A Multi-country Retrospective Study of Patient Characteristics and Treatment Patterns in Chronic Myeloid Leukemia

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BACKGROUND

- Chronic myeloid leukemia (CML) is a slowly progressing hematological malignancy that begins in the bone marrow, but also involves the blood and spleen
- CML is usually characterized by a balanced genetic translocation between chromosome 9 and chromosome 22, resulting in an abnormal chromosome known as the Philadelphia chromosome (Ph)
- Although a relatively common form of leukemia, overall CML is a rare malignancy
  - In the United States (US), there are approximately 4500 new cases of CML per year, and the age-adjusted annual incidence rate is 1.75 cases per 100,000 adults[1]
- CML has 3 phases (chronic, accelerated, and blast), determined by the number of blast cells in the blood and bone marrow and by the extent of symptoms
- Prior to 2001, treatment for CML was limited to alkylating agents, hydroxyurea, interferon-alfa, or high-dose chemotherapy with hematopoietic stem cell support
- Imatinib (Gleevec®), a tyrosine kinase inhibitor (TKI), became available in 2001
  - Imatinib has demonstrated a complete cytogenetic response rate of over 80% for first-line therapy of chronic phase CML[2,3]
- Other TKIs (dasatinib and nilotinib) initially approved for patients with resistance or intolerance to imatinib have recently also been approved for first-line therapy

OBJECTIVE

- To examine patient and disease characteristics and treatment patterns among patients with CML in multiple countries

METHODS

Study Design

- Retrospective review of medical records

Data Source

- Physicians in 4 countries (US, United Kingdom [UK], Germany, and Japan) were identified, screened for eligibility, and recruited by local health care market research agencies by telephone or e-mail from the entire database of providers within a country
- Physicians were required to select a random sample of patients that met the inclusion criteria (listed below)
- Data on patient demographics, treatment patterns, and treatment response (not included in this poster) were collected via an electronic Web-based form filled out by the physicians
- Data validation/resolution was conducted over the phone directly with the physicians
- Institutional Review Board exemption was obtained prior to data collection
- All data were analyzed using SAS® (version 9) statistical software

Inclusion Criteria

Physicians

- Medical specialty of medical oncology or hematology
- Between 2 and 35 years in clinical practice
- An annual caseload of ≥5 patients with CML
- Personally prescribes imatinib, dasatinib, and/or nilotinib to patients with CML

Patients

- A confirmed diagnosis of CML
- Aged ≥18 years at time of CML diagnosis
- In chronic phase at time of diagnosis
- Treated for CML between 1 January 2005, and 31 December 2009, with first-line imatinib and/or second-line dasatinib or nilotinib
- Ph-positive and/or BCR/ABL-positive
- Of the overall patient sample, ≥20% were required to have second- and/or third-line treatment with dasatinib or nilotinib so that outcomes in those lines could be assessed
- Not enrolled in any randomized clinical trial related to CML between the start of first-line imatinib treatment and the end of the recorded follow-up

Study Measures

- All analyses conducted for overall study cohort and separately by country

Physician characteristics

- Number of years in practice
- Specialty
- Average number of patients with CML treated per year
- Region of practice

Patient characteristics

- Demographic characteristics: age, gender, and ethnic origin (except in Japan)
- Educational status
- Employment status
- Health insurance status (only in the US)
- Availability of private health insurance in addition to national health insurance (except in the US)

Baseline medical history and comorbidities

- CML phase (chronic, accelerated, or blast) at treatment initiation
- Spleen size
- Blood counts
- Bone marrow aspirate and biopsy results
- Results of molecular marker testing (quantification of BCR/ABL expression)
- The rate of commonly occurring comorbidities
- Sokal risk score categories: low risk (score <0.8), intermediate risk (score 0.8–1.2), and high risk (score >1.2)

