Witness Name: Charles R.M. Hay
Statement No.: WITN3289171
Exhibits:WITN3289172 & WITN3289173
Dated: 30 May 2022

INFECTED BLOOD INQUIRY

EXHIBIT WITN3289173

The incidence of lymphoma in the UK haemophilia population between 1978 and 1999

Jonathan T. Wilde[a], Christine A. Lee[b], Sarah C. Darby[c], Sau Wan Kan[c], Paul Giangrande[d], Andrew N. Phillips[e], Mark Winter[f], Rosemary Spooner[d] and Christopher A. Ludlam[g], on behalf of the UK Haemophilia Centre Doctors' Organisation

Objective: To determine the incidence of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) in the UK haemophilia population during the 22 year period 1978–1999.

Design and methods: An analysis of patient data included on the UK Haemophilia Centre Doctors' Organisation lymphoma register. The number of cases of NHL and HD occurring in HIV-positive and negative patients in each 3-year period were compared with the expected incidence in the general male population.

Results: Eighty-nine cases of lymphoma were identified. Seventy-two cases (81%) occurred in HIV-positive patients (67 NHL, five HD), and 17 cases (19%) in HIV-negative patients (nine NHL, eight HD). The incidence of NHL in the HIV-positive cohort was significantly increased, with a ratio of observed to expected cases of 83.92 ($P < 0.001$) in the period 1985–1996. The ratio reduced to 42.15 during the period 1997–1999, presumably as a consequence of the introduction of highly active antiretroviral therapy (HAART). There was a significant excess of HD in HIV-positive patients, with an observed to expected ratio of 10.50 between 1985 and 1999 (based on five cases, $P < 0.001$). During the whole observation period, there was a significant excess of HD in HIV-negative patients, with an observed to expected ratio of 2.66 (based on eight cases, $P < 0.05$).

Conclusion: The incidence of lymphoma is significantly higher in HIV-positive UK haemophilia patients compared with HIV-negative individuals. Since the introduction of HAART, the incidence of lymphoma has tended to fall in the HIV-positive group.

AIDS 2002, **16**:1803–1807

Keywords: HAART, haemophilia, HIV, Hodgkin's disease, non-Hodgkin's lymphoma

From the [a]Department of Haematology, University Hospital Birmingham NHS Trust, Edgbaston, Birmingham B15 2TH, UK; [b]Haemophilia Centre and Haemostasis Unit, The Royal Free Hospital, London NW3 2QG, UK; [c]Clinical Trial Service Unit and Epidemiological Studies Unit, Radcliffe Infirmary, Oxford OX2 6HE, UK; [d]Oxford Haemophilia Centre, The Churchill Hospital, Oxford OX3 7LJ, UK; [e]Department of Primary Care and Population Sciences, Royal Free and University College Medical School, Royal Free Campus, London NW3 2PF, UK; [f]Kent Haemophilia Centre, Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG, UK; and [g]Department of Haematology, Edinburgh Royal Infirmary, Edinburgh EH3 9YW, UK.

Correspondence and reprint requests to: Dr Jonathan T. Wilde, Department of Haematology, University Hospital Birmingham NHS Trust, Edgbaston, Birmingham B15 2TH, UK.

Tel: GRO-C; fax: GRO-C; e-mail: jonathan.wilde@GRO-C

Received: 7 December 2001; revised: 4 April 2002; accepted: 29 April 2002.

ISSN 0269-9370 © 2002 Lippincott Williams & Wilkins

Introduction

Shortly after the characterization of AIDS in the early 1980s, it was observed that the condition was associated with a high incidence of non-Hodgkin's lymphoma (NHL) [1]. The development of these malignancies was presumed to be a consequence of the immunosuppressive effects of HIV infection. As lymphomas became established as a common clinical manifestation of HIV disease, the Centers for Disease Control included intermediate and high-grade NHL as AIDS-defining illnesses in 1985 [2]. As management strategies including infection prophylaxis improved, patients began to live longer in a state of advanced immunosuppression, and the incidence of lymphoma in HIV-infected individuals progressively increased [3,4]. By 1989, the overall incidence of NHL in HIV-positive patients in the United States was at least 59-fold that of the general male population [5], and by 1996 it was estimated at 200-fold [6]. However, since the widespread introduction of highly active antiretroviral therapy (HAART) in late 1996–early 1997 there has been a significant reduction in the incidence of NHL in HIV-positive patients [7–9], although interestingly the incidence of Hodgkin's disease (HD) does not appear to have changed significantly [7].

