Published in final edited form as:

Transfus Apher Sci. 2011 April ; 44(2): 161–166. doi:10.1016/j.transci.2011.01.007.

Impact of the HIV epidemic and Anti-Retroviral Treatment policy on Lymphoma incidence and subtypes seen in the Western Cape of South Africa, 2002–2009:

Preliminary findings of the Tygerberg Lymphoma Study Group

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Abstract

The Tygerberg Lymphoma Study Group was constituted in 2007 to quantify the impact of HIV on the pattern and burden of lymphoma cases in the Western Cape of South Africa which currently has an HIV prevalence of 15%. South Africa has had an Anti-Retroviral Treatment (ART) policy and roll out plan since 2004 attaining 31% effective coverage in 2009. This study is designed to qualify and establish what impact the HIV epidemic and the ARV roll-out treatment program is having on the incidence of HIV related Lymphoma (HRL). Early data documents that despite the ART roll out, cases of HRL are increasing in this geographical location, now comprising 37% of all lymphomas seen in 2009 which is an increase from 5 % in 2002. This is in contrast to trends seen in developed environments following the introduction of ART. Also noted, are the emergence of subtypes not previously seen in this location such as Burkitt and plasmablastic lymphomas. Burkitt lymphoma is now the commonest HRL seen in this population followed by diffuse large B Cell lymphoma subtypes. The reasons for this observed increase in HRL is not ascribable to improved diagnostic capacity as the tertiary institute in which these diagnosis are made, has had significant expertise in this regard for over a decade. We ascribe this paradoxical finding to an ART treatment environment that is ineffective for a diversity of reason, paramount of which are poor coverage, late commencement of ART and incomplete viral suppression.

Background

The Tygerberg Lymphoma Study Group set out to establish the impact of HIV and the effect of the South African Anti Retroviral Treatment (ART) roll out program on the pattern of lymphoma presentations in the Western Cape of South Africa (SA) and in this publication we are presenting our initial findings. The HIV epidemic began in South Africa in the early 90s and is believed to have reached its maturity within the population around 2005 with a national average HIV prevalence amongst antenatal attendee plateau of about 30%. The disease has a peak incidence in the 20 to 40 year age group occurring earlier in females. The national HIV policy on treatment began in 2004 with a nationwide ART roll out program, which has been gaining momentum with each passing year (1). There is a high level of certainty that compared to the non HIV infected population, persons living with HIV (PLWH) have about a 70 to 200 times greater risk of developing one of the HIV Related Lymphomas (HRL) (2). The subtypes currently recognized as HRL are: Burkitt lymphoma (BL) (including anaplastic phenotypes) Diffuse large B cell lymphoma (DLBCL) (including immunoblastic features), Non-Hodgkin lymphoma with intermediate features between DLBCL and BL, pleural effusion lymphoma (PEL), plasmablastic lymphoma (PBL) and DLBCL with plasmablastic features arising from multi centric Castleman disease (MC CD). The oncogenic viruses EBV and HHV8 are typically associated with many of these subtypes (3,4). Evidence from numerous international HIV treatment cohorts suggest a significant reduction in HRL incidence with effective management on ART (5,6). Lymphomas arising in the setting of HIV/AIDS have to some extent been characterized in the developed world particularly prior to the onset of ART programs (7,8). By far the majority of cases are now found in the setting of the HIV epidemics in the developing world and in Africa in particular. There is a paucity of information and less certainty as to the extent of how geographical location, treatment policies, HIV subtypes and environmental factors are influencing this emerging disease complex especially in Africa where 90% of HIV global burden exists (9). The characteristics of this phenomenon are likely to differ compared to more resourceful environments. Inherently will be considerations of genetics and other factors specific to this continent such as poverty, malnutrition and other disease burdens (10, 11, 12). It is also likely that the patterns will differ from region to region within the Africa

sub Continent perhaps regulated by the variation in distribution and prevalence of known and unknown oncogenic viruses and ART policies (8, 9, 13).

