

Incidence patterns and review of Hodgkin lymphoma in the Republic of Armenia

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Abstract

Hodgkin lymphoma (HL) accounts for roughly 10% of all lymphomas and 0.6% of all malignant tumours analysed worldwide yearly. Data regarding HL in developing world are exceptionally constrained. The main objective of this research is to investigate the incidence patterns of HL within the Republic of Armenia and to portray disease distribution according to age and sex. There is a very strict evidence on the frequency of HL in Armenia. The results of our research find out that the frequency of HL in Armenia has not changed altogether over the past 15 years and is comparable to that detailed from the USA and Europe.

Keywords: *Hodgkin lymphoma, incidence, Armenia, developing world*

Introduction

Armenia is situated at the cross roads between Eastern Europe, Middle East and Western Asia occupying the north-eastern region of the historic Armenian plateau and highlands. As of 1 January 2018, the permanent population of Armenia was 2,972,732. The ethnic background of the population includes Armenians (98.1%), Yezidis, Russians, Assyrians, Ukrainians, Kurds, Greeks and other minorities.

Compared to non-Hodgkin lymphoma (non-HL), HL is a relatively infrequent lymphoma which is characterised by the pathognomonic malignant Reed–Sternberg cell with the cell of origin thought to be derived from the B-cell. Its annual incidence is 2–3 cases per

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100,000 in Europe and the USA [1]. According to the Global Cancer Observatory (GLOBOCAN) (2018) [2], the greatest recorded all-age incidence rates of HL are in Greece, Lebanon and Saint Lucia. Rates are particularly low in India, Japan and China. Incidence rates of HL have not varied much since the mid-1970s, but mortality rates have steadily declined from 1.3 cases per 100,000 in 1975 to 0.3 cases per 100,000 in 2014. The 5-year overall survival (OS) for stage 1/2a is approximately 90%; on the other hand, stage 4 disease has a 5-year OS of approximately 60% [3–5].

There are numerous studies investigating the epidemiological aspects of HL in both developed and developing countries throughout the globe [2, 4, 6–8]. Cancer incidence and mortality vary significantly between developed and developing countries [4, 8, 9]. The variation in survival may be related to differences in the availability of resources (not limited to access to novel therapies but also technologies for diagnosis and monitoring) as well as other dimensions of access and quality of cancer treatment, early detection and prevention [8, 10, 11]. The lack of reliable statistics is a major concern in developing and under-developed countries including the Republic of Armenia. A synthesis of epidemiologic and molecular data from different clinical groups and diverse geographic regions might provide key information about the biology of this disease. Without health data on structure, treatment and outcome, it is difficult to determine whether healthcare implemented programmes and treatment protocols which have been successful in relatively wealth developed countries can be extrapolated to resource-limited settings. Therefore, population-based effectiveness studies in developing countries are essential in the development of their healthcare infrastructure [12]. For example, there is some early evidence suggesting that healthcare-related programmes and treatment protocols/procedures determined to be effective in the developed world might not always be as effective in the developing world which might be attributable to a combination of factors including patient, tumour, treatment and system-related factors [13–15]. In the developing world, the majority of patients are delayed in cancer diagnosis and present with advanced disease, which is more challenging to treat and cure, if even possible [16]. The delay in presentation is often due to a variety of factors, but commonly include a lack of awareness of the signs and symptoms of cancer, a lack of finances to travel to a hospital and cover the costs of diagnosis and treatment [17, 18].

There are few studies published from the developing world including Armenia regarding this topic. Fortunately, the success story in curing HL is not restricted to the developed world. Avagyan *et. al* [21] reported on a hospital based cohort study investigating the treatment challenges of HL in developing world [22]. This retrospective study showed that the treatment of HL could be successfully performed in a resource-limited setting and that the epidemiology and outcomes of HL in Armenia are possibly reaching those of developed countries [19]. The paucity of information and absence of a formal national cancer registry system in Armenia along the lines of Surveillance, Epidemiology, and End Results (SEER) in the USA, led us to conduct this study to evaluate the clinic-epidemiological characteristics of HL over a 15-year period.

