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Prognostic influence of myc aberrations and other clinicopathological factors of aggressive b-cell non-Hodgkin lymphomas

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2024

https://hdl.handle.net/10539/37605

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ABSTRACT

Introduction: Up to 30% of cancers in Africa are linked to infectious agents and in the context of the aggressive B-cell non-Hodgkin lymphomas (NHL), human immunodeficiency virus (HIV) infection is an established risk factor. Aggressive B-cell NHLs are frequently confirmed at the Chris Hani Baragwanath Academic Hospital due to the high seroprevalence of HIV infection. Therefore, an array of clinicopathological characteristics of these tumours was evaluated with the aim of identifying poor prognostic factors.

Materials and methods: HIV-associated plasmablastic lymphoma (PBL), HIV-associated diffuse large B-cell lymphoma (DLBCL) and DLBCL, not otherwise specified (NOS) were included from October 2013 to June 2017. Formalin-fixed paraffin-embedded tissue sections were subjected to c-MYC immunohistochemistry (IHC), dual-colour chromogenic and fluorescence *in situ* hybridisation (CISH and FISH) for assessment of *MYC* gene rearrangement and *MYC* gene copy number enumeration. Thereafter, the clinicopathological characteristics were explored.

Results: The study included 67 PBL patients and 63/64 (98%) were HIV-seropositive. HIV-associated PBL was typified by a mean age of 41 (standard deviation [SD] ± 10.1) years and a 54% female predominance. The patients received combination antiretroviral therapy (c-ART) prior to, or shortly after, the lymphoma diagnosis was confirmed. The median CD4 count was 170 (interquartile range [IQR] 249) cells/mm^3 and 37% of the patients had CD4 counts <100 cells/mm^3. The median viral load was 55 587 (IQR 273 582) copies/mL and 15% of patients had a lower than detectable limit viral load. Advanced stage of lymphoma, i.e., Ann Arbor stage III-IV, occurred in 77% of the patients and there was a predominance of extra-oronasal topographic involvement. A starry-sky (SS) appearance was documented in 33% of these tumours, mainly in association with monomorphic morphology (P=0.02). Expression of c-MYC protein (i.e., ≥40%) occurred in 81% of PBL. Epstein-Barr virus (EBV) latent infection was detected in 90% of these tumours by utilising CISH. *MYC* gene aberrations included *MYC* rearrangement (70%) and a low-level increase in *MYC* gene copy numbers (43%). Concurrent *MYC* rearrangement with increased *MYC* gene copy numbers (49%) were also detected. In addition, there was low-level polysomy of chromosome (C) 8 (6%). *MYC* aberrations in HIV PBLs were significantly associated with a SS appearance (P=0.01), monomorphic morphology (P=0.03), c-MYC protein

expression (*P*=0.03) and mortality (*P*=0.03). The median overall survival (OS) for HIV PBL was 75 days (95% CI 14–136). *MYC* aberrations in HIV PBL did not significantly influence the median OS [*MYC*+ 65 days (95% CI 0–143 days) and *MYC*- 71 days (95% CI 3–139 days), *P*=0.61].

There were 22 HIV seronegative DLBCL, NOS patients (19%) with a mean age of 57 (SD ±16.7) years and a 59% male predominance. There were 93 patients (81%) with HIV-associated DLBCL, typified by a mean age of 42 (SD ±10.8) years and a 55% male predominance. The HIV seropositive patients were significantly younger at the time of presentation with lymphoma (*P* <0.01). c-ART was commenced prior to, or shortly after, the lymphoma diagnosis was confirmed. The median CD4 count was 162 (IQR 215) cells/mm^3 and 33% of the patients had CD4 counts <100 cells/mm^3. The median viral load was 217 (IQR 182 981) copies/mL and 30% of the patients had a lower than detectable limit viral load. An advanced stage of lymphoma, i.e., stage III-IV, at presentation occurred in 87% of the patients. HIV DLBCL demonstrated a germinal centre (GC) and non-germinal centre (NGC) immunophenotypic cell of origin (COO) in 53% and 47%, respectively. Expression of c-MYC protein occurred in 58% of the HIV DLBCLs and this was significantly associated with a SS appearance (*P*=0.04) and high tumour proliferation indices, i.e., Ki-67 ≥90%, (*P*<0.01). Double expression of c-MYC and BCL2 proteins were significantly associated with the NGC COO immunophenotype (*P*<0.01). *MYC* aberrations included a low-level increase of *MYC* gene copy numbers (57%) and *MYC* rearrangements (12%). Infrequently, C8 polysomy, *MYC* gene clusters and concurrent *MYC* rearrangement with increased *MYC* gene copies were also identified in HIV DLBCL. The median OS was 228 days (95% CI 54–402) and 825 days (95% CI 309–1341) in the HIV seropositive and seronegative DLBCL groups, respectively (*P*=0.08). Compared with the HIV seronegative DLBCL group, an inferior median OS outcome occurred in the HIV seropositive group when the CD4 counts were <100 cells/mm^3 (*P*=0.04) and when the Internal Prognostic Index (IPI) was 3–5 (*P*=0.01). *MYC* aberrations did not significantly influence the median OS [*MYC*+ DLBCL 155 days (95% CI 0–356) and *MYC*- DLBCL 154 days (95% CI 53–256), *P*=0.67]. In the multivariate regression analysis, the presence of concomitant infections negatively impacted the overall survival (hazard ratio 4.01 [95% CI 1.86–12.20], *P*=0.02).

Conclusion: An array of clinicopathological features of aggressive B-cell NHLs was explored. Greater awareness of these aggressive tumours, early and accurate diagnosis, timeous referral and appropriate treatment, may improve the outcome of the patients who tend to present with advanced stage disease, IPI scores of 3-5 and low CD4 counts. In many regions of the world, the timeous implementation of c-ART has led to a noteworthy reduction in the incidence of HIV-associated NHL. Accordingly, a decline in the incidence of aggressive HIV-associated B-cell NHL in SA is optimistically anticipated.