RESEARCH ARTICLE

Leukemia in Iran: Epidemiology and Morphology Trends

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Abstract

   Background: Leukemia accounts for 8% of total cancer cases and involves all age groups with different prevalence and incidence rates in Iran and the entire world and causes a significant death toll and heavy expenses for diagnosis and treatment processes. This study was done to evaluate epidemiology and morphology of blood cancer during 2003-2008. Materials and Methods: This cross- sectional study was carried out based on re-analysis of the Cancer Registry Center report of the Health Deputy in Iran during a 6-year period (2003 - 2008). Statistical analysis for incidence time trends and morphology change percentage was performed with joinpoint regression analysis using the software Joinpoint Regression Program. Results: During the studied years a total of 18,353 hematopoietic and reticuloendothelial system cancers were recorded. Chi square test showed significant difference between sex and morphological types of blood cancer (P-value<0.001). Joinpoint analysis showed a significant increasing trend for the adjusted standard incidence rate (ASIR) for both sexes (P-value<0.05). Annual percent changes (APC) for women and men were 18.7 and 19.9, respectively. The most common morphological blood cancers were ALL, ALM, MM and CLL which accounted for 60% of total hematopoietic system cancers. Joinpoint analyze showed a significant decreasing trend for ALM in both sexes (P-value<0.05). Conclusions: Hematopoietic system cancers in Iran demonstrate an increasing trend for incidence rate and decreasing trend for ALL, ALM and CLL morphology.

Keywords: Epidemiology - trend - leukemia - hematopoietic system - Iran

Introduction

   Cancer is set to become a major cause of morbidity and mortality in the coming decades in every region of the world (Bray et al., 2012). Today, Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries (Jemal et al., 2011). Malignant disorders in hematopoietic system include different conditions which some of them are related to bone marrow and other may be related to lymphatic system. Three main types of blood cancer are leukemia, lymphoma myeloma and plasma cell disorders (Rodriguez-Abreu et al., 2007).

   Leukemia is a metastatic and malignant disease for blood-making organs which is resulted due to incomplete evolution and problematic proliferation of white blood cells (WBCs) and its substrates in blood and bone marrow (Howlader N NA, , based on November 2013 SEER data submission, posted to the SEER web site, April 2014). Leukemia is responsible for 8% of total cancer cases (Zand et al., 2010) and involves all age groups with different prevalence and incidence rate in Iran and whole the world and causes significant death toll and heavy expenses for diagnosis and treatment process (Tahmasebi et al., 2006).

Although overall incidence is rare, leukemia is the most common type of childhood cancer. It accounts for 30% of all cancers diagnosed in children younger than 15 years (Belson et al., 2007), but it is not limited to children and has higher incidence among adults with more complicated treatment process (Tahmasebi et al., 2006).

   Leukemia is classified to main four categories with different clinical symptoms: AML or acute myeloid leukemia which mostly involves adults and consists about 30% of total adults' leukemia cases, ALL or acute lymphatic leukemia which is the most common type of disease among children and almost 80% of leukemia cases among children is attributed to this type and finally, CML or chronic myeloid leukemia which usually is seen among adults and CLL or chronic lymphatic leukemia the most common type of leukemia in adults which 90% of this type cases happens after 50 years old (Rodriguez-Abreu et al., 2007). Also multiple myeloma or plasma cell myeloma is a malignant blood disease in which plasma cells (which produce anti body) involve by cancer (Raab et al.). Multiple myeloma consists less than 1% of total cancer cases and less than 10% of total cancer cases and 10% of total blood malignancies and mostly involves old ones between 65-70 years old (Rodriguez-Abreu et al.,

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2007). Regarding increasing number of old age groups during past decades, multiple myeloma incidences have been increased (Rodriguez-Abreu et al., 2007).

According to United state statistics, leukemia incidence rate has been increased during 2002-2011 (Howlader N NA, based on November 2013 SEER data submission, posted to the SEER web site, April 2014). Also an incidence increase has been observed in a twenty years period in Netherlands among women between 50-64 years old (Van den Broek et al., 2012) and for Denmark between 1943-2003 (Thygesen et al., 2009).

In Iran, based on performed studies, blood malignancies have been surged during 1997-2003 for both sexes (Tahmasebi et al., 2006). Studies around the world show that blood malignancy incidence is increased by age (Coebergh et al., 2006; Sant et al., 2010; Dores et al., 2012; Novak et al., 2012). Performed studies in Iran confirm increasing trend of blood cancer incidence by age increase so that age groups higher than 70 years old has the most incidence rate (Tahmasebi et al., 2006). Studies in Iran and other countries have shown that blood malignancies incidence is higher among men than women (Tahmasebi et al., 2006; Sant et al., 2010; Zand et al., 2010; Dores et al., 2012; Novak et al., 2012; Howlader N NA, based on November 2013 SEER data submission, posted to the SEER web site, April 2014).

