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Pediatric Cancer Burden and Treatment Resources within the Pediatric IeDEA Consortium

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Abstract

Introduction—The incidence and treatment of cancer in HIV-infected children from resource-limited settings has not been extensively studied.

Objectives—Develop and implement a cross-sectional survey to evaluate pediatric cancer burden, diagnostic modalities in use, and treatment availability as perceived by HIV clinic staff at regional International Epidemiology Databases to Evaluate AIDS (IeDEA) sites.

Methods—IeDEA regional investigators developed a cross-sectional clinical site survey which included questions on the numbers and types of pediatric cancers observed, modalities used to treat identified cancers and treatment options available at individual sites in the Asia-Pacific, Latin America, Central Africa, East Africa, West Africa, and Southern Africa regions.

Results—Kaposi sarcoma, non-Hodgkin lymphoma and Burkitt lymphoma were reported by site personnel to be the most prevalent types of cancer in the pediatric HIV population. Survey results

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indicate access to comprehensive cancer treatment modalities is very limited for children in these regions despite HIV care and treatment sites reporting that they diagnose pediatric cancers. Responses also showed evaluating cancer in the pediatric HIV population is a challenge due to a lack of resources and varying treatment availability within regions.

Conclusion—Further study is needed to increase our understanding of the changing epidemiology of cancer in HIV-infected pediatric populations. Increased financial and technical resources are critical to aid in the advancement of health services to support treatment of these children in resource-constrained settings.

Keywords

HIV; Cancer; Pediatrics; Resource-limited settings

Introduction

Globally, 1.8 million children were estimated to be living with HIV at the end of 2015, with the vast majority from low- and middle-income (LMI) countries¹. Antiretroviral treatment (ART) coverage for children younger than 15 years of age in LMI regions increased from approximately 14% in 2010 to 32% in 2014². Given the improvement in ART availability in these areas, HIV-infected children are likely to survive longer with HIV-related co-morbidities. Prolonged immunosuppression and concomitant viral infections are risk factors for malignancy among HIV-infected people³; therefore further study of these patients may lead to a better understanding of the pathogenesis of HIV-related pediatric malignancies⁴.

Limited data from LMI regions suggest increasing incidence of cancer in HIV-infected children. In South Africa, prevalence of Burkitt lymphoma was over 46 times more likely with HIV infection and all cases of Kaposi sarcoma (KS) (n=10) were observed in HIV-positive children⁵. Similar patterns were observed in Uganda with significant increases in the rates of KS (95-fold increase) and Burkitt lymphoma (7-fold increase) in HIV-infected children⁶. Reported cancer incidence rates from resource-constrained countries may under-represent true incidence rates owing to many factors, including lack of systematic cancer data collection and limited diagnostic capabilities^{7,8}.

Furthermore, there are regional differences in pediatric cancer mortality with high-income countries reporting a survival rate nearing 80%, whereas sub-Saharan African countries, for example, report that roughly 80% of children die without access to adequate cancer care⁸. Chemotherapy is not routinely available in many LMI settings and thus may not be accessible for appropriate cases such as KS refractory to ART⁹. Additionally, radiation, which is used as an adjuvant modality in the treatment of many cancers, is often not available in resource-poor settings.

Although medical care is improving in these regions and some localities have established cancer registries, accurate metrics on diagnosed cases as well as specific cancer services and treatment availability, especially from a pediatric HIV clinic perspective, are still inadequate in many areas. Given the insufficient data regarding disease burden and treatment availability among pediatric HIV patients, a cross-sectional clinical site survey was

developed and implemented by the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium to evaluate pediatric cancer burden, diagnostic modalities in use, and treatment availability at each site.

Methods

Study Design

This cross-sectional survey of sites within IeDEA received approval under the umbrella of the East African IeDEA Consortium by the Indiana University School of Medicine Institutional Review Board, as well as by all required regulatory bodies of the collaborating sites and countries.

