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Short Communication

Environmental Contributors to the Pathogenesis of Chronic Myelocytic Leukemia

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Chronic myelocytic leukemia (CML), once an invariably fatal disease terminating often in a blastic phase, has been transformed into a chronic disease managed successfully by the continued oral treatment of kinase inhibitors such as imatinib [1]. Appropriate medication is not always available to all patients, however, and therefore attention to the risk factors for developing CML continues to be important in the control of this disease. Thus far the single widely accepted causative agent for CML is radiation, having been demonstrated in a number of studies such as the monitoring of the aftermath of the atomic bombings in Hiroshima and Nagasaki [2] and the observation of an increased risk of CML in women treated for carcinoma of the cervix with radiation therapy [3]. Agricultural and occupational exposures have also been considered as being etiologically related to CML [4,5] but a causative relationship has not yet been confirmed.

The success of imatinib, first released as Glivec by Novartis Oncology, led to wide distribution of this drug which included the Glivec Patient Assistance Program (GIPAP), which supplied Glivec free of charge to patients with CML living in low and middle income countries who were unable to afford the daily treatment [6]. Between January 2002 and August 2010, 35,045 CML patients from 118 countries had applied for Glivec through GIPAP and the data collected from this program served as the basis for our first investigation into international patterns of CML [7]. In this study, we noted a striking difference in age of onset among GIPAP patients in different countries and observed that the age of onset correlated with the income of the countries where they resided, the age of onset being earlier in patients from low income countries compared to higher income countries. For example, overall the mean age of onset in GIPAP patients was 38.5 years compared to 64.0 years in the U.S. Within the GIPAP population, Asian patients were the youngest (38.3 years, 95% CI. 38.2-38.5), significantly younger than the patients in Southern/ Eastern Europe (41.1 years, CI. 40.1-42.0) and Latin American patients (41.3 years, 95% CI. 40-7-41.9). These data were intriguing but interpretation of these results were limited by the selective nature of the participants (uninsured and underinsured patients living in low and middle income countries) and the inconsistent collection of certain demographic and clinical data, such as race/ethnicity and response to treatment. A major strength, however, in addition to the large numbers of patients, was the selection of sites and investigators chosen for their ability to diagnose and treat patients with diagnosis requiring their being Philadelphia chromosome and/or BCR-ABL positive.

In order to follow up on the geographic patterns of age of onset, we next moved to collect international incidence data using population-based cancer registries evaluated by the International Agency for Research in Cancer (IARC) [8]. IARC evaluates population-based cancer registries for quality and publishes the data from those countries and other jurisdictions that meet the criteria indicating reliable data. The basic conclusions from the GIPAP paper [7] were confirmed with major differences in median age being identified, the median age at diagnosis being lowest in Africa and Asia (47 years) and the highest in Oceania (72 years). The most important conclusion emerging from this analysis that was suggested in the previous study was that there was a clear correlation between age of diagnosis and gross national income (GNI) as estimated by the World Bank, lower income regions having an earlier age of diagnosis than upper income regions (Table 1). Differences in incidence as well as age of distribution were also apparent in this analysis. The incidence was lowest among Asian females (0.55/100,000) which was strikingly different than the incidence among both males and females in Oceania, 1.78 and 0.96/100,000 respectively. Of interest is that the geographic variation in incidence rates was greater in the older population than the younger population; early onset CML in African males was diagnosed in 0.33/100,000 vs 0.59 /100,000 in males living in South Central America, a much smaller difference than the gap between late onset CML in African males (1.77/100,000) vs. males in Oceania (6.7/100,000).

The ability to investigate racial/ethnic differences that could contribute to these differences was limited. Data from the Surveillance, Epidemiology and End Results (SEER) Program in the United States showed an earlier mean onset in Blacks than Whites, Black males and females having a median age of 54.5 and 57.0 respectively vs 67.0 for White males and females. This could be the result of socioeconomic differences, however, rather than racial/ethnic differences. An opportunity to minimize racial/ethnic differences arose in a study focusing on one country, India, where data from GIPAP included 14,167 CML patients [9]. In this study, a younger age of onset was observed in families of Indian CML patients making less than $1,000/ yr. compared to those earning more than $1,000 per year but the data also showed occupational and geographical differences that were not universally related to income. The earlier age of onset in families engaged in farming/fishing, mostly in agriculture, compared to government office workers had a strong economic explanation but environmental exposures also became a concern. Similarly, there was a general geographic pattern of early age of onset in less affluent parts of India but there were some striking exceptions. Studies of

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Table 1: Descriptive Statistics of CML Diagnosis from IARC Version IX (1998-2002).

Region	# of Registries	Males			Females		
		N	Median (IQR)	ASR (95% CI)	N	Median (IQR)	ASR (95% CI)
Africa	5	91	47.0 (32.0-57.0)	0.61 (0.47-0.76)	100	42.0 (32.0-57.0)	0.69 (0.55-0.84)
Asia	47	2856	47.0 (32.0-62.0)	0.86 (0.82-0.89)	1873	47.0 (37.0-67.0)	0.55 (0.52-0.57)
Europe	100	8962	67.0 (52.0-77.0)	1.07 (1.05-1.09)	7169	67.0 (52.0-77.0)	0.68 (0.66-0.70)
North America	25	4899	67.0 (47.0-77.0)	1.30 (1.26-1.34)	3543	67.0 (52.0-82.0)	0.78 (0.75-0.81)
Oceania	9	1492	72.0 (54.5-77.0)	1.78 (1.68-1.87)	969	72.0 (57.0-82.0)	0.96 (0.89-1.03)
South/Central America	10	583	52.0 (37.0-67.0)	1.26 (1.16-1.37)	432	52.0 (37.0-67.0)	0.78 (0.70-0.85)
Gross National Income							
High	146	15885	67.0 (47.0-77.0)	1.15 (1.13-1.17)	11847	67.0 (52.0-77.0)	0.70 (0.69-0.71)
Upper middle	27	1976	57.0 (39.5-67.0)	0.96 (0.92-1.00)	1539	57.0 (42.0-72.0)	0.65 (0.62-0.68)
Lower middle	10	1005	42.0 (27.0-57.0)	0.95 (0.89-1.02)	687	42.0 (32.0-52.0)	0.71 (0.66-0.77)
Low	2	17	37.0 (27.0-52.0)	0.26 (0.10-0.42)	13	52.0 (32.0-67.0)	0.42 (0.16-0.69)

Adapted from [9].

agricultural practices in different parts of India and their possible relationship to age of CML diagnosis are in progress.

The importance of these descriptive studies is that they suggest there are strong environmental factors other than radiation influencing the pathogenesis of CML. Descriptive epidemiology is an important tool to describe suggestive patterns of cancer distribution that could be related to environmental carcinogens. Several examples of such studies, described in more detail elsewhere [10], include the use of cancer mapping to show clustering of a malignancy such as lung cancer in males and oral cancer in females in the Southeast United States that eventually led to the identification of asbestos exposure [11] and snuff dipping [12] as etiologic agents respectively. Follow-up of these descriptive studies of CML need to be undertaken investigating specific environmental factors associated with socioeconomic status as well as specific exposures in occupational groups such as agricultural workers in high risk areas.

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