Breast cancer, human immunodeficiency virus and highly active antiretroviral treatment; implications for a high-rate seropositive region

Subash Chirkut

King Edward VIII Hospital, Durban; Department of General Surgery, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal (UKZN), South Africa

Abstract

Sub-Saharan Africa is the region in the world with the most people infected with the human immunodeficiency virus (HIV). The incidence of breast cancer is also rising in the region. This transcript focuses on the burden of these two diseases when they converge in the same populace. This comprehensive literature review of the topic suggests a trend towards an increasing incidence of breast cancer in the HIV-infected population, and the rationale for such a tendency is hypothesized, especially in the context of the availability of highly active antiretroviral therapy. Besides the age at diagnosis, all other clinical characteristics appear to be similar in HIV-positive and HIV-negative breast cancer populations. Outcomes of the different treatment modalities for breast cancer in HIV-positive patients are also appraised and finally innovative areas of future research are suggested along with plausible recommendations.

Introduction

Globally, the majority of people living with HIV and AIDS (PLWHA) reside in Sub-Saharan Africa (SSA). Women comprise 53% of the estimated 4 million HIV-infected adults living in South Africa. Worldwide, the life expectancy of HIV-infected individuals has increased with the introduction of highly active antiretroviral therapy (HAART) which coincides with a dramatic decrease in the incidence of opportunistic infections and AIDS-defining cancers (ADC).

The incidence of breast cancer (BC) is however increasing in SSA and has since 1995 overtook invasive cervical cancer (ICC) as the leading cause of cancer in South African women. The coexistence of these two diseases in a patient has become a reality, which significantly affect health in women. This narrative review focuses on BC in PLWHA with particular reference to: epidemiology, treatment outcomes and future areas of research. The evidence presented will be interpreted in the context of three historical time frames: pre-HAART, early HAART and HAART. While BC does occur in men living with HIV/AIDS (MLWHA), this review will mainly focus on BC in women living with HIV/AIDS (WLWHA).

Key words: Breast cancer; HIV; HAART; chemotherapy; Sub-Saharan Africa.

Incidence of breast cancer in people living with HIV and AIDS

The first case of BC in an HIV-infected person was reported in the literature in 1988 and only 42 detailed patient reports were available until the early 2000s. While two relatively small cohorts reported a marginal increased incidence in BC in WLWHA; the vast majority document a statistically significant deficit. Amir and colleagues' evaluation of the Tanzanian Cancer Registry (1966 to 1996) showed a statistically significant decrease in the incidence rate of BC in both males (P=0.001) and females (P=0.021) after 1982, coinciding with the appearance of HIV/AIDS.

Standardized incidence ratio (SIR) is the ratio of the rate of observed cancer incidence in a sample population, compared to the cancer incidence expected for the general population. A value of 1 will indicate the same incidence rate and less than 1 indicating fewer cancers occurring than expected. The SIR for the incident BC among WLWHA in Women's interagency HIV study (WIHS) was 0.7. Other cohorts have shown the equivalent. Matching population based cancer registries with HIV/AIDS registries may provide the best level of evidence to verify this trend. Using this method, the majority of studies have shown a significantly lower SIRs for BC in WLWHA than compared to the general population (SIR 0.74, 95% Confidence Interval (CI) [0.56-0.97]). However, this seemingly changed with introduction of HAART in the mid-1990s and its increased availability in early 2000s.

More recent and updated cohort studies have clearly shown a shift towards increasing SIR, approaching that of the general population. In a contemporary report of 151 HIV-infected BC patients in Soweto, South Africa, which constitutes the largest
Hypothesis for the decreased incidence of BC in PLWHA

Under-reporting and competing mortalities

Published case reports are likely to select patients in whom the outcome was poor, and include only a small fraction of individuals in whom both HIV infection and BC has been diagnosed.35 BC is rarely explored and recognized in WLWHA36 and asymptomatic HIV infection is under-recognized in cancer patients.37 Underreporting of cancer cases in SSA countries is confounded by several reasons such as the use of alternative remedies, systemic failure in referrals, and economic difficulty.20 Added to this, there are few reliable population-based national cancer registries, and the information available is gleaned from individual units in the larger healthcare centres.38-40

In the pre-HAART period, PLWHA may have succumbed to other illnesses before the development of BC.9

Traditional BC risk factors

The apparent deficit of BC among females in the WIHS was explained by a general overall lower risk of established BC risk factors: lower social class, early age at first childbirth, high parity, and low alcohol intake.21 The endogenous estrogen microenvironment contributes to the proliferation of breast tissue and is an important prognostic factor. Lower estrogen levels may place BC cells at a survival disadvantage and decrease their malignant potential. Early in the HIV/AIDS epidemic estrogen levels have been reported to be lower in HIV-infected premenopausal women compared to HIV-uninfected controls.34,41

