Malignancy and all-cause mortality; incidence in adolescents and young adults living with perinatally acquired HIV

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Abstract

Background: Adults living with HIV have an increased risk of malignancy yet there is a paucity of data for adolescents and young adults (AYA) with perinatally acquired HIV (PaHIV).

Methods: Retrospective cohort analysis of all-cause mortality and malignancies in AYA with PaHIV aged 10–24 years attending a tertiary unit from 01 January 2004 to 31 December 2017, assessing cancer presentation, immunology and comparing mortality and malignancy incidence to age-matched UK general population rates.

Results: A total of 290 AYA with PaHIV contributed 2644 person-years of follow up. Six (2.0%) died within the study period at a median age of 17 years (interquartile range [IQR]15–19), 3 of malignancy, 2 with end-stage HIV and 1 with cryptococcal meningitis. Overall mortality rate was 2.3/1000 person-years, with an age-matched general population rate of 0.2/1000 person-years. Eight (2.8%) were diagnosed with a malignancy; 6 with lymphoma (*n*=3 Hodgkin's, *n*=1 Burkitt's, *n*=2 B-cell) and one each with hepatocellular carcinoma and gastrointestinal adenocarcinoma. At cancer diagnosis the median age was 19 years (IQR 14–23), median CD4 T cell count was 453 cells/mm^3 (IQR 231–645) and median length of HIV viremia was 15 years (IQR 12–17). The incidence rate of a malignancy was 3.0/1000 person-years in AYA with PaHIV, whilst that in the age-matched general population is 0.2/1000 person-years.

Conclusion: AYA living with PaHIV had an increased risk of all-cause mortality and of malignancy compared to their uninfected peers, with the excess in malignancy driven by lymphomas. It is hoped that earlier access to antiretroviral therapy will mitigate some of the AIDS-defining and non-AIDS defining risks for future generations.

Keywords: malignancy, mortality, adolescents, perinatally acquired HIV, lymphoma

Introduction

Despite suppressive antiretroviral therapy (ART) and restoration of near normal life expectancy, people living with HIV (PLWH) are at increased risk of both AIDS-defining and non-AIDS defining malignancies when compared to uninfected age-matched populations [1]. However, there is a paucity of data disaggregated by age and route of transmission for adolescents (aged 10–19 years) and young adults (aged 20–24 years) (AYA) living with HIV, as highlighted by Bohlius *et al.* [2]. Adolescents are the only age group in which HIV-related mortality continues to rise, with minimal data on mortality incidence and causation following transition to adult care [3,4].

The excess risk of malignancy in PLWH is driven by the interplay of immunosuppression, HIV viremia, and the persistence of oncogenic viruses [5]. Whilst suppressive ART markedly reduces the risk of AIDS defining malignancies in adults, AYA have poorer rates of retention in care and adherence to ART, with viral suppression rates falling below 25% in some cohorts [6]. Furthermore, AYA with perinatally acquired HIV (PaHIV) have life-long exposure to HIV and immune dysregulation, with a proportion co-infected with oncogenic hepatitis B and C viruses (HBV, HCV) increasing the risk of hepatocellular carcinoma (HCC) [7]. In American youth living with HIV, 49% of malignancies in 15–19 year olds and 69% in 20–29 year olds were attributed to oncogenic infections [8].

The commonest cancers reported in AYA living with HIV are Kaposi's sarcoma and non-Hodgkin lymphoma (NHL), associated with human herpes virus 8 and Epstein–Barr virus co-infection

respectively [2,9,10]. A single centre cohort study from the UK reported increased rates of new NHL diagnoses in AYA with PaHIV compared to the general age-matched population, with an incidence rate ratio (IRR) of 25.9 (95% CI 8.31–61.7, *P*<0.0001) [10]. Five of 147 (3.4%) youth developed NHL at a median age of 19 years (range 18–23), presenting with advanced disease, low nadir CD4 T cell counts and an average of 14 years of prior HIV viremia. Treatment outcomes were not reported and to date there is no longitudinal data on the outcomes for AYA living with HIV and a malignancy following transition to adult care.

We conducted a single centre retrospective review of all AYA with PaHIV aged 10–24 years and in those with a malignancy diagnosis looking at presentation, diagnosis, risk factors and treatment outcomes and compared incidence rates for all-cause mortality and malignancy to age-matched UK general population data. The incidence rate of mortality and malignancy in 2015 amongst AYA aged 10–24 in the general UK population was 0.23/1000 person-years (95% CI 0.23–0.25) and 0.23/1000 person-years (95% CI 0.23–0.24) respectively [11,12].

Methods

We conducted a single centre retrospective review of all-cause mortality and malignancy diagnoses with onset occurring from 10–24 years of age in AYA with PaHIV between 01 January 2004 and 31 December 2017. Inclusion criteria included; those aged 10–24 years, PaHIV, and a minimum of two outpatient appointments within the study period. Data were taken from case records and anonymised. All AYA were followed from the age of 10 years or from the start of the study period if they were already >10 years of age on 01 January 2004, to the end of the study period/their 25th birthday/death/transfer of care/loss to follow-up, whichever was sooner.