Treatment patterns

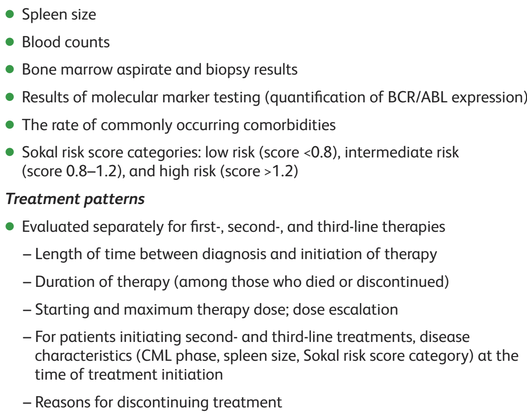
- Evaluated separately for first-, second-, and third-line therapies
  - Length of time between diagnosis and initiation of therapy
  - Duration of therapy (among those who died or discontinued)
  - Starting and maximum therapy dose; dose escalation
  - For patients initiating second- and third-line treatments, disease characteristics (CML phase, spleen size, Sokal risk score category) at the time of treatment initiation
  - Reasons for discontinuing treatment

RESULTS

Physician and Patient Characteristics

- A total of 214 physicians provided data on 1063 patients
  - US: 60 physicians, 300 records
  - UK: 45 physicians, 220 records
  - Germany: 49 physicians, 243 records
  - Japan: 60 physicians, 300 records
- On average, physicians had a caseload of 32.5 CML patients per year (range: 28 patients [US] to 39 patients [Japan]; **Table 1**)
- Physicians had been in clinical practice for an average of 15 years (no variation across countries)
- The proportion of medical specialties (medical oncologist, hematologist, or hematologist/oncologist) varied between countries (**Figure 1**)
- Across all 4 countries, patients had a median age at diagnosis of 56 years; approximately 60% were male (**Table 2**)
- The majority of patients in the US (73%), UK (85%), and Germany (98%) were white; ethnicity data were not collected in Japan
- Overall, 39% of patients were employed full-time
- Of patients in the US, 46% had commercial insurance; 19% of patients in the UK, Germany, and Japan had private insurance in addition to the national health plan

Figure 1. Medical specialties of physicians by country.



Baseline Medical History and Comorbidities

- Most patients had no treatment prior to imatinib (74% overall; 100% in Japan; **Table 3**)
- Almost all patients (98% overall) were in chronic phase at the time of imatinib initiation
- Overall, 35% of patients were at low risk of rapid disease progression and death, as determined by the Sokal score; an equal proportion was at intermediate risk (Sokal scores were not available in the medical records for 15% of patients)
- Nearly 79% of all patients (100% in Japan) had a bone marrow aspiration performed; a median of 6% myeloblasts were detected
- BCR/ABL status was detected at 50% across all patients (range: 8% [Japan] to 79% [UK])
- Fifteen commonly occurring comorbidities were documented. At the time of first-line therapy initiation
  - Approximately one-third (33%) of the overall study sample had ≥1 comorbidity of interest
  - Diabetes was the most commonly observed comorbidity, occurring in 13% of all patients (range: 5% [Japan] to 18% [Germany])
  - Chronic pulmonary disease was the second most common comorbidity, occurring in 6% of all patients (range: 1% [Japan] to 11% [US])
- Comorbidity patterns remained unchanged at the time of initiation of second-line therapy

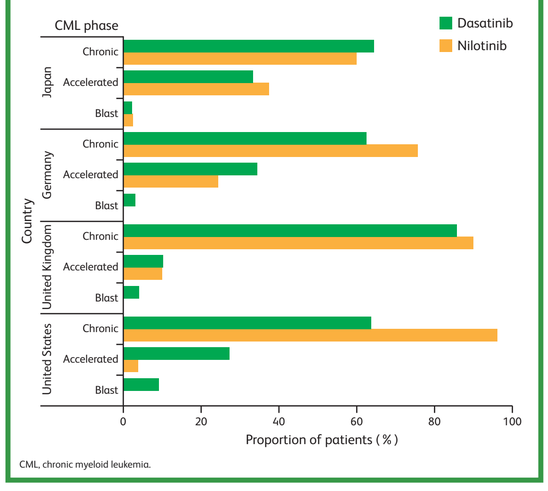
First-line Treatment Patterns

- Patients initiated imatinib within 3 months after diagnosis, at a starting daily dose of 400 mg/day (for >88% of patients; **Table 4**)
- Approximately 13% of patients (range: 8% [Japan] to 16% [UK]) had a dose escalation to a median dose of 800 mg/day
- Nearly one-third (29%) of patients discontinued therapy
- The leading reasons for therapy discontinuation (not mutually exclusive) were resistance to therapy (36%), failure to achieve response (32%), and disease progression (27%)
- Overall, 6.2% (n = 19) of all patients died while on therapy, with a median time between treatment initiation and death of 16 months (range: 13.5 months [Japan] to 24.5 months [UK])
- The median duration of treatment (among those who discontinued therapy or died) was 22 months (range: 19 months [US] to 25 months [Japan])