Immunosuppression

It is not clear what role immunosuppression may play in the pathogenesis of BC.42 One is also not able to eliminate the possibility that immunodeficiency may protect PLWHA from developing BC.43,44 Analyses of cancer incidence in chronically immunosuppressed transplant recipients have demonstrated a similar unexpected low incidence of BC relative to other malignancies.43,45 Grulich et al. examined seven studies of people with HIV/AIDS (n=44,172) and five of transplant recipients (n=31,977). For 20 of the 28 types of cancer examined, there was a significantly increased incidence in both populations. Rates for BC was no different from population rates in both groups, thus suggesting that HIV infection may counteract oncogenesis in PLWHA.

HIV virus

HIV may directly and indirectly affect the glandular, mesenchymal, and intra-mammary lymphoid tissue in seropositive patients.11 In vitro studies suggest that HIV replication in human breast cells hinders their growth by affecting growth factor receptors, suggesting that HIV infection may counteract oncogenesis in BC cells.57,48 While HIV may infect breast tissue, its main target is T lymphocytes with cluster differentiation 4 (CD4) receptors on its surface. HIV-1 uses CD4 and a chemokine receptor for cellular entry. After the binding of the HIV-1 envelope glycoprotein (Env) gp120 to CD4, gp120 changes its conformation to bind to a chemokine receptors and initiates fusion with the cellular membrane. The chemokine receptors CCR5 and CXCR4 are the main co-receptors for the cellular entry of HIV-1. In general, viral strains are classified into R5, X4 and R5X4 according to the usage of chemokine receptor.49

CXCR4 has recently been shown to be expressed not only on immune cells, but on primary tumours of human invasive lobular or ductal breast carcinoma and to mediate organ-specific metastasis.49,50 Thus, it seems that CXCR4-using variants of HIV preferentially infect (and terminate) BC cell lines that express CXCR4. The low BC risk with HIV have been reported to be specifically linked to CXCR4-using variants of HIV.50

Hypotheses for the increasing incidence of BC in PLWHA

Aging

With HAART now being widely available in most of SSA and in HIC, PLWHA are living longer. The increase in incidence of non-AIDS-defining cancers (NADC) in PLWHA has mainly been driven by growth and aging of the AIDS population29,51 and as WLWHA get older, the incidence of BC is likely going to increase.52,53

Additionally, HAART has been shown to enhance events seen in biological aging - that is to say HAART accelerates the aging process.54,55

Comorbidities and HAART

Metabolic syndrome (MS) has been shown to be more prevalent in BC patients and is an independent risk factor for BC. MS consists of a constellation of metabolic abnormalities which include central obesity, hyperglycemia, hyperinsulinemia, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, hyperuricemia, and increased levels of fibrinogen. It confers an increased risk of cardiovascular disease and diabetes mellitus.56,57 The prevalence of MS among HAART-exposed PLWHA has been shown to be significantly higher compared to HAART-naive PLWHA.58 Several published studies found an overall increase in the incidence of MS in patients with HIV receiving HAART over time, making this comorbidity particularly relevant for PLWHA and BC.48 It seems that HAART prevents the wasting syndrome of AIDS (common in the pre-HAART period)34 which may increase endogenous estrogen levels.41 During the HAART period it has been shown that WLWHA in the USA tended to have significantly higher body mass index (BMI),34 an established risk factor for BC development.59

Finally, if the deficit in BC reflects the ability of HIV to infect, replicate in, and impair proliferation of breast cells, then HAART would likely reduce HIV replication and perhaps allow cancer cell proliferation, either directly or indirectly.34

With regard to individual antiretroviral agents, studies have demonstrated that efavirenz directly binds and activates estrogen receptors in breast tissue, providing a plausible mechanistic explanation for efavirenz-induced gynecomastia in PLWHA and may encourage BC development.60
HAART as a carcinogen

The carcinogenic potential of individual drugs in the HAART regimen may itself be a possible risk factor for malignancy. Though there have been some reports of an association between some antiretroviral agents and the occurrence of cancer,61,62 a correlation has not been confirmed.63 Pharmaceutical companies have nevertheless listed this as a possibility in the prescribing information for some antiretroviral drugs.64