Methods and materials

In Armenia, the National Institute of Health collects information nationwide from the countries hospitals and outpatient clinics. We obtained population-based HL incidence data from the National Institute of Health of the Republic of Armenia which contains information on incidence for a period of 15 years (1 January 2000 to 30 December 2014) from all treatment centres across the country. Histologically proven HL (morphology and immunochemistry) cases, diagnosed by an oncologic pathologist, of all ages were included in the study. The incidence, age distribution and sex distribution were the parameters studied. Incidence rates were described as new cases per 100,000 person-years.

Results

Age-specific incidence

During the 15-year period, 1,154 new cases of HL were diagnosed of which 148 (12.8%) patients were <20 years, 369 (32%) patients were 20–34 years, 183 (15.9%) patients were 35–44 years, 174 (15%) patients were 45–54 years, 122 (10.6%) patients were 55–64 years and 158 (13.7%) patients were ≥65 years of age (Figure 1; Table 1). In the majority of age groups, the highest morbidity rates were observed till 2007. In subsequent years, the rate has decreased and stabilised and is comparable to that observed in the USA and Europe. The peak incidence was different each year but it has bimodal age distribution. The average incidence per year during the 15-year period was 2.3 cases per 100,000 (Figure 2). The average age during the 15-year period was 38 (38.4 ± 17.8) per 100,000.

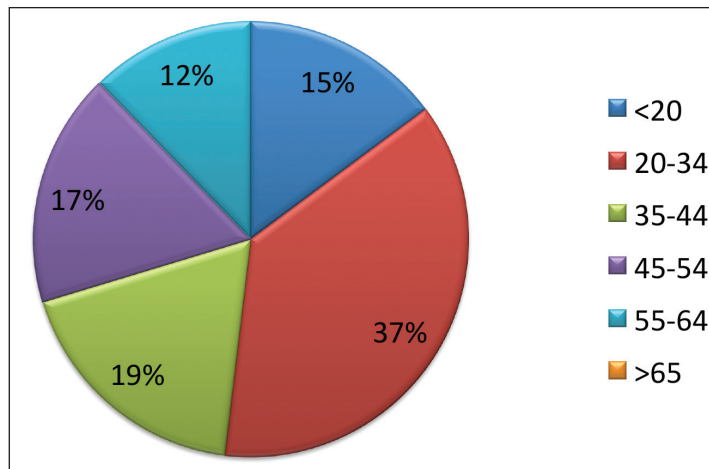


Figure 1. Age specific incidence of HL (%).

Table 1. Incidence and distribution of HL in Armenia according to age.

	<20, n	20-34, n	35-44, n	45-54, n	55-64, n	≥65, n
2000	18	27	16	17	9	12
2001	14	17	20	10	9	8
2002	15	18	9	11	6	2
2003	5	20	15	15	7	11
2004	8	18	10	8	5	20
2005	6	31	10	8	12	19
2006	8	19	10	8	8	11
2007	9	36	10	15	7	11
2008	12	25	19	16	9	12
2009	12	22	14	16	12	9
2010	9	32	15	11	4	12
2011	7	31	10	8	12	19
2012	7	19	10	8	8	11
2013	5	36	10	15	7	11
2014	13	25	19	16	9	12

Sex

In our patient cohort, there were 642 male patients compared to 512 females. The male to female ratio was 1.25:1 (Table 2). Age-specific incidence rates of HL were consistently higher among males than females in Armenia during the 15-year period. The largest sex-specific difference in age specific incidence rates occurred in the 0-20 and 20-34 year age groups. In the first group, male sex was more predominant and in the second group, female sex was more predominant. Relatively speaking, age-specific rates were generally 15%-30% higher in males than females.