Study Sites

The IeDEA network is a global research consortium established in 2005. Researchers from clinical sites collaborate to collect and define key variables, harmonize data, and implement methodologies to generate large data sets to address high priority HIV/AIDS research questions. This study describes responses to a pediatric cancer survey conducted in IeDEA regions which care for HIV-positive children and included sites from the Asia-Pacific, Caribbean, Central and South America (CCASAnet), Central Africa, East Africa, West Africa, and Southern Africa IeDEA regions¹⁰. Study sites surveyed comprised a diverse group of healthcare settings (urban/rural) at several facility care levels. The majority of sites from Asia-Pacific, CCASAnet, Central Africa, and West Africa were located in urban areas while East Africa and Southern Africa sites predominately represented mixed urban/rural settings. Seventeen sites were primary health centers, none of which were from the West Africa region. Central Africa and CCASAnet were the only regions without a secondary (district/provincial hospital) site, and all regions had a least one tertiary (teaching/national referral hospital) site.

Data Collection, Management and Analysis

Regional investigators developed a standardized site assessment tool including 253 questions regarding site resources, clinical practices, and access to drugs and laboratory monitoring for adult and pediatric clinical settings. The pediatric cancer section included 38 questions about estimated numbers and types of pediatric cancers seen in the previous 5 years, modalities used to treat cancers and general questions about available treatment options. Separate databases were created for each of the participating regions using REDCap, a secure, web-based application designed and hosted at Vanderbilt University to support data capture for research studies¹¹. The survey was translated from English into French and Spanish by professional translators at the NIH Clinical Center in Bethesda, USA¹⁰.

Regional data centers coordinated distribution of the survey to the sites and monitored completion. The initial pediatric data collection was completed by January 2010 by the primary contact pediatrician at each site or by staff under their direction. Respondents were part of the HIV care and treatment program and did not possess any specialized skills related to cancer medicine. Site-level responses were evaluated for inconsistencies and queries were sent to IeDEA regional pediatric representatives for reconciliation. Sites in Southern Africa

had completed a comparable regional survey between January-March 2009, and were subsequently asked to complete the pediatric cancer module as a supplement survey. Summary statistics were calculated using SAS version 9.4 (SAS System for Windows, Copyright © 2016 SAS Institute Inc.).

Results

The pediatric cancer module was completed by 62 out of 112 eligible sites: 10 (67%) in Asia-Pacific (Cambodia, Indonesia, Malaysia, and Thailand), 3 (75%) in CCASAnet (Argentina, Haiti, and Honduras), 4 (36%) in Central Africa (Burundi, Cameroon, and Democratic Republic of Congo), 32 (65%) in East Africa (Kenya, Tanzania, and Uganda), 4 (22%) in Southern Africa (South Africa and Mozambique) and 9 (60%) in West Africa (Benin, Côte d'Ivoire, and Senegal). Nineteen (30.6%) of these sites reported providing pediatric care exclusively while the rest provided combined adult and pediatric services. Respondents at 7 (11.3%) sites reported identifying no cancers within the last 5 years, 13 (21.0%) sites reported that it was unknown if they had identified cases of cancer, and 42 sites (67.7%) reported at least one case of cancer with varying patterns of occurrence by type. Fifty percent of responding sites reported diagnosing KS, 43.5% non-Hodgkin lymphoma (NHL), 37.1% Burkitt lymphoma, 37.1% leukemia, 32.3% Wilm's tumor, 30.6% bone/soft tissue sarcoma, 29.0% Hodgkin's disease, 25.8% neuroblastoma, 24.2% conjunctival carcinoma, 22.6% laryngeal papillomatosis, 9.7% retinoblastoma and 1.6% hepatic tumors (Table 1). No cases of cervical cancer were reported by any sites.

Approximately one-third of these sites recorded more than 5 cases of KS while one-fourth reported greater than 5 cases of both Burkitt lymphoma and NHL. Of the 42 sites reporting at least one case of pediatric cancer, the majority of cancer treatment was reported to be provided at general tertiary referral hospitals and dedicated cancer centers, with a small number of sites indicating most of their patients received cancer care at HIV clinical sites.