To date, there have been few publications detailing AIDS-associated lymphoma in patients with hereditary bleeding disorders. In this communication we report the pattern of lymphoma in the United Kingdom haemophilic population during the period 1978–1999.

Materials and methods

United Kingdom Haemophilia Centre doctors are invited to submit details of patients with hereditary bleeding disorders who develop lymphoproliferative conditions to the UK Haemophilia Centre Doctors' Organisation (UKHCDO) lymphoma register. For patients with haemophilia A or B who had developed a lymphoma, the date of diagnosis was combined with information held by the ongoing UKHCDO mortality study, which includes details of all patients with haemophilia A or B on the UKHCDO National Register [10–12]. At present, the study includes information on 7250 individuals who have been living in the UK during 1977–2000, together with vital status on 1 January 2000 and, where relevant, the date of death or loss to follow-up. For HIV-positive patients, the estimated date of seroconversion is held in the mortality study. An ascertainment of HIV status is thought to be virtually complete for the haemophilia population from 1 January 1985. Further details of this data collection are given elsewhere [10].

Person-years at risk were calculated as the time from the first inclusion on the UKHCDO National Register to the earliest of: the development of a lymphoma; death; loss to follow-up or 1 January 2000. Person-years were then subdivided into 5-year age groups for the calendar period 1977–1981, and the subsequent 3-yearly periods from 1981–1983 to 1997–1999, and from 1985, also by HIV status. The expected numbers of lymphoma cases were obtained by combining this information with age- and calendar-year-specific cancer incidence rates in the general male population of England and Wales, supplied by the Office of National Statistics. Confidence intervals for the ratio of observed to expected deaths (O/E) and tests for the departure of O/E from unity were calculated using exact Poisson theory. For NHL, O/E for 1978–1996 was compared with that for 1997–1999 using a Poisson regression model and a likelihood ratio test.

Results

In total, 89 cases of lymphoma were identified during the period 1977–1999. The bleeding disorder diagnoses of these patients were: severe haemophilia A = 67, moderate/mild haemophilia A = 19, severe haemophilia B = 3.

There was a high proportion of an extranodal presentation of NHL in the HIV-positive group, including 16 primary cerebral and seven gut-related lymphomas out of a total of 67 (see Fig. 1). Two patients presented with primary lung and jaw tumours, respectively, and of particular interest were two brothers who presented within 5 years of each other with an upper back soft-tissue lymphoma in almost the same site. There were two extranodal presentations of NHL (one gut-related

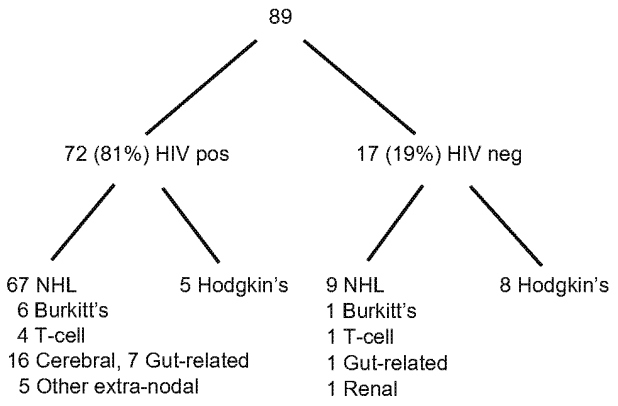

Fig. 1. Breakdown of diagnoses in 89 UK haemophilic patients with lymphoma diagnosed between 1978 and 1999. NHL, Non-Hodgkin's lymphoma.

and one renal) in the HIV-negative group out of a total of nine.

