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Regional variations in age at diagnosis and overall survival among patients with chronic myeloid leukemia from low and middle income countries

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ABSTRACT

Introduction: The epidemiology of chronic myeloid leukemia (CML) in low and middle income countries is limited. As a result, we analyzed a contemporary cohort of patients from low and middle income countries treated with Imatinib through The Glivec® International Patient Assistance Program (GIPAP).
Methods: Generalized estimating equations (GEE) and Kaplan–Meier estimation were utilized to test for regional variations in age at diagnosis and overall survival among 33,985 patients from 94 countries.
Results: Patients participated from Asia (79.2%), Africa (9.4%), Latin America (8.7%) and Southern/Eastern Europe (2.5%). Sixty-one (61.2%) percent were male. Mean age at diagnosis was 38.5 years (9.4% <20 years and only 4.7% ≥65 years). Using GEE, Asians were youngest (38.3 years), followed by Africans (39.5 years), Southern/Eastern Europeans (41.1 years) and Latin Americans (41.3 years; $p < 0.0001$). Diagnoses were predominately in chronic stage (78.3%). In 2002, 85.2% of patients had a delay in treatment >1 year; decreasing to 15.5% in 2010 ($p < 0.0001$). The 3-year overall survival probability was 89.4% (95% CI, 88.9–89.9). In multivariate analysis, risk of death increased among patients 65 years or older at diagnosis ($p < 0.0001$), time from diagnosis to treatment >1-year ($p < 0.0001$), diagnoses in the accelerated or blast crisis ($p < 0.0001$), initial dose of Imatinib >400 mg ($p < 0.0001$) and among Latin Americans and Africans ($p < 0.0001$).
Conclusion: The GIPAP cohort is the largest series of patients with CML described from low and middle income countries. Differences in age at diagnosis and overall survival exist within and between regions. Additional epidemiological studies should be conducted to assess for possible environmental factors associated with the earlier age at onset.

1. Introduction

CML is a myeloproliferative disease with a median age at diagnosis of 64.0 years in the United States of America (USA) [1]. Incidence rates in the USA increase with age peaking after the age of 65 [2]. The Surveillance, Epidemiology and End Results (SEER) registries estimated the age-adjusted incidence rate to be 1.6 per 100,000 [1]. The worldwide incidence is considered to range between 1.0 and 1.5 per 100,000 with no known geographic or ethnic variation [2]. Etiological factors are not well understood with the exception being an increased incidence of CML among survivors of the atomic bombings of Hiroshima and Nagasaki [3]. Agriculture and occupational exposures have been considered as potential etiological factors but a strong association has yet to be established [4–7].

Novartis Oncology initiated the Glivec® International Patient Assistance Program (GIPAP) in 2001, which supplied Imatinib for treatment of CML and gastrointestinal stromal tumors (GIST) free of charge to patients in low and middle income countries [8]. Preliminary data from GIPAP suggested that patients from lower and middle income countries were diagnosed at an earlier age as compared to the West [8]. An earlier age at diagnosis of CML in developing countries has been previously reported with median ranging between 32 and 44 years; however, these were limited to single institution series [9–20]. Among the aforementioned single institution series, overall survival (OS) post-Imatinib has varied ranging from a 3-year OS of 72% in Africa to 94% at 29 months in India [10,12]. As age is one of the most important risk factors for cancer, we aimed to determine if there were differences in age at

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diagnosis among patients from low and middle income countries. Differential age patterns would suggest the presence of a risk factor that predisposes individuals to CML at an earlier age. Secondly, we aimed to describe the survival experience among patients from low and middle income counties and determine if age at diagnosis impacts OS.

2. Materials and methods

The Max Foundation (Edmonds, Washington) is a US-based non-profit that facilitates GIPAP. Patients were screened by physicians who then submitted a registration form online for an independent review. Eligibility included a diagnosis of CML based on Philadelphia chromosome positivity (Ph+) and/or presence of the BCR-ABL gene, documented absence of insurance and no governmental coverage. A maximum income level for each country was specified to ensure consistency in defining low and middle income. Classification of low and middle income countries is based on The World Bank classification [21]. GIST was excluded from this analysis.

Patient characteristics collected on the registration form included sex, date of birth, city, state, country of residence, date of diagnosis, stage of disease at diagnosis [22], Ph+ and/or BCR-ABL status, and a financial evaluation (an assessment of income, occupation, and number of household members). Imatinib was provided for a 3 month period to allow for follow-up and evaluation for dose modification, if necessary.

2.1. Statistical considerations

The primary objective of this study was to compare the distribution in age at diagnosis across the participating regional components of GIPAP. The primary hypothesis was that there is no difference in age at diagnosis between regional components that participate in GIPAP. The United Nations World Macro Regions and Components were used to group countries into four macro geographical regions: Asia, European, Latin America and Africa [23]. Countries were further classified into 14 geographical component sub-regions. Analysis of the primary endpoint was undertaken using generalized estimating equations (GEE) methodology [24]. The "population-average" approach of Liang and Zeger focuses on the marginal effects of individuals averaged across a cluster; i.e. component region [25]. Linear contrasts were defined to test by macro and component sub-regions. Least square means (LSMean) and 95% confidence intervals (CI) were estimated.