Limited access to combined surgical, chemotherapy, and radiation treatment services was reported across all IeDEA regions. Although 48 sites (77.4%) reported having access to at least one of these major treatment modalities, only 23 (37.1%) indicated access to all three. Radiation was most often the limiting service as it was available at only 23 (37.1%) sites, while surgery was available at 46 (74.2%) and chemotherapy at 48 (77.4%) sites. Regional differences in reported access to treatment services were observed. Surgery was available more often at Asia-Pacific, East Africa, and Southern Africa sites (90%, 81%, and 75% respectively), while less available in West Africa (55%), Central Africa (50%) and CCASAnet (33%). Similar patterns were observed regarding access to chemotherapy and radiation as well, with Asia-Pacific, East Africa, and Southern Africa sites generally providing more treatment resources than other regions. West Africa was the only region where all sites reported that radiation was unavailable. CCASAnet and Central Africa each had one site report no access to any of these modalities.

Survey responses also indicated the use of treatment modalities varied across sites reporting at least one type of cancer, which was likely driven by the availability of services and the fact that not all modalities would be appropriate for all types of cancers. According to survey results of sites reporting at least one cancer case, chemotherapy was used sometimes or often

(for greater than 25% of pediatric HIV patients) at 30 (71.4%) sites, followed by surgery at 21 (50.0%) and radiation at 3 (7.1%) sites. Survey respondents estimated that palliative care was available and provided for the majority of cancer patients at approximately half of all sites. Hormone replacement therapy, traditional forms of treatment and ART were additional treatment options used in a small number of cases depending on the underlying malignancy.

Discussion

Similar patterns of cancer distribution from previous findings were observed in survey responses showing NHL, KS and Burkitt lymphoma as the most prevalent cancers among HIV-infected children in resource-constrained areas^{5,6,12}. Regional differences were observed in some of the higher reported types of cancer. For example, the number/percentage of sites reporting diagnoses of KS in the Asia-Pacific and CCASAnet regions was much lower than the African sites. KS and leukemia were the only cancer types reported by at least one site in every African region. It is unclear if these differences are due to regional epidemiologic trends or the diagnostic capabilities of the individual sites.

Missing data may limit interpretation of these results; 33% of responding sites had missing data regarding treatment and 21% reported it being unknown if they had diagnosed any cancer cases within the last 5 years. As these data were reported at the site level, detailed patient-level analyses, including total number of cancer cases, are not feasible. Additionally, many of the sites participating in IeDEA have academic or research collaborations and as such may be better resourced than others in the region, although the majority of sites are routine public sector locations. Treatment availability and overall case reporting results suggest the possibility that sites better equipped for diagnosis and treatment of cancer were more likely to fully complete the survey, which may have resulted in an underreporting of the disease burden in HIV clinics within the IeDEA consortium.

The varying number of sites surveyed between regions reflects the pediatric HIV patient population differences among regions but was also impacted by programmatic differences. East Africa has two programs with multiple sites and thus had more sites reporting data. However, single site programs in other regions may have coverage over a far greater number of patients than sites in East Africa, which was the case for all responding Southern Africa sites for example. The overall response rate of 55% was lower than expected. However, given that the 42 sites reporting cancer cases represented multiple countries within each region (except Southern Africa) and included several types of health care centers and settings, we feel they provide a general view of the status of cancer diagnostics for HIV-infected children within the regions assessed. Centers not reporting any cases had no observed spatial or facility level patterns.