Only two HIV-positive patients remain alive. One patient was successfully treated for NHL in 1987. The other patient was successfully treated for HD in 1990 but relapsed in 1997. After further chemotherapy, he remains in remission at the time of writing. Four HIV-negative patients had never received factor concentrate before the development of lymphoma, and four patients (two HD, one NHL, and one Burkitt's lymphoma) remain alive after successful therapy.

The vast majority of patients died as a direct consequence of their lymphoma. Three patients, however, were successfully treated with chemotherapy, but died from AIDS-wasting syndrome between 9 months and 3 years after the diagnosis of NHL, with their tumours in remission. A further patient had widespread lymphoma at the time of accidental death. The median survival of patients from the time of lymphoma diagnosis was 4 months (range 7 days to 9 months). This figure was influenced by the especially poor prognosis of patients with primary cerebral lymphoma.

Table 1 and Table 2 summarize the numbers of NHL and HD in HIV-positive and negative patients compared with the expected numbers in the general male population. The number of cases of NHL in HIV-negative individuals (nine) is equal to the number expected. However, during the period 1985–1996 there was a huge excess in HIV-positive patients (60 observed compared with 0.72 expected, $P < 0.001$). The ratio of observed to expected numbers reduced to 42.15 in the period 1997–1999, corresponding to the period after the introduction of HAART. This reduction, however, just fails to reach statistical significance ($P = 0.06$).

During 1985–1999, there was a significant excess of HD in the HIV-positive group (five cases observed versus 0.48 expected, $P < 0.001$). The incidence of HD in HIV-negative individuals during the whole study period was also significantly higher than the expected rate (eight cases observed versus 3.01 expected, $P < 0.05$).

Discussion

The high incidence of lymphoma in HIV-infected individuals is likely to be a consequence of multifactorial immunosuppressive and immunomodulatory effects of the virus [13]. In the early years of the AIDS epidemic, Stehr-Green *et al.* [14] reported a striking lack of cases of lymphoma in HIV-positive haemophilic patients, suggesting that this patient group was not at increased risk of developing these malignancies. However, in 1991 Beral *et al.* [5] reported that the incidence of lymphoma in HIV-infected patients with hereditary bleeding disorders was higher than in any of the other HIV-positive groups. Furthermore, in 1992 the US National Cancer Institute's Multicenter Hemophilia Cohort Study [15] reported an incidence of NHL in HIV-positive haemophilic patients 24-fold that of age-matched normal men. In a second multicentre US study of over 1300 HIV-positive haemophilic patients monitored between 1978 and 1989 [16], the incidence of lymphoma was found to be 29 times that observed

Table 1. Numbers of observed and expected cases of non-Hodgkin's lymphoma in HIV-positive and negative patients in the UK between 1978 and 1999.

Calendar year	No. of cases observed (O)	No. of cases expected (E)	O/E	95% CI for O/E	*P* value for departure of O/E from 1
Not infected with HIV-1					
1978–81	2	0.74	2.71	(0.33, 9.78)	–
1982–84	2	0.75	2.66	(0.32, 9.60)	–
1985–87	3	0.82	3.65	(0.75, 10.66)	–
1988–90	1	1.17	0.85	(0.02, 4.76)	–
1991–93	1	1.48	0.68	(0.02, 3.76)	–
1994–96	0	2.03	0.00	(0.00, 1.82)	–
1997–99	0	2.19	0.00	(0.00, 1.69)	–
Total 1978–99	9	9.18	0.98	(0.45, 1.86)	–
Infected with HIV-1					
1985–87	6	0.16	38.45	(14.11, 83.68)	< 0.001
1988–90	23	0.18	125.27	(79.43, 187.97)	< 0.001
1991–93	14	0.17	82.51	(45.12, 138.44)	< 0.001
1994–96	17	0.21	82.48	(48.05, 132.05)	< 0.001
Total 1985–96	60	0.72	83.92*	(64.04, 108.22)	< 0.001
1997–99	7	0.17	42.15*	(16.95, 86.83)	< 0.001
Total 1985–99	67	0.88	76.14	(59.00, 96.69)	< 0.001

CI, Confidence interval.
**P* value comparing O/E during 1985–1996 with O/E during 1997–1999 = 0.06.