Some epidemiological research is now beginning to emerge from local centers of experience on the African continent. Data from Gauteng Province of SA, where the HIV prevalence is averaging 25%, show a significant and growing burden of HRL over the last decade (14). The incidence and pattern of HRL in the Western Cape, a province of SA, with a population of 5 million, differing in environmental and ethnic constitution from the rest of SA and an estimated HIV prevalence of 15% (census report 2002) has not been previously documented.

Survival Data following the commencement of ART, show that only 53% of persons survive 12 months from the time of commencement (15). The viral load profile, the best measure we have of monitoring response to treatment, reveals that viral suppression is not optimally achieved in patients who do survive. Where adequate suppression is usually and practically considered to be a viral load of less than 400 copies/ml (16). Ideal targets are undetectable viral load levels of at least less than 50 copies/ml. Although the current National HIV treatment policy in SA is gradually evolving at least philosophically in concert with the global and general evidence that early treatment is better the policy as it stands is to commence ART at a CD4 count of 200/ml or below. Even at this low level of CD4 qualification for ART therapy, the roll out plan, has failed to reach 50 % coverage for eligible patients. Furthermore majority of PLWH who are commenced on ART, do so when their CD4 counts are below 100/ml. This is due to poor case identification, ineffective case retention and late presentation (16). Numerous studies in Africa and globally demonstrate that the capacity to regenerate a CD4 count that exceeds 500/ml on ART, when the immune system is damaged to this extent is limited (16, 17). There is evidence from epidemiological studies that the risk of developing an HRL increases in proportion to the depth of the CD4 nadir prior to ART commencement (18).

The above realities of late commencement of ART, low coverage and sub optimal viral suppression targets have four implications. The first is that even with the generally unacceptably late South African national treatment policy strategy, there are still a significant number of people who are not getting ART (16). Secondly those that do commence ART will do so when their immune system will have suffered severe and in many cases irreversible immune attrition, thirdly those that survive on ART will live longer but still remain immunocompromised to some extent and finally for those on ART, the permitted viral turn over due to incomplete suppression creates a persisting inflammatory milieu. The implications of all of the above is inadequate coverage and a sustained disease progression which equates to too little done too late (4, 5, 6). In summary ART delivery is significantly sub optimal in its current format in SA and by extension most of sub Saharan Africa. The objective of this study is to document the manner and pattern in which HRL is evolving in the region of the Western Cape of South Africa in light of the above observations. The expectation is that HRL will decrease with the introduction of effective ART, but our clinical observations do not suggest this is the case. The Tygerberg Lymphoma Study Group in concert with our collaborators in the sub Saharan Africa Lymphoma Consortium (SSALC), AIDS and Cancer Specimen Resource (ACSR) based in The Ohio State University and the US National Institute of Health (NIH), hope to give a clearer picture on the manner and pattern of how HIV is changing the demographics of malignant lymphoma in this region, provide clues as to some of the aetiological agents and form the basis for informed decisions on future strategic policy and resource allocation. This kind of data will go a long way to inform cost effective diagnostic and management algorithm and provide clues as to how national ARV treatment policies might provide the best environment to prevent this impending malignant epidemic from escalating. This paper reports on the findings of this group with respect to annual incidence, pattern and subtype of

HRL compared to lymphomas arising in the non infected population and will set the platform for further ongoing research, characterization modeling and projections.