Second-line Treatment Patterns

- Second-line treatment patterns were studied among 261 patients (dasatinib, n = 148; nilotinib, n = 113; **Table 5**)
- Greater proportions of patients in the US and Germany were treated with nilotinib (54% in each country) compared with dasatinib (46% in each country); only 17% of patients in the UK received nilotinib
- On average, patients initiated treatment approximately 25 months after initial diagnosis (no variation between the 2 drugs)
- Patients on dasatinib received treatment for an average of 11 months (range: 7 months [UK] to 17 months [Japan]), whereas those on nilotinib received treatment for an average of 8 months (range: 6 months [Germany] to 11 months [US])
- Slightly more patients initiating second-line dasatinib had advanced disease (25% accelerated phase; 4% blast phase) compared with nilotinib (25% accelerated phase; <1% blast phase; **Figure 2**)
- Median daily dose was 100 mg/day for dasatinib and 800 mg/day for nilotinib; only 1 patient (on nilotinib) received a dose escalation

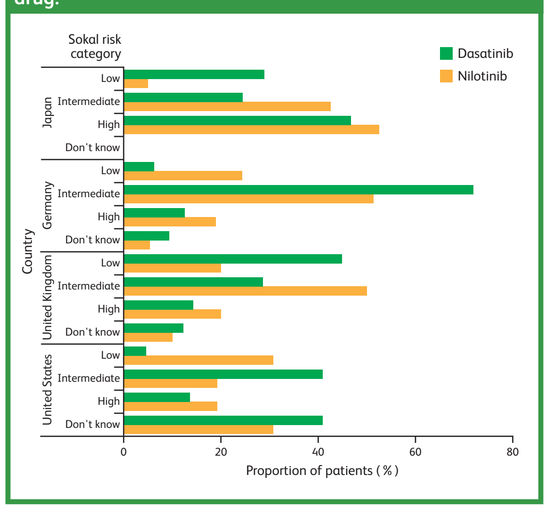
Figure 2. CML stage at second-line treatment initiation by country and second-line drug.



CML, chronic myeloid leukemia.

- On average, 28% of patients treated with dasatinib discontinued therapy compared with 14% of patients treated with nilotinib; the most common reasons were disease progression and lack of efficacy (ie, no response achieved)
- Four patients on dasatinib and 1 patient on nilotinib died while on treatment, with a median time between second-line treatment initiation and death of 10.5 months for dasatinib and 7 months for nilotinib
- Overall, 71% of patients who initiated second-line treatment were still in chronic phase, whereas 25% and 4% had progressed to accelerated and blast phases, respectively
- The distribution of Sokal risk score categories indicated that patients treated with nilotinib (low, 18%; intermediate, 41%; high, 31%; unknown, 10%) on average had a somewhat worse prognosis than those who received dasatinib (low, 26%; intermediate, 38%; high, 24%; unknown, 12%; **Figure 3**)

Figure 3. Sokal risk category by country and second-line drug.



Third-line Treatment Patterns

- Thirty-two patients received third-line treatment (dasatinib, n = 4; nilotinib, n = 28)
- There were no patients on third-line dasatinib in the UK or Germany
- Most patients on third-line nilotinib were from the US (37%), followed by the UK (25%), Germany (21%), and Japan (18%)
- Because of the small sample sizes, no further analyses were performed on third-line treatment patterns

LIMITATIONS

- Patients selected for study inclusion represented a "convenience" sample; study findings therefore may not be generalizable to the overall CML populations in these countries
- Although physicians were asked to select medical records for patients whose last names began with certain random letters of the alphabet (assigned by the fieldwork team), all patients did not have an equal probability of inclusion in the study
- Although physicians were recruited from all geographic regions, it was not possible to construct sampling weights that would allow generalization to the national population in these countries
- The data were entered directly by the treating physicians, and therefore were potentially subject to entry errors and resulting inaccuracies in reporting; although there were data checks in place to ensure internal consistency of the data, responses were not validated against patients' medical records by an independent reviewer
- At the time of this study, dasatinib and nilotinib were not approved for first-line treatment of CML. Because both drugs are now approved for first-line treatment of CML, current treatment patterns likely vary from those reported here