Table 2. Numbers of observed and expected cases of Hodgkin's disease in HIV-positive and negative patients in the UK between 1978 and 1999.

Calendar year	No. of cases observed (O)	No. of cases expected (E)	O/E	95% CI for O/E	*P* value for departure of O/E from 1
Not infected with HIV-1					
1978–81	0	0.46	0.00	(0.00, 7.99)	–
1982–84	2	0.41	4.90	(0.59, 17.70)	–
1985–87	2	0.31	6.37	(0.77, 22.98)	–
1988–90	3	0.34	8.80	(1.81, 25.70)	< 0.05
1991–93	0	0.36	0.00	(0.00, 10.18)	–
1994–96	0	0.54	0.00	(0.00, 6.79)	–
1997–99	1	0.58	1.72	(0.04, 9.59)	–
Total 1978–99	8	3.01	2.66	(1.15, 5.23)	< 0.05
Infected with HIV-1					
1985–87	2	0.11	18.49	(2.24, 66.78)	< 0.05
1988–90	3	0.10	29.12	(6.01, 85.09)	< 0.001
1991–93	0	0.09	0.00	(0.00, 41.59)	–
1994–96	0	0.10	0.00	(0.00, 38.39)	–
Total 1985–96	5	0.40	12.63	(4.10, 29.46)	< 0.001
1997–99	0	0.08	0.00	(0.00, 45.99)	–
Total 1985–99	5	0.48	10.50	(3.41, 24.51)	< 0.001

CI, Confidence interval.

in the general US male population and 37 times that of HIV-negative haemophilic patients. With the widespread introduction of HAART in late 1996–early 1997, it was anticipated that the occurrence of HIV-associated lymphomas would reduce markedly as a consequence of the restoration of immune competence. Although there was an immediate reduction in the incidence of opportunistic infections once HAART regimens were established, this was not initially the case for lymphomas [17,18]. However, three studies have recently reported that there has been a significant reduction in the overall incidence of NHL since the introduction of HAART [7–9], although one of the studies has shown that the incidence of HD has not changed significantly [7].

During the 22-year period 1978–1999 we observed 89 cases of lymphoma (NHL and HD) in the UK haemophilia population. The excess incidence of NHL among HIV-positive patients has tended to decline since the introduction of HAART therapy. There was no excess of NHL in HIV-negative patients. Although numbers are small, there has been an excess incidence of HD in the HIV-positive patient group. Interestingly, an excess has also been observed in the HIV-negative group.

In the study reported by Rabkin *et al.* [15], 12 cases of NHL and two cases of HD were observed in 1065 HIV-positive haemophilic patients and two cases of HD in 636 HIV-negative patients during a 12-year follow-up period. In the other US haemophilia study [16], 14 cases of NHL were observed in 1295 HIV-positive patients and three cases in 1125 HIV-negative patients during the period 1978–1989. No case of HD was observed in either patient group in that study.

There was a high proportion of high-grade NHL, extranodal presentations and cerebral lymphoma in our HIV-positive patients, similar to the disease pattern reported in other HIV-positive groups [19,20]. The prognosis of lymphoma in our cohort was very poor, with only two patients entering a sustained remission after chemotherapy. The median survival of HIV-positive patients after a diagnosis of lymphoma was comparable with the 7 months observed in the US study of Ragni *et al.* [16]. The survival period in our patients after presentation with primary cerebral lymphoma was particularly short.

Conclusion

Our study has therefore confirmed that the incidence of lymphoma is significantly higher in HIV-positive UK haemophilic patients compared with HIV-negative individuals. Since the introduction of HAART, however, the incidence of lymphoma has tended to fall in the HIV-positive group.

Sponsorship: Central funding for the UKHCDO mortality study was provided by Cancer Research UK (formerly Imperial Cancer Research Fund), the UK Medical Research Council, and Oxford Haemophilia Centre.

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