Materials and methods

We reviewed all diagnoses of lymphoma made within the National Health Laboratory Service (NHLS) business unit of the Tygerberg Academic Hospital, Faculty of Health Sciences, University of Stellenbosch in the Western Cape of SA from 2002 to 2009, a total of 8 years inclusively. Tygerberg Hospital is a tertiary referral academic facility hospital with a catchment population of about 2.5 million which is about half the population of the Western Cape Province of 5 million. The catchment area does extend into neighboring provinces in certain cases because of superior health care systems available at our facility. This may have a distorting effect on the epidemiology due to the fact that in some cases, only the specimens are referred for diagnosis and the patients are retained in the neighboring province for care. We have attempted to separate cases that were managed in our facility from those in which material was sent for diagnosis only. With ethical consent, archival data was initially retrieved using *snowmed* coding from the NHLS of SA, Central Database Warehouse for the Western Cape Tygerberg catchments area and arranged according to the year of presentation and diagnosis. Results retrieved were screened on an individual basis to exclude duplication and classified by HIV status. Original results from tissue biopsy, fine needle aspirate and bone marrow examinations were extracted from the facilities electronic data base. In this time frame, 1076 cases of lymphoma were identified of which 720 were actually treated at Tygerberg hospital. The remainder which comprised of 356 cases, were cases referred for diagnostic work up only from an adjacent province or the private sector. The Lymphoma diagnosis was established and sub-typed according to 2008 WHO classification (3) by qualified specialists from the divisions of anatomical and hematological pathology of the Tygerberg Academic Hospital, based on cell or tissue morphology, molecular and immunophenotypic techniques. Some assays are not done in house at the Tygerberg NHLS business unit and in such cases, material would be referred to other NHLS labs in neighbouring tertiary referral centers to complete the work up. Established panels for immunohistochemistry included CD [45, 20, 10, 3, 4, 5, 8, 15, 30, 34, 68, 38, 56, 138], MUM1, Bcl-2, Bcl-6, Ki-67(Mib I), cyclin D-I, EMA, kappa, lambda, and EBV. These are performed on the BondMax automated immunohistochemistry staining platform by Leica Microsystems. Panels for flowcytometry include: CD [1a, 2, 3, 4, 5, 7, 8, 10, 11b, 11c, 13, 19, 20, 22, 23, 25, 33, 34, 38, 45, 138, 79a, 56, 61, 117], FMC-7, HLA-DR, MPO, TdT, lambda, kappa and μ . Cytogenetics and molecular studies done by fluorescent *in situ* hybridization (FISH) or polymerase chain reaction (PCR) are performed within the NHLS network. H&E staining was performed on formalin preserved tissue according to established international Standard Operating Procedures.

Results

Lymphoma cases increased each year from 2002 to 2005 and remain elevated in both the HIV negative and positive patients through to 2009. HRL increased from 5% in 2002 to 37% in 2009 with a profile of subtypes differing from the HIV negative cases (diagrams 1 and 2). A total of 1076 cases of lymphoma were identified of which 857 were HIV negative and 219 HIV positive and are shown in Table 1. The pattern and spectrum of HRL disease is not unexpected, and typical of that seen in most HIV populations, however the progressive increase in HRL disease burden is contrary to observations in the developed world in response to ART programs. This finding echoes the observation and is now documented. The possible reasons for this will be addressed in discussion.

Discussion

The total lymphoma cases seen in the Tygerberg catchment area of the Western Cape of SA increased from 2002 to 2009 primarily due to a dramatic increase in HRL, currently at 37% of all cases, a significant rise from 6% in 2002. This changing pattern of subtypes in PLWH presents new challenges to histopathology diagnosis as well as to clinicians who will have to manage a more therapeutically difficult patient population. The most startling observations are that the introduction of ART in 2004 does not appear to have impacted much on the emergence of HRL in this region (figure 1), and Burkitt lymphoma previously rarely seen in this population is now the predominant type of HRL (figure 2 and 3). Similarly plasmablastic lymphoma, is now an new and emerging entity. These findings are indeed a paradox, as one would expect a significant reduction of HRL as the ART roll out gains momentum. A likely explanation in our setting is the sub optimal coverage, late commencement of ART and ineffective viral suppression of those on ART. Further studies are ongoing to evaluate the clinical characteristics including ART status, CD4 nadir, HIV viral load profile, and how these parameters are contributing to define outcomes and disease sub categories in this study group. Emergence of more aggressive lymphoma subtypes inevitably poses a major strategic health concern in the region. The introduction of ART appears not to be having the desired impact as observed in programs delivered in the developed world. This could be for a number of reasons that relate to host and viral properties as well as perhaps a different profile of opportunistic and environmental factors. However in our opinion ineffective delivery of ART is likely to be playing a significant role. Evidence from large European HIV cohorts reveal that the depth of immune aberration prior to commencing ART, inadequate suppression of viral replication leading to poor immune reconstitution are significant predictors of risk of lymphoma development (19, 20). Zouflay et al showed that the long term and cumulative viral load burden over and above desired suppressive threshold levels has a relationship with the evolution of lymphoma and the Burkitt subtype in particular (19). When the relationship between viral suppression and the rate of immune reconstitution is examined, it is evident that it is contingent on the timing of ART commencement and efficiency of viral suppression. Early commencement and tight viral control result in impressive immune recovery (21). From the updated accounts of HIV clinical cohorts in the same geographical population of the Western Cape of South Africa, it is apparent that while ART has made significant impact on longevity and rescues PLWH from fatal complication of serious opportunistic infection, the depth of viral suppression to undetectable levels is not as rigid as one would expect in a similar cohort from developed country with adequate resources and less HIV burden (22). Insufficient recovery of a robust immune system will likely create the environment for persistent EBV infection and the sustained non specific activation of the B cell compartment within the adaptive immune system and provides the ideal environment for B cell lymphoma pathogenesis.