CONCLUSIONS

- **This study is unique in that it captures clinical and treatment data in a standardized manner from multiple countries and from a variety of practice settings**
- **Results show that there is substantial variation in the rate of comorbidities**
- **The duration of therapy and rate of treatment discontinuation also varied across countries, with patients in Germany having the greatest rate of discontinuation during first-line treatment with imatinib as well as second-line treatment with nilotinib. Patients in the US had the highest discontinuation rate during second-line treatment with dasatinib**
- **Providers, payers, and health care decision makers should be aware of variations in patient characteristics and practice patterns when considering future approaches to CML care and management**

REFERENCES

1. Altekruse SF, et al, eds. SEER cancer statistics review, 1975-2007. Available at: http://seer.cancer.gov/csr/1975_2007/. Accessed 17 November 2010.
2. O'Brien SG, et al. *N Engl J Med*. 2003;348(11):994-1004.
3. Kantarjian H, et al. *Blood*. 2004;103(8):2873-2878.

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Table 1. Characteristics of Physicians Contributing Medical Record Data

	All physicians		Country							
			United States		United Kingdom		Germany		Japan	
	N	%	n	%	n	%	n	%	n	%
No. of physicians	214	100.0	60	28.0	45	21.0	49	22.9	60	28.0
CML patient caseload										
Mean (SD)	32.50 (23.90)		27.85 (25.01)		33.07 (28.82)		29.69 (21.51)		39.17 (19.14)	
Median (range)	25 (5–100)		20 (5–100)		20 (5–100)		25 (6–100)		37.5 (10–100)	
No. of years in practice										
Mean (SD)	14.94 (6.84)		14.45 (6.63)		16.87 (6.77)		13.69 (5.45)		15.02 (7.88)	
Median (range)	14 (2–33)		13 (4–31)		15 (9–30)		13 (2–26)		14.5 (2–33)	
Prescribes imatinib	214	100.0	60	100.0	45	100.0	49	100.0	60	100.0
Prescribes dasatinib	206	96.3	55	91.7	44	97.8	47	95.9	60	100.0
Prescribes nilotinib	198	92.5	54	90.0	38	84.4	46	93.9	60	100.0

CML, chronic myeloid leukemia; SD, standard deviation.

Table 2. Patient Characteristics

	All patients		Country							
			United States		United Kingdom		Germany		Japan	
	N	%	n	%	n	%	n	%	n	%
No. of patients	1063	100.0	300	28.2	220	20.7	243	22.9	300	28.2
Age at diagnosis										
Mean (SD), years	54.59 (14.48)		56.36 (12.57)		54.58 (13.67)		53.57 (12.44)		53.67 (17.87)	
Median (range), years	56 (18–96)		57 (19–89)		55 (20–84)		54 (19–85)		55 (18–96)	
Distribution										
18–24 years	29	2.7	3	1.0	2	0.9	2	0.8	22	7.3
25–34 years	75	7.1	10	3.3	18	8.2	16	6.6	31	10.3
35–44 years	148	13.9	41	13.7	33	15.0	39	16.0	35	11.7
45–54 years	247	23.2	75	25.0	46	20.9	69	28.4	57	19.0
55–64 years	296	27.8	91	30.3	71	32.3	66	27.2	68	22.9
≥65 years	268	24.2	80	26.7	50	22.7	51	21.0	87	29.0
Gender										
Male	641	60.3	192	64.0	134	60.9	141	58.0	174	58.0
Female	422	39.7	108	36.0	86	39.1	102	42.0	126	42.0

SD, standard deviation.