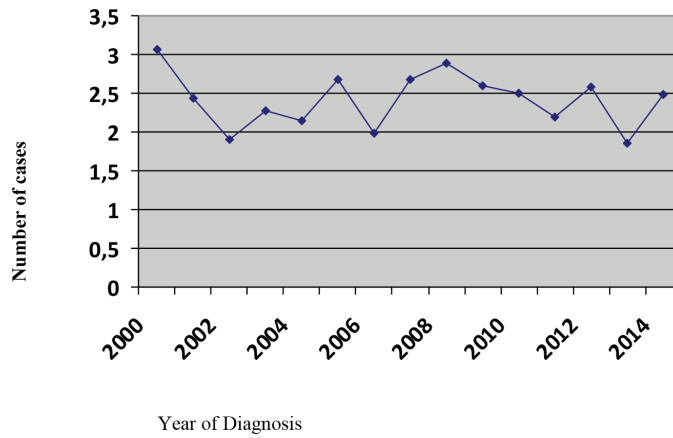


Figure 2. Incidence rate per 100,000 people.

Table 2. Incidence and distribution of HL in Armenia according to year and sex.

Year	Male, n	Female, n	Male/female ratio
2000	53	46	1.15
2001	43	35	1.23
2002	31	30	1.03
2003	44	29	1.52
2004	34	35	0.97
2005	53	33	1.61
2006	37	27	1.37
2007	53	33	1.61
2008	48	45	1.07
2009	48	37	1.30
2010	45	38	1.18
2011	31	37	0.84
2012	38	40	0.95
2013	32	24	1.33
2014	52	23	2.26
Total	642	512	1.25

Discussion

Armenia's health care system features three principal components: the national or 'republican' service level, which provides patients with large tertiary care hospital centres and an epidemiological service; the regional service level provides smaller hospitals and less sub-speciality care; the municipal and community service level provides primary health care services in community-based clinics with primary care physicians [23, 24].

Similar to many other developing countries, the Republic of Armenia also lacks a population-based national cancer registry (e.g. SEER) leading to assumptions being made as to the relative frequencies of the varying stages of different cancers based on global trends, which can be misleading and so efforts to improve cancer registries are required. Developing countries lack the funding to invest in comprehensive national cancer registries [25, 26]. In those developing countries where resources exist and cancer control policies have been formulated, there is often a lack of political will to implement these policies [27].

Current statistics are based largely on figures from hospital-based registries, which are often incomplete. Consequently, we had limitations regarding collection of some epidemiological data including data on patient survival. The major specialised medical institution dealing with the diagnosis and treatment of haematologic malignancies is the Hematology Center after prof. R.H.Yeolyan of the Ministry of Health located in the capital city Yerevan. The majority of HL patients are diagnosed and treated at this institution. A smaller volume of lymphoma patients receives their treatments at the National Center of Oncology named after V.A. Fanarjyan of the Ministry of Health, Muratsan Hospital Complex of Yerevan State Medical University. Lastly, there are a few private oncology clinics that also provide cancer treatment for those with financial resources, all the above centres are located in the same capital city. In the second and third largest cities, Gyumri and Vanadzor, respectively, each has a single state-owned outpatient clinic that also treats a few patients with HL.

Lymphomas are among the most common haematologic malignancies affecting the Armenian population. HL comprises a substantial proportion of these tumours [25]. In Armenia, HL is treated according to the standard international treatment regimens such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) with or without radiation therapy [26–28]. The treatment of patients is primarily guided by the clinical stage of disease as determined by the Cotswolds classification [29]. Patients with early stage disease (stage I to II) are usually treated with a combination of chemotherapy plus radiation therapy. The amount of chemotherapy and dose of radiation differ for patients with favourable and unfavourable prognosis disease. Chemotherapy alone is an acceptable alternative for patients with favourable disease characteristics at higher risk for complications from radiotherapy. For patients with advanced stage (stage III to IV), combination chemotherapy is the main treatment. Radiation therapy may be used for select patients as consolidation [30, 31].

During the last few years, salvage therapy methods of treatment have been introduced at the Ministry of Health's Hematological Center and Muratsan Hospital Complex of Yerevan State Medical University, which were not available in Armenia previously, including high-dose chemotherapy (HDC), stem cell harvest and rescue and a stem cell processing laboratory. HDC and autologous stem cell transplantation (ASCT) can salvage 40%–70% of patients with relapsed or refractory HL [32, 33]. More importantly, in resource limited countries without access to new therapeutics, HDC with stem cell rescue is much more financially feasible.