Although the etiology of leukemia is unknown, but some environmental factors such as ionizing radiations, chemical materials such as benzene, pesticides, chemotherapy, smoking, genetic disorders, family history about CLL, infection with HTLV-1, financial and social level have been recognized as the risk factors for blood cancer (Novak et al., 2012).

Some studies have confirmed changes in the Epidemiology and morphology trends of the cancers in some countries and Iran (Keyghobadi et al., 2014; Razi et al., 2014; Almasi et al., 2015; Mirzaei et al., 2015; Rafiemanesh et al., 2015). Considering different incidence rate around the world, so performed studies abroad the country cannot determine the cancer situation in Iran and also there has not been yet any study about epidemiology, morphology and trend of this important disease during recent years in Iran and on the other hand, epidemiological studies are necessary for successful planning, therefore this study was done to evaluate epidemiology and morphology of blood cancer during 2003-2008.

Materials and Methods

Data source

This is analytic cross-sectional study, carried out based on re-analysis national registry of cancer (NCR), and Disease Control and Prevention (CDC) report of ministry of Health and Medical Education in Iran. Deputy for health of each university is responsible for health issues of the population and all health activities are managed by these deputies. All deputies for health have been included in the NCR. Registrar would apply the national registration software which was developed by CDC. For pathologic centers, without software, the cancer records were gathered manually. The Cancer Office of CDC should

provide techniques and funding supports. The data are transmitted every 3 months, by electronic file and also hard copy of 'Cancer Registry Data Collection Form'; this form is comprised of three parts: part I, regarding patient's identity characteristics in addition to the name of biopsy-taker physician, name of hospital, location of which the biopsy is taken, clinical diagnosis and date of biopsy sent to histological laboratory and demographic information of the patients includes race and residence. Part II includes the most important findings of patient's clinical history. Part III includes preclinical findings. The information includes primary location of tumor, date of cancer diagnosis, morphology and histology and its behavior and diagnosis method. Physicians fill the form of clinical data and the official personnel fill the identity and demographic information. Quality control has been coordinated in five main areas by Cancer Office of CDC:

Regarding completeness of coverage; *ii)* completeness of details; *iii)* accuracy of data; *iv)* accuracy of reports; *v)* accuracy of interpretation and *vi)* repeated cases are deleted from national data. Surveillance of pathology is based on the cancer record in several selected provinces to compare it with the present pathology cancer record for a general and complete evaluation and also for the accuracy of the collected data. IARC software provides a way to identify inaccuracies in data coding. Data were collected retrospectively reviewing all new hematopoietic and reticuloendothelial systems cancer patients in Cancer Registry Center report of health deputy for Iran during a 6-year period (2003 - 2008) (Bray et al., 2012). Accordance of The International Classification of Diseases for Oncology (ICD-OC: topography with ICD-OM: morphology) Hematopoietic and reticuloendothelial systems cancer was defined as ICD-O C42(Fritz, 2000). This study investigated all cases of the morphology of Acute Myeloid Leukemia (AML)(9861/3), Acute Lymphoblastic Leukemia, NOS (ALL)(9821/3), Chronic Lymphocytic Leukemia (CLL)(9823/3) and Multiple Myeloma(MM) (9732/3).

Statistical analysis

We calculated crude incidence rate (CIR) and the Age-standardized incidence rate (ASIR) per 100,000 persons. We used direct standardized method using world standard population(Santos, 1999). To describe incidence time trends, we carried out joinpoint regression analysis using the software Joinpoint Regression Program, Version 4.1.1.1 October 2014. As well to evaluate the morphological changes, were obtained the percentage allocated for kind of morphological types. So to analysis morphology change percentage trends for six year, we carried out joinpoint regression analysis using the software Joinpoint Regression Program. The analysis included logarithmic transformation of the rates, maximum number of one joinpoints, and minimum of six years between zero joinpoints. All other program parameters were set to default values. The test of significance uses a Monte Carlo Permutation method (i.e., it finds "the best fit" line). joinpoint regression analysis involves fitting a series of joined straight lines on a log scale to the trends. The aim of the approach is to identify possible joinpoints where

a significant change in the trend occurs. In this study 0 joinpiont (Full model) was a significant model. The final model selected was the most parsimonious of these, with the estimated annual percent change (APC) based on the trend within each segment. In describing trends, the terms "significant increase" or "significant decrease" signify that the slope of the trend was statistically significant (P < 0.05). All statistical tests were two sided.