Table 3. Baseline Medical History

	All patients		Country							
			United States		United Kingdom		Germany		Japan	
	N	%	n	%	n	%	n	%	n	%
No. of patients	1063	100.0	300	28.2	220	20.7	243	22.9	300	28.2
History of CML treatments prior to imatinib										
Interferon	15	1.4	4	1.3	4	1.8	7	2.9	0	0.0
Hydroxyurea	237	22.3	64	21.3	93	42.3	80	32.9	0	0.0
Other	5	0.5	1	0.3	0	0.0	4	1.6	0	0.0
None	790	74.3	218	72.7	121	55.0	151	62.1	300	100.0
Don't know	26	2.4	14	4.7	4	1.8	8	3.3	0	0.0
CML phase at baseline										
Chronic	1037	97.6	288	96.0	216	98.2	233	95.9	300	100.0
Accelerated	21	2.0	8	2.7	4	1.8	9	3.7	0	0.0
Blast	3	0.3	2	0.7	0	0.0	1	0.4	0	0.0
Don't know	2	0.2	2	0.7	0	0.0	0	0.0	0	0.0
Sokal risk score at baseline										
Low	371	34.9	79	26.3	108	49.1	93	38.3	91	30.3
Intermediate	367	34.5	97	32.3	62	28.2	110	45.3	98	32.7
High	170	16.0	17	5.7	13	5.9	30	12.3	110	36.7
Don't know	155	14.6	107	35.7	37	16.8	10	4.1	1	0.3
Common comorbidities at baseline										
Cerebrovascular disease	32	3.0	16	5.3	4	1.8	10	4.1	2	0.7
Chronic pulmonary disease	68	6.4	32	10.7	14	6.4	18	7.4	4	1.3
Congestive heart failure	27	2.5	15	5.0	6	2.7	3	1.2	3	1.0
Myocardial infarction	38	3.6	11	3.7	6	2.7	18	7.4	3	1.0
Peripheral vascular disease	45	4.2	17	5.7	8	3.6	19	7.8	1	0.3
Ulcer disease	26	2.4	12	4.0	2	0.9	7	2.9	5	1.7
Diabetes	137	12.9	51	17.0	28	12.7	44	18.1	14	4.7
Renal disease	40	3.8	17	5.7	6	2.7	11	4.5	6	2.0
None	711	66.9	167	55.7	154	70.0	141	58.0	249	83.0
Other	100	9.4	28	9.3	16	7.3	28	11.5	28	9.3

CML, chronic myeloid leukemia.

Table 4. First-line Treatment Patterns (Imatinib)

	All patients		Country							
			United States		United Kingdom		Germany		Japan	
	N	%	n	%	n	%	n	%	n	%
No. of patients	1063	100.0	300	28.2	220	20.7	243	22.9	300	28.2
Time between CML diagnosis and imatinib initiation										
Mean (SD), months	2.69 (9.67)		2.07 (3.75)		2.62 (5.73)		5.14 (18.83)		1.38 (0.65)	
Median (range), months	1 (1–201)		1 (1–51)		2 (1–61)		2 (1–201)		1 (1–4)	
Duration of imatinib treatment										
Mean (SD), months	22.08 (14.07)		18.81 (13.5)		20.97 (14.08)		22.27 (15.94)		25.07 (13.22)	
Median (range), months	19 (1–66)		15 (2–59)		17 (1–60)		17.5 (3–66)		24 (4–61)	
Starting daily dose										
Mean (SD), mg	412.89 (57.19)		411.33 (51.77)		422.27 (77.07)		422.22 (72.73)		400 (0)	
Median (range), mg	400 (200–800)		400 (200–800)		400 (300–800)		400 (200–800)		400 (400–400)	
Had dose escalation	141	13.3	43	14.3	35	15.9	38	15.6	25	8.3
Highest daily dose										
Mean (SD), mg	702.84 (114.61)		674.42 (115.66)		654.29 (106.67)		715.79 (119.74)		800 (0)	
Median (range), mg	800 (400–800)		600 (400–800)		600 (400–800)		800 (400–800)		800 (800–800)	
Therapy discontinuation	303	28.5	62	20.7	70	31.8	82	33.7	89	29.7
Reason for therapy discontinuation (not mutually exclusive)[a]										
Died while on therapy	19	6.3	6	9.7	2	2.9	5	6.1	6	6.7
Did not achieve treatment response	96	31.7	15	24.2	18	25.7	23	28.0	40	44.9
Became resistant to therapy	109	36.0	16	25.8	16	22.9	27	32.9	50	56.2
Disease progression	83	27.4	19	30.6	23	32.9	15	18.3	26	29.2
Patient request	33	10.9	6	9.7	4	5.7	9	11.0	14	15.7
Patient intolerance	55	18.2	13	21.0	21	30.0	15	18.3	6	6.7
Other	5	1.7	2	3.2	0	0.0	3	3.7	0	0.0
Time between treatment initiation and death[b]										
Mean (SD), months	16.32 (10.71)		17.50 (15.78)		24.50 (10.61)		15.40 (10.31)		13.17 (3.92)	
Median (range), months	16 (4–47)		15.5 (4–47)		24.5 (17–32)		15 (5–29)		13.5 (9–17)	

CML, chronic myeloid leukemia; SD, standard deviation.
[a]Percentages are among those who discontinued therapy. [b]Among those who died.

