR tests were standardised to the IS.^{44,45} This limits comparisons between centers and proper implementation of milestone-based treatment algorithms. The importance of standardization is emphasized by recent studies suggesting 3 and 6-month milestone values on the IS correlate with long-term survival.^{18,19} The 3- and 6-month logistic regression models showed that patients who started their TKI prior to 2013 were less likely to have response monitoring by 3 or 6 months than in 2013 or later. However, this result was not significant.

One of the strengths of observational research is it allows us to understand better how clinical trial experience translates into routine clinical practice and a wider patient population than normally included

in RCTs.⁴⁶ However, the robustness of observational research methodologies has been questioned, as their nonrandom design may increase selection bias and confounding, and thus the results from such studies need to be interpreted in clinical context.^{46,47} Importantly, while SIMPLICITY has been able to capture how patients have been managed in the routine clinical practice setting, reasons for declining participation in the study, and reasons behind the investigators' decisions to include patients in the study were not collected and thus there may be selection bias with respect to the patients included in the study. Selection bias is a known limitation of nonrandomized studies and requires careful inference about study findings.^{46,47} A multivariable logistic regression model allowed for evaluation of response monitoring while simultaneously adjusting for distributional differences in patient characteristics. Age, region, practice type, and whether the patient was still on first-line TKI were all significant predictors at specified timepoints, independent of other variables in the model like first-line TKI and year of TKI initiation.

Other potential study limitations include bias introduced by year of enrollment into SIMPLICITY and choice of TKI – owing to known changes in management practices over the duration of the study – and possible site attrition over the duration of the study. Of the 241 SIMPLICITY sites that were initiated in the study, 193 were still active in the study at time of data download. However, SIMPLICITY patients may well better represent CML patients seen in routine clinical practice. The observational data provided by SIMPLICITY gives important insights into CP-CML management in routine clinical practice and suggest that further efforts should be made to deliver individualised care to patients with CP-CML. Furthermore, although analysis of monitoring patterns according to year of TKI initiation has demonstrated a shift in line with the evidence-based management recommendations, the monitoring practices of physicians participating in SIMPLICITY are still not fully in accordance with these recommendations, particularly in the US and in community practices, and in older patients and those no longer receiving first-line therapy. In the absence of appropriate monitoring practices, clinical response to TKI therapy cannot be established, any needed changes to treatment strategy will thus not be implemented, and long-term patient outcomes are likely to be impacted. The extent to which the early response monitoring practices identified here on long-term outcomes in SIMPLICITY patients still needs to be determined, and will be the focus of future analyses.

ACKNOWLEDGMENTS

We thank all SIMPLICITY study investigators, the patients who consented to be part of the study and LATITUDE (AXON Communications) who provided medical writing services on behalf of the authors and Bristol-Myers Squibb Pharmaceuticals Ltd. In memory of Dr H. Jean Khoury, esteemed colleague and invaluable member of the SIMPLICITY study team.

CONFLICT OF INTERESTS

SG has received grants and/or consultancy fees from BMS, Ariad, Novartis, and Pfizer. JC has received grants and/or consultancy fees

from Ariad, BMS, Novartis, Pfizer and Teva. CGP has received grants and consultancy fees from BMS, and honoraria/grants from Pfizer. RH has received consultancy fees from BMS and grants from Novartis. JK has received grants from BMS, Pfizer, Ariad and Teva. MMichallet reports grants from BMS, consultant fees/honoraria from BMS, Pfizer, Novartis, Astellas Pharma, MSD and Genzyme. RP and BS declare no conflict of interest. TZ is a BMS employee, and AF an employee of ICON Clinical Research. EA has received grants from BMS, and consultancy fees from Novartis, Wyeth, Ariad, and Takeda. DA received grants from BMS and Celgene, and consultancy fees from Gilead, CTI, Janssen and Celgene. AB has received grants from BMS. PCM has received grants/honoraria from BMS and Novartis, and consultancy fees from Pfizer. RHansen has received grants/honoraria from BMS. EL reports consultant fees/honoraria from Novartis, BMS and Pfizer. EO declares no conflict of interest. MMAuro has received grants from Novartis Oncology and Ariad/Takeda, and consultancy fees from BMS, Ariad/Takeda and Pfizer.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Goldberg SL, Cortes J, Gambacorti-Passerini C, et al. First-line treatment selection and early monitoring patterns in chronic phase-chronic myeloid leukemia in routine clinical practice: SIMPLICITY. *Am J Hematol*. 2017;92:1214–1223. <https://doi.org/10.1002/ajh.24887>