There are variations in the epidemiologic and clinico-pathological characteristics of HL in relation to geography and socioeconomic status. In the industrialised countries, HL has a bimodal incidence with the main peak in young adults of 15–35 years and the second one occurring after the age of 50. On the other hand, the disease appears more in young children in the developing countries. The current epidemiologic understanding of HL would suggest that the first peak (15–35 years) relates to specific factors affecting children (Epstein Bar Virus (EBV)-positive) and young adults (predominantly EBV-negative). The second peak (50 years) relates to the determinants of HL affecting older adults (largely resulting from a lack of immunologic control of latent EBV infection) [34, 35].

In one study from the USA covering the years from 2000 to 2007, 16,710 cases of HL showed that Asians and African Americans had a low incidence. The bimodal pattern of incidence also was less prominent for African American males. Asian and African American patients presented at a mean age of 38 years compared to 42 years for Caucasians ($p < 0.001$) [6]. Among the demographic characteristics of the different age groups, our results found a characteristic bimodal distribution, with the first, larger peak seen for adolescents and young adults (15–35 year age group) and a second, smaller peak occurring for adults (around 59 years of age).

The differences in incidence of HL by sex might suggest the importance of host factors [36–40]. In HL patients, high male to female ratio has been observed consistently in various studies [42]. A number of explanations have been put forward to explain this male predominant pattern of HL. Correa and O'Connor [41] suggested that females appeared to be less susceptible and more resistant than males to the initiating process and causative factors of HL. The excess of male patients in adult group might be partly explained on the basis of hormonal factors [39]. As expected, our results also demonstrated male predominance during this period of time. It should be noted that during the abovementioned 15 years, many significant changes took place in the diagnosis and treatment of haematologic malignancies in Armenia. Particularly,

immunohistochemical analysis was launched in 2006, radiotherapy techniques have changed significantly over the past decade, HDC and ASCT have become available and many doctors and nurses received training abroad from leading American and European institutions.

Unfortunately, there are also some gaps in managing cancer patients; for example, PET-CT isn't available in Armenia and the only option for patients is to travel to another country to access this imaging modality, which in fact, for most patients is not an option due to financial reasons and the lack of more sensitive imaging modalities may very well impact patient outcomes [43–46]. Fortunately in the case of HL, the curative regimen of ABVD is relatively affordable, however, treating relapsed refractory HL with novel therapies such as immune-checkpoint inhibitors becomes financially problematic.

One of the greatest challenges of modern cancer medicine is to introduce evidence based curative procedures into developing countries to benefit patients of diverse socioeconomic classes [14, 19]. As a developing country, Armenia faces serious problems concerning diagnosis and treatment of these diseases. The reasons include late diagnosis, lack of treatment compliance, fragmented care, financial difficulties, cultural and social factors, distrust and belief in alternate medicine, etc. Another critical problem is the shortage of oncologists and specialised oncology nurses in Armenia [18, 19]. It is known, that experienced staff and a coordinated multidisciplinary approach are essential components of appropriate cancer care and result in significant cancer health disparities reduction. Avagyan *et al* [21] reported, that in the resource limited setting, it is possible to get similar results as those reported from developed countries by incorporating the appropriate standards of care and by the coordinated teamwork [47]. In Armenia, steps forward have already been implemented to make the treatment and follow-up of HL more efficient and complete. These include detailed collection of patient data and disease related characteristics, accurate follow-up and continuous training of staff. To the best of authors' knowledge, the major limitation of this evaluation is that these parameters have not yet been validated in other population-based studies in Armenia.

Conclusion

Armenia is an ethnically homogeneous country and any epidemiologic study becomes a population or cohort study, thus creating good prospects for conducting experimental and clinical trials. Retrospective studies like ours may provide baseline data for future prospective studies. Such data may also give an insight into the aetiology and pathogenesis of HL in Armenia's geographical region. The results of our study show that the incidence of HL in Armenia has not changed significantly over the past 15 years and is similar to the rates in the western world.

Conflicts of interest

The authors have no conflicts of interest to report.

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