Distribution of age at diagnosis was described using kernel density estimation [26–28]. This non-parametric method for estimating the probability density function was constructed using 1-year age increments with a smoother method of the corresponding age at diagnosis frequency histogram. Plots can be interpreted as the area under the curve consisting of 100% of the CML cases. The vertical axis represents the smoothed estimate of the density or proportion and the horizontal axis corresponds to the age at diagnosis.

Probability of OS at 1 and 3 years was estimated from the time of first dose using the Kaplan–Meier method with date of death marking the event and censoring patients at the date of last contact [29]. Follow-up was complete for a subset of patients enrolled between August 2003 and May 2007 ($N = 17{,}999$). Comparisons between groups were made using the log-rank test [30]. Risk of death was quantified using univariate and multivariate Cox proportional hazards models with backward model selection criteria [31]. Factors considered in the multivariate analysis

Table 1
Patient characteristics at diagnosis by macro region.

Patient characteristics	Europe ($N=862$)		Latin America ($N=2970$)		Asia ($N=26{,}916$)		Africa ($N=3209$)		Oceania ($N=28$)		All patients ($N=33{,}985$)	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Sex												
Female	352	(40.8)	1337	(45.0)	10,075	(37.4)	1398	(43.6)	11	(39.3)	13,173	(38.8)
Male	510	(59.2)	1633	(55.0)	16,841	(62.6)	1811	(56.4)	17	(60.7)	20,812	(61.2)
Age at diagnosis (years)												
0–4	1	(0.1)	17	(0.6)	75	(0.3)	19	(0.6)			112	(0.3)
5–9	2	(0.2)	30	(1.0)	315	(1.2)	41	(1.3)			388	(1.1)
10–14	14	(1.6)	88	(3.0)	733	(2.7)	103	(3.2)	3	(10.7)	941	(2.8)
15–19	41	(4.8)	173	(5.8)	1373	(5.1)	158	(4.9)	2	(7.1)	1747	(5.1)
20–39	343	(39.8)	1105	(37.2)	12,776	(47.5)	1392	(43.4)	8	(28.6)	15,624	(46.0)
40–64	418	(48.5)	1270	(42.8)	10,510	(39.0)	1278	(39.8)	15	(53.6)	13,491	(39.7)
≥65	37	(4.3)	266	(9.0)	1082	(4.0)	210	(6.5)			1595	(4.7)
Unknown	6	(0.7)	21	(0.7)	52	(0.2)	8	(0.2)			87	(0.3)
Diagnosis year												
<2000	247	(28.7)	269	(9.1)	1582	(5.9)	122	(3.8)			2220	(6.5)
2000–2003	336	(39.0)	737	(24.8)	5166	(19.2)	455	(14.2)	2	(7.1)	6696	(19.7)
2004–2006	226	(26.2)	1028	(34.6)	10,418	(38.7)	946	(29.5)	6	(21.4)	12,624	(37.1)
2007–2010	53	(6.1)	936	(31.5)	9750	(36.2)	1686	(52.5)	20	(71.4)	12,445	(36.6)
Stage of disease at diagnosis												
Accelerated	230	(26.7)	346	(11.6)	2281	(8.5)	225	(7.0)	2	(7.1)	3084	(9.1)
Blast crisis	49	(5.7)	172	(5.8)	1926	(7.2)	121	(3.8)			2268	(6.7)
Chronic	564	(65.4)	2239	(75.4)	21,306	(79.2)	2477	(77.2)	23	(82.1)	26,609	(78.3)
Remission	16	(1.9)	203	(6.8)	1380	(5.1)	381	(11.9)	3	(10.7)	1983	(5.8)
Unknown	3	(0.3)	10	(0.3)	23	(0.1)	5	(0.2)			41	(0.1)
Time from diagnosis to approval (days)												
<30	94	(10.9)	479	(16.1)	7405	(27.5)	750	(23.4)	7	(25.0)	8735	(25.7)
30–100	96	(11.1)	852	(28.7)	6148	(22.8)	1015	(31.6)	9	(32.1)	8120	(23.9)
100–365	150	(17.4)	631	(21.2)	5255	(19.5)	641	(20.0)	7	(25.0)	6684	(19.7)
>365	515	(59.7)	991	(33.4)	8010	(29.8)	787	(24.5)	5	(17.9)	10,308	(30.3)
Unknown	7	(0.8)	17	(0.6)	98	(0.4)	16	(0.5)			138	(0.4)
First dose (mg)												
<400 mg	15	(1.7)	123	(4.1)	723	(2.7)	133	(4.1)	1	(3.6)	995	(2.9)
400 mg	538	(62.4)	2333	(78.6)	22,031	(81.9)	2756	(85.9)	24	(85.7)	27682	(81.5)
>400 mg	309	(35.8)	512	(17.2)	4156	(15.4)	320	(10.0)	3	(10.7)	5300	(15.6)
Unknown			2	(0.1)	6	(0.0)					8	(0.0)