Table 5. Second-line Treatment Patterns

	All patients				Country													
					United States				United Kingdom				Germany				Japan	
	Dasatinib		Nilotinib		Dasatinib		Nilotinib		Dasatinib		Nilotinib		Dasatinib		Nilotinib		Dasatinib	Nilotinib
	N	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No. of patients	148	100.0	113	100.0	22	14.9	26	23.0	49	33.1	10	8.8	32	21.6	37	32.7	45	30.4	40	35.4
Time between CML diagnosis and second-line treatment initiation																		
Mean (SD), months	25.44 (16.89)		25.88 (13.93)		22.27 (12.75)		22.00 (12.15)		26.65 (19.13)		21.60 (10.43)		26.41 (19.44)		27.95 (16.28)		24.98 (14.22)	27.55 (13.09)
Median (range), months	23 (4–105)		25 (3–71)		22 (5–52)		21 (3–48)		22 (4–99)		23 (5–41)		24 (5–105)		25 (6–71)		23 (4–61)	31 (7–54)
Duration of second-line treatment																		
Mean (SD), months	11.02 (6.93)		7.94 (5.16)		11.57 (4,64)		11.00 (4.24)		7.00 (3.86)		10.00 (0)		11.00 (8.06)		6.17 (5.78)		16.86 (9.75)	7.20 (5.36)
Median (range), months	11.5 (1–38)		7 (2–17)		12.5 (3–21)		10.5 (7–16)		5.5 (1–13)		10 (10–10)		12 (2–26)		4 (2–17)		13 (10–38)	7 (2–16)
Starting daily dose																		
Mean (SD), mg	1114.46 (20.01)		723.89 (101.13)		118.18 (20.39)		730.77 (97.03)		104.49 (15.82)		700 (105.41)		116.25 (19.96)		740.54 (103.98)		122.22 (20.10)	0
Median (range), mg	100 (70–140)		800 (400–800)		100 (100–140)		800 (600–800)		100 (70–140)		700 (600–800)		100 (100–140)		800 (400–800)		140 (100–140)	0
Therapy discontinuation	42	28.4	16	14.2	14	63.6	4	15.4	12	24.5	1	10.0	9	28.1	6	16.2	7	15.6	5	12.5
Reason for therapy discontinuation (not mutually exclusive)[a]																		
Died while on therapy	4	9.5	1	6.3	1	7.1	0	0.0	2	16.7	0	0.0	0	0.0	1	16.7	1	14.3	0	0.0
Did not achieve treatment response	11	26.2	5	31.3	1	7.1	1	25.0	4	33.3	1	100.0	2	22.2	0	0.0	4	57.1	3	60.0
Became resistant to therapy	5	11.9	4	25.0	5	35.7	1	25.0	0	0.0	0	0.0	0	0.0	2	33.3	0	0.0	1	20.0
Disease progression	12	28.6	2	12.5	4	28.6	0	0.0	2	16.7	1	100.0	4	44.4	0	0.0	2	28.6	1	20.0
Patient request	3	7.1	2	12.5	1	7.1	0	0.0	2	16.7	0	0.0	0	0.0	2	33.3	0	0.0	0	0.0
Patient intolerance	10	23.8	0	0.0	3	21.4	0	0.0	4	33.3	0	0.0	3	33.3	0	0.0	0	0.0	0	0.0
Other	5	11.9	3	18.8	1	7.1	2	50.0	2	16.7	0	0.0	2	22.2	1	16.7	0	0.0	0	0.0
Time between treatment initiation and death[b]																		
Mean (SD), months	17.5 (17.37)		7 (0)		14 (0)		0		6.5 (0.71)		0		0		7 (0)		43 (0)	0
Median (range), months	10.5 (6–43)		7 (7–7)		14 (14–14)		0		6.5 (6–7)		0		0		7 (7–7)		43 (43–43)	0

CML, chronic myeloid leukemia; SD, standard deviation.
[a]Percentages are among those who discontinued therapy. [b]Among those who died.

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