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We described HIV-related parameters (CD4 T cell count [cells/mm^3], viral load [copies/mL], years of viremia [viral load >50 copies/mL detected by branch DNA assay]), presentation, treatment and outcomes of AYA diagnosed with malignancy during the study period. Results are presented as medians with interquartile ranges (IQR) and incidence rates (IR) per 1000 person-years with 95% confidence intervals (CI). IRs were modelled using a Poisson distribution and were presented for all-cause mortality, all malignancy and lymphomas. IR of death and malignancy in the general population was retrieved from the UK Office for National Statistics and Cancer Research UK respectively. All statistical analysis was performed using MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; 2018).

Results

Mortality and malignancy and incidence

A total of 290 AYA with PaHIV aged 10–24 years were registered with the service between 2004 and 2017 and were included in the analysis, contributing 2644 years of follow-up. During the study period, 2 (0.7%) were lost to follow-up, 14 (4.8%) transferred care and 6 (2.1%) died, 3 of causes other than malignancy: 1 from cryptococcal meningitis (15 years, 2006), 1 from end-stage HIV and poor adherence to ART (20 years, 2008) and 1 from end stage HIV, poor adherence to ART and gram-negative sepsis (19 years, 2009). Eight AYA with PaHIV were diagnosed with a malignancy at a median age of 19 years (IQR 14–23, range 10–24); 6 with lymphoma, 1 with HCC and 1 with metastatic adenocarcinoma of upper gastrointestinal (GI)/biliary origin (Table 1). Three out of 8 died within the study period; all from progression of the primary malignancy.

The IRs of malignancy and mortality in the cohort are shown in Table 2.

Malignancy presentations

Of the AYA with PaHIV diagnosed with a malignancy, 7/8 were male, 6/8 black British/African. All patients were engaged in HIV follow-up; 4 in paediatric care and 4 in specialist AYA services post transition to adult care. The patients with lymphoma presented primarily with systemic features of fever and weight loss (n=3), cervical lymphadenopathy (n=2) and superior vena cava obstruction owing to mediastinal lymphadenopathy (n=1). Four out of 6 presented with advanced disease; Ann Arbor stage III/IV.

The adolescent with GI adenocarcinoma presented with a 4-month history of abdominal pain and weight loss on returning from a year abroad, off ART with a CD4 T cell count of 420 cells/mm^3. MRI showed narrowing of the common bile duct and endoscopic biopsies at biliary stenting were consistent with HIV associated cholangiopathy. However, 5 months later emergency laparotomy for bowel obstruction revealed a disseminated adenocarcinoma. He underwent palliative care and died soon after.

The HCC diagnosis was made on routine alpha-fetoprotein screening in an adolescent on suppressive ART for HIV and HBV for a decade and is described in detail elsewhere [7]. In summary, he underwent partial right hepatectomy for a solitary 5cm HCC, however subsequently relapsed and died from metastatic disease.

Immunology and virology

The median CD4 T cell count at malignancy diagnosis was 453 cells/mm^3 (IQR 231–645) with a median nadir CD4 T cell count of 220 cells/mm^3 (IQR 9–417). Median length of detectable viremia prior to malignancy diagnosis was 15 years (IQR 12–17). Six out of 8 patients had a history of longstanding poor adherence to

ART, 4 with a detectable HIV viral load at malignancy diagnosis. All had suppressive ART regimens available although 4/8 had at least dual class HIV-1 associated resistance mutations.

Diagnostic complexities

A potential delay in diagnosis was reported retrospectively in the first five cases; median 12 weeks (maximum 20 weeks) from presentation to cancer diagnosis. Two had severe learning difficulties with inability to accurately report symptoms, and a third presented with non-specific symptoms with a delay in investigation of weight loss. Two patients, (n=1 Hodgkin's lymphoma (HL), n=1 GI adenocarcinoma), had falsely reassuring negative biopsies by lymph node fine needle aspirate and biliary brushings respectively.

Treatment and outcomes

Referral for cancer care was made to paediatric (n=3), adolescent (n=1) and adult (n=3) oncological services and directly to palliative care (n=1). At latest follow-up 5 were in remission, and 3 had died (Table 1). Deaths were owing to B-cell NHL, GI adenocarcinoma and HCC, aged 13, 15 and 20 years respectively. Those in remission were a patient with B-cell NHL (completed treatment for 2 months), 1 with Burkitt's lymphoma (completed treatment for 5 years) and 3 with HL (completed treatment for 14 years, 9 months and 2 years, respectively). All those alive are on suppressive ART, viral load <200 copies/mL.