Survey results indicate evaluating cancer in the pediatric HIV population at the point of HIV care and treatment has been a challenge due to a lack of resources to both accurately diagnose and treat these malignancies. Although there are limitations to the interpretation of these results, the large geographic coverage of this survey highlights the magnitude of the investment that is needed across several regions for cancer diagnosis, surgery, chemo- and radiotherapy. There are also additional epidemiologic patterns worth further investigation,

such as recent evidence that a reduction in some HIV-related cancers is observed when ART is initiated prior to severe immunodeficiency¹³. Thus, collaboration with HIV clinics in establishing databases and accurate registries while continuing surveillance of treatment modalities is essential to further current understanding of the coexistence of these diseases.

Conclusion

This study indicates that access to comprehensive cancer treatment modalities has been limited for HIV-positive children despite reports that HIV care and treatment sites are diagnosing pediatric cancers. Significant investment, including increased financial and technical resources to aid the advancement of health services to support treatment of these children in LMI settings is critical. Further studies would also increase our understanding of the changing epidemiology of cancer in HIV-infected pediatric populations and help to monitor evolving health services at the point of HIV care in LMI countries.

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Number of sites reporting cases (and estimated number of reported cases) within the last 5 years of surveyed cancer types by region (n = number of sites in each region).

Table 1

Cancer Type	Asia-Pacific n=10	CCASAnet n=3	Central Africa n=4	East Africa n=32	Southern Africa n=4	West Africa n=9	Total n=62
Number of Sites							
Kaposi sarcoma							
1 – 5 Cases	1		1	6	2	2	12
> 5 Cases			1	17	1		19
% Sites *	10.0	0	50.0	71.9	75.0	22.2	50.0
Non-Hodgkin lymphoma							
1 – 5 Cases	4	1		1	3	2	11
> 5 Cases				16			16
% Sites *	40.0	33.3	0	53.1	75.0	22.2	43.5
Burkitt lymphoma							
1 – 5 Cases	1			4	1	1	7
> 5 Cases				15	1		16
% Sites *	10.0	0	0	59.4	50.0	11.1	37.1
Leukemia							
1 – 5 Cases	2		1	16	2	2	23
> 5 Cases							
% Sites *	20.0	0	25.0	50.0	50.0	22.2	37.1
Wilm's tumor							
1 – 5 Cases		1	1	16		2	20

Cancer Type	Number of Sites					Total n=62
	Asia-Pacific n=10	CCASAnet n=3	Central Africa n=4	East Africa n=32	Southern Africa n=4	West Africa n=9
> 5 Cases						
% Sites*	0	33.3	25.0	50.0	0	22.2
32.3						
Bone/soft tissue sarcoma						
1 – 5 Cases	1		16	2		19
> 5 Cases						
% Sites*	10.0	0	0	50.0	50.0	0
30.6						
Hodgkin's disease						
1 – 5 Cases	1		16	1		18
> 5 Cases						
% Sites*	0	33.3	0	50.0	25.0	0
29.0						
Neuroblastoma						
1 – 5 Cases			15			16
> 5 Cases						
% Sites*	0	0	0	46.9	0	11.1
25.8						
Conjunctival carcinoma						
1 – 5 Cases			15			15
> 5 Cases						
% Sites*	0	0	0	46.9	0	0
24.2						
Laryngeal papillomatosis						
1 – 5 Cases	1		12			14
> 5 Cases						

Cancer Type	Asia-Pacific n=10	CCASAnet n=3	Central Africa n=4	East Africa n=32	Southern Africa n=4	West Africa n=9	Total n=62
	Number of Sites						
% Sites*	10.0	0	0	37.5	0	11.1	22.6
Retinoblastoma							
1 – 5 Cases	1			5			6
> 5 Cases							
% Sites*	10.0	0	0	15.6	0	0	9.7
Hepatoma							
1 – 5 Cases						1	1
> 5 Cases							
% Sites*	0	0	0	0	0	11.1	1.6
Any Cancer Diagnosis							
% Sites**	40	66.7	100	78.1	75	44.4	67.7

* Percentage of sites within each region that reported at least 1 case within the last 5 years.

** Percentage of sites that reported at least 1 case of any surveyed cancer type within the last 5 years.