Results

During studied years (2003-2008) totally 18353 cancer for hematopoietic and reticuloendothelial systems were recorded which 37.76% (6930 cases) related to women and 62.24% (11423 cases) were related to men. Sex ratio (male to female) is equal to 1.65 (table 1).

Morphological diversity for blood cancer cells is higher in men than women. Chi square test showed significant difference between sex and morphological type of blood cancer (P-Value<0.001).
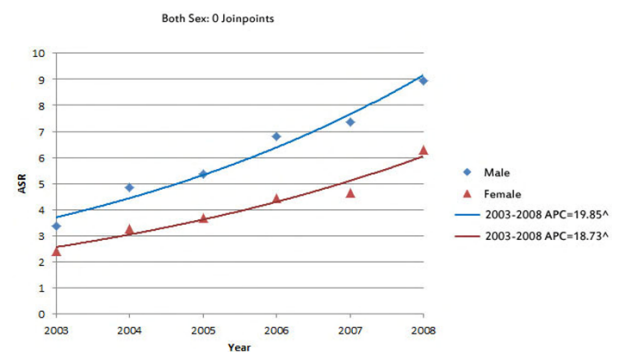
Epidemiologic trend

Joinpoint analyze showed a significant increasing trend for adjusted standard incidence rate (ASIR) for both sexes. Annual percent change (APC) for women was 18.7 (CI: 13.4 - 24.3) and for men equal to 19.9 (CI: 14.1 - 25.9) which can be seen in Figure1.

Morphological trend

The most common morphological blood cancer are Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM) and Chronic Lymphocytic Leukemia (CLL) which include 22.19%, 15.66%, 11.39% and 10.09% of total hematopoietic system for women, respectively. These values for men are 21.14%, 12.24%, 13.11% and 14.36% for men, respectively.

It means that these 4 morphological types consist 60% and 60.84% of total hematopoietic system for women and men, respectively. (Table 2)

Joinpoint analyze shows a decreasing trend for ALL,

Table 1. Frequency, Crude and age Standardized Incidence of Hematopoietic Systems Cancer by Sex, During the years 2003 to 2008

	Female			Male		
	N.	CIR	ASIR	N.	CIR	ASIR
2003	677	2.09	2.43	1057	3.1	3.39
2004	946	2.87	3.26	1550	4.47	4.85
2005	1068	3.11	3.68	1728	4.78	5.36
2006	1263	3.7	4.44	2148	5.97	6.8
2007	1283	3.76	4.65	2240	6.22	7.36
2008	1693	4.96	6.29	2700	7.5	8.94

CIR: crude incidence rate (per 100,000 persons); ASIR: Age-standardized incidence rate (per 100,000 persons)

Figure 1. Hematopoietic systems cancer change trend for ASIR by sex group between 2003-2008

Table 2. Frequency and percent Change in the percentage allocated to the four morphology data for hematopoietic systems cancer (2008-2003)

		2003		2004		2005		2006		2007		2008	
		N	%	N	%	N	%	N	%	N	%	N	%
Female	ALL*	157	23.19	216	22.83	235	22	295	23.36	301	23.46	334	19.73
	AML	165	24.37	250	26.43	141	13.2	162	12.83	186	14.5	181	10.69
	MM	54	7.98	107	11.31	130	12.17	162	12.83	127	9.9	209	12.34
	CLL	75	11.08	103	10.89	121	11.33	122	9.66	106	8.26	172	10.16
Male	ALL	220	20.81	418	26.97	347	20.08	500	23.28	459	20.49	471	17.44
	AML	209	19.77	270	17.42	191	11.05	206	9.59	270	12.05	252	9.33
	MM	97	9.18	200	12.9	223	13.31	271	12.99	291	14.6	287	13.48
	CLL	156	14.76	223	14.39	271	15.68	291	13.55	287	12.81	412	15.26

Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM) and Chronic Lymphocytic Leukemia (CLL)

Table 3. Joinpoint Analyses of Cancers Percentage Allocated to the four Morphology Data for Hematopoietic Systems Cancer (2008-2003)

	Female		Male	
	APC	95% CI	APC	95% CI
Acute Lymphoblastic Leukemia	-1.9	-5.9 to 2.3	-4.4	-12.6 to 4.7
Acute Myeloid Leukemia	-15.6^	-26.8 to -3.3	-13.3^	-23.2 to -2.1
Multiple Myeloma	5.4	-5.8 to 17.9	6.7	-1.5 to 15.5
Chronic Lymphocytic Leukemia	-4	-10.2 to 2.7	-0.9	-6.2 to 4.6

^APC is significantly different from zero at alpha = 0.05

AML and CLL types among both sex groups. Decreasing trends for ALM type with significant annual percent of change (APC) were equal to -15.63 and -13.32 for women and men, respectively (P-Value<0.05) (Table 3).