Discussion

The overall mortality in this cohort of AYA with PaHIV aged 10–24 between 2004 and 2017 was low at 6/290 (2.1%). However, despite access to free healthcare including ART in a well-resourced setting, this was markedly higher than the age-adjusted general UK population rate [11]. Malignancies accounted for half of all deaths, the remainder associated with poor adherence to ART and end-stage HIV/AIDS events, all occurring >6 months after HIV diagnosis. Within the general population, deaths in 15–24 year olds in 2016 where most frequently due to external causes; accidents and intentional self-harm (58%), with 12% of death attributed to cancers, most frequently brain tumours and leukaemias [11]. The increased rate of malignancy in our cohort was driven by lymphomas (6/8 cases). Whilst NHL is an AIDS-defining cancer with rates in the pre-ART era markedly increased, rates of both NHL and HL are increased in PLWH, with the excess risk reduced but not eradicated by suppressive ART [13]. More recent data suggest further benefit of earlier initiation of ART prior to overt immunosuppression in adults and it is hoped that improved access to ART in early childhood globally will show similar benefit in those living with PaHIV [14].

Eades et al. reported an NHL incidence of 4.25/1000 person-years, 25 times that of the general population in a comparable UK PaHIV cohort post transition to adult care [10]. Our findings are remarkably similar in age, prolonged history of prior viremia, low nadir CD4 T cell count and advanced malignancy at presentation. The five cases presented by Eades were all cases of NHL but post treatment outcomes were not reported. Encouragingly results in adults living with HIV and a lymphoma suggest survival rates approaching HIV negative populations with dramatic improvement over the last 3 decades [15,16]. However, in the general population AYA have poorer overall cancer survival rates when compared to younger children, with survival further reduced in young men compared to young women [17,18]. In this cohort, although numbers are small, half have died from their malignancy, all young men, with a male preponderance in all malignancies (7/8, 88%). Factors associated with poorer outcomes in AYA include late presentation, lack of access to specialist oncology

Table 1 HIV-related variables, malignancy diagnosis and outcomes in AYA with PaHIV

| Case number | HIV-related variables | | | Malignancy diagnosis | | | | | Malignancy outcome | |
	Age of HIV diagnosis	Nadir CD4 T cell (cells/mm3)	viremia duration (years)	Classification	Year	Age (years)	CD4 T cell (cells/mm³)	Viral load (cells/mL)	Treatment	Outcome
1	2 years	490	13	B-cell lymphoma of descending colon (NHL)	2004	13	490	8493	Surgery and chemotherapy	Died
2	2 months	0	10	Classical Hodgkin's lymphoma. Stage IV	2004	10	100	275,675	Chemotherapy	In remission
3	At birth	420	15	Disseminated adenocarcinoma of upper GI/biliary origin	2009	15	1000	<50	Palliative care	Died
4	11 months	416	17	Burkitt's lymphoma (NHL). Stage IV	2012	18	416	23,515	Chemotherapy	In remission
5	13 years	180	15	Mixed cellularity classical Hodgkin's lymphoma in 2013. Stage IVa Relapse of nodular sclerosis Hodgkin's lymphoma in 2014, 2017.	2013	21	810	<50	Chemotherapy and autologous stem cell transplant (1) and radiotherapy allograft with maternal donor (2)	In remission
6	6 years	260	6	Hepatocellular carcinoma associated with Hepatitis B infection (HBV DNA <20 c/mL). Stage pT2N0M0	2014	19	590	<50	Surgery and Chemotherapy and Palliative care	Died
7	4 years	5	23	Nodular sclerosis Hodgkin's lymphoma. Stage Ia	2016	23	274	4863	Chemotherapy and radiotherapy	In remission
8	2 months	10	17	Primary mediastinal B-cell lymphoma (NHL). Stage IIa	2017	24	101	<50	Chemotherapy	In remission

AYA: adolescents and young adults; NHL: non-Hodgkin's lymphoma; PaHIV: perinatally acquired HIV.

Table 2 Incidence rates of mortality and malignancy in the general UK population aged 10–24 and present study cohort of AYA with PaHIV

	IR general population (95% CI)	IR AYA PaHIV cohort (95% CI)
Overall mortality	0.2 (0.2–0.3)	2.3 (0.8–4.9)
Malignancy	0.2 (0.2–0.2)	3.0 (1.3–6.0)
Lymphoma	0.05 (0.05–0.06)	2.3 (0.8–4.9)
HL	0.03 (0.03–0.04)	1.1 (0.2–3.3)
NHL	0.02 (0.01–0.02)	1.1 (0.2–3.3)

Incidence rates IR (IR) are expressed per 1000 person-years. AYA: adolescents and young adults; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma; PaHIV: perinatally acquired HIV.

services and the impact of the unique developmental transitions of adolescence [19]. Potential delay in the malignancy diagnoses were identified in the first five cases, highlighting the complexity of the cohort with learning difficulties, migratory populations and the need for adequate tissue biopsies, with two false negative results.

Due to the small absolute number of cases of malignancy and mortality in AYA, our data should be considered exploratory. Large cohort studies in high, middle and low-income settings, disaggregated by age and route of transmission with linkage of paediatric and adult datasets as AYA transition are required to evaluate incidence rates of malignancy and mortality in long-term survivors of the perinatal epidemic.

Conclusion

In summary, in this small cohort of AYA with PaHIV, the risk of death, malignancy and particularly lymphoma was increased when compared to their peers without HIV. It is hoped that with earlier access to sustained suppressive ART some of the excess risk will be ameliorated [14,20].

Acknowledgements

Conflicts of interest

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