It is possible that errors may have been introduced into our data capture and retrieval for reasons associated with patient mobility across provinces and referral of certain cases for more sophisticated diagnosis and treatment protocols to our facility. However when we extracted such referred cases from our master data base, an identical pattern of increasing HRL is still observed. Tygerberg Hospital has had high levels of diagnostic capacity well before the advent of the emergence of HRL in this environment and therefore it is unlikely that this scenario can be explained by improved diagnostic capacity.

Conclusion

Emerging evidence from around the country and the region suggest that the South African health infrastructure, burdened by one of the highest levels of HIV per capita in the world, is now challenged by a dramatic rise in cancer cases in background of a sustained HIV

epidemic, rising tuberculosis problem and worsening climatic aberrations and malnutrition (9, 15, 16). There is a danger that the economic gains achieved by the introduction of ART will be in part reversed by the evolution of this new and escalating phenomenon. Among the cancers likely to increase in this setting, HRL are the most complex and challenging for the pathologist and clinicians. The data supports a prediction that, despite the ART roll out initiative, the trend shown by this study will continue because of an inadequate treatment policy and capacity. The Tygerberg Lymphoma study program is ongoing and interrogates these issues in greater depth.

Acknowledgments

The data mining team Tygerberg Lymphoma Study Group (Bongani Nkambule, Tim Reid, Stanley Loots), David Nohle Ohio State University and the ACSR for illustrations design and construct of the article, Christine and Natasha.....

Funding was provided by the MRC/NHLS Research Trust pathology award, the sub Sahara Africa Lymphoma Consortium project funded by the AIDS Cancer Specimen Repository, Office of the HIV AIDS Malignancy and National Cancer Institute of USA.

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Figure 1.
Trend of lymphoma incidence by HIV status, 2002–2009

Figure 2.
Pie charts showing distribution of lymphoma types by HIV status

Figure 3.
Distribution of HIV related lymphomas by year

Table 1

Counts and percentages of lymphoma by subtypes and HIV status over 8 year period.

<i>subtype</i>	HIV–			HIV+		
	<i>n</i>	% of HIV–	% of all	<i>n</i>	% of HIV+	% of all
Burkitt lymphoma	0	0	0	68	31	6
Diffuse large B-cell lymphoma	291	34	27	53	24	5
Plasmablastic lymphoma	0	0	0	35	16	3
Follicular lymphoma	78	9	7	1	0	0
Hodgkin lymphoma	172	20	16	15	7	1
Small cell lymphoma	32	4	3	1	0	0
Anaplastic large cell lymphoma	29	3	3	8	4	1
Marginal zone lymphoma	59	7	5	3	1	0
Lymphoblastic lymphoma	48	6	4	1	0	0
Peripheral T-cell lymphoma	23	3	2	4	2	0
Primary effusion lymphoma	0	0	0	2	1	0
Castleman lymphoma	1	0	0	3	1	0
Other	124	14	12	25	11	2
<i>Total</i>	857	100	80	219	100	20