Discussion

According to obtained results, blood cancer in Iran has an increasing trend. During a study which was done by Tahmasebi et al. in Mazandaran province during 1996-2003, an increasing trend for 8 years period was observed, with non-Hutchkin lymphoma as the highest incidence rate and myeloma leukemia has the lowest incidence rate (Tahmasebi et al., 2006). Farahmand et al. found during their study that standard incidence rate for blood cancer among children during a 8 years' time period i.e. 2000-2008 has been increased significantly for both sex groups and the highest incidence rate was related to ALL type (Farahmand et al., 2011).

Hejazi conducted a research in western Azerbaijan province in Iran for children less than 15 years old during 2003-2008 showed that acute blood cancer incidence has not a regular decreasing or increasing trend during studied years (Hejazi et al., 2010). In a study which was done by Rajabli et al. from 2004-2009 in Golestan province, standardized incidence rate for leukemia among men and women were respectively 10.4 and 7.8 (per 100000 population), respectively. Similar age standardized incidence rate for multiple myeloma among men and women were obtained equal to 2.1 and 2 (per 100000 populations) which is higher than country and whole world (Rajabli et al., 2013).

Based on last data released by United States, leukemia incidence rate has been increased annually 0.2% from 2002 to 2011 and attributed death toll has been decreased on average 1% from 2001 to 2010 (Howlader N NA, , based on November 2013 SEER data submission, posted to the SEER web site, April 2014). During a research which conducted in Korea from 1999-2008, blood cancer incidence has been raised from 10.2 to 13.7 and lymphatic myeloma and multiple myeloma were the most common types of malignant blood diseases (Park et al., 2012).

During a research which was done in Kazakhstan from 2003-2012, blood cancer incidence has been decreased from 4.3 to 3.2 (Igissinov et al., 2014) and one study in Hong Kong showed a stable trend for blood cancer from 1990- 2008 (Xie et al., 2012).

Also performed study in Croatia showed a significant ALL stable trend for ALL incidence rate from 1988- 2009, meanwhile AML incidence has been decreased and CML incidence showed decrease for female but it has been stable among male group. Also this study showed a stable incidence rate for ALL which is similar to England, USA and New Zealand. An increased incidence rate for CLL in Croatia is similar to Denmark and Netherlands (Novak et al., 2012).

Similar studies in USA concerning blood cancer in Europe and USA in 2005 showed that overall incidences for hematopoietic malignancies have been raised along western countries and AML incidence had slow decrease or stable trend in the most European countries but it has

been surged in Wales and England about 70% from 1971 for both sexes (Rodriguez-Abreu et al., 2007).

Also researches have shown that different blood cancer incidence are higher among men (than women) which is comparable in the countries including Iran, Kazakhstan, Croatia, European union and United states (Coebergh et al., 2006; Tahmasebi et al., 2006; Rodriguez-Abreu et al., 2007; Hejazi et al., 2010; Sant et al., 2010; Dastgiri et al., 2011; Farahmand et al., 2011; Modak et al., 2011; Smith et al., 2011; Dores et al., 2012; Novak et al., 2012; Rajabli et al., 2013) and higher incidence among men may be attributed to genetically or environmental factors (Rajabli et al., 2013; Igissinov et al., 2014).

Also this study showed that blood cancer incidence in Iran is being increased although some part of this increase may be attributed to improvements on cancer registry system, but there is the possibility for blood cancer increase due to increasing related risk factors and regarding the fact that etiology of disease is not known completely, so identification of risk factors for this disease around different parts of the country is essential for preventing and diagnosis at initial stages for better control over this disease.

Conclusion: It can conclude that the incidence of leukemia cancer is increasing in Iran. Therefore, the plan for the control and prevention of this disease must be a high priority for health policy makers. Our findings was obtained from the descriptive study on the incidence trend of the disease in recent years and it is recommended that analytical studies should be conducted to obtain a causal relationship and solve problems related to the disease.

Limitations:It should be stated that the cancer registry system in Iran is still not fully and equally in all area and sometimes the differences in the quality and coverage of data is observed and in some cases there is Undercount and misclassification.

Acknowledgements

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