Other viruses

The role of a preexisting viral infection in the pathogenesis of BC has been suggested8,10 but at present unproven.65 However, an animal model exists to demonstrate this conjecture. The mouse mammary tumour virus (MMTV) is a retrovirus that can infect mice and it is known to cause the majority of murine mammary tumours.66,67 Human herpesvirus 8-induced KS and Epstein-Barr virus-induced NHL are ADCs and are associated with a low CD4 count. With immune reconstitution as a result of HAART, their incidence has declined in PLWA. The association between Human papillomavirus (HPV)-induced ICC and low CD4 is tentative.68 With the availability of HAART, an increased incidence of other viral-related non-AIDS-defining cancers (NADC) have emerged in PLWA. These include Hepatitis B-induced Hepatocellular carcinoma and HPV-induced genitourinary,69 anal,70 conjunctival,71 head and neck cancers.72 These cancers are not associated with a low CD4 count. In contrast to ADC, HAART has had little impact on the incidence of NADC.72 If BC does have a viral association then, with immune reconstitution, its incidence may increase with time.

Reconciling the hypotheses

BC develops as a result of the complex interplay of host, genetic, metabolic, immunologic, and environmental factors,8,48 and with the evolution of HIV/AIDS epidemic, factors abetting BC pathogenesis may have emerged, mainly driven by the availability of HAART.

Clinical and pathological characteristics of BC in PLWHA

Age at presentation

Case reports, case series and cohorts from the HIC and low-to-middle-income countries (LMIC) have consistently demonstrated that BC occurs at a younger age in PLWA.3,41,53,73,74 A 2-year study at the Tygerberg Academic Hospital in Cape Town, South Africa, reported similar tendencies, with a median age at presentation of 54 years for patients without HIV compared with 42 years for patients with HIV (P=0.001).75 This finding has been confirmed by other SSA studies.5,7,76,77

Some studies noted a great proportion of patients with a family history of breast or ovarian cancer, suggesting a possible influence of HIV on acceleration of oncogenesis and increased penetrance in patients who may already have a heritable risk.78

In general, the age at diagnosis for most cancers in PLWHA is ~20 years younger than their general population.71,79

CD4 count at presentation

The vast majority of case series and cohorts have shown little or no association between CD4 count and the development of BC.5,34,53,73,74,80-82 In the ONCOVIIH study (France), consisting of 21 BCs in WLWHA, the median CD4 cell count was 347 cells/mm³ (range: 180-1039),51 while in Durban, South Africa the median CD4 count was 435 cells/mm³ (range 80-945).77 BC in WLWHA is certainly not associated with a low CD4 count74 implying that the degree of immune-compromise does not correlate with tumorogenesis.82

CD4 count is also not associated with BC stage at presentation, histological subtypes, or tumor grade.58

Stage of presentation, pathology and grade

Early in the HIV epidemic many authors perceived that BC, in the setting of HIV infection, tends to occur at a relatively early age, usually with increased bilateral disease, unusual histology and early metastatic spread, resulting in a poor outcome and early relapse.10,19,36,41,83,84 Over time, as more data appeared in the literature, this statement has been refuted.85,73 In their updated case series from Harlem, New York, Sarhan and Oluwole demonstrated that the cancer stage, pathological cancer characteristics and survival outcome was similar in HIV-positive and HIV-negative patients.9 More recent legitimately credible studies from SSA also demonstrated no statistically significant difference in the stage at presentation, histologic subtype, tumor grade, or nodal involvement between HIV-positive groups and the other groups.7,75,77,86

BC treatment and its outcome in PLWHA

Surgery, radiotherapy, hormonal therapy, and chemotherapy are the most common means of treatment for BC patients.59

Surgery

Current literature suggests that healthier patients with HIV infection, on HAART, have better surgical outcomes,87 and that HIV infection is not associated with increased in-hospital mortality.88 In the only study that looked specifically at surgery in HIV-infected women with BC Phakathi et al. discovered that HIV-infected patients did not experience more surgical complications than the non-infected patients. Rather, the risk ratio of HIV-infection for complications was 0.20, and the odds ratio 0.23, albeit with a wide 95% confidence interval (0.03 to 1.45).7 The higher rate of surgical complications in the HIV-non-infected patients was explained by the fact that they were significantly older than the HIV-infected patients. This age difference was not unexpected as BC in PLWHA occurs at a younger age.57

Radiotherapy

Very little data is available regarding the use of radiotherapy in HIV-infected BC patients.7 In a recent prospective study (n=160), 12 (86%) and 40 (98%) of HIV-infected and HIV-non-infected patients respectively completed their course of radiotherapy with no increase in acute infection, dermal or mucosal toxicity.7 The available evidence suggests that patients with BC and HIV should be treated according to the guidelines for those who are immunocompetent.89,90

Hormone therapy

Tamoxifen is a selective estrogen receptor antagonist, and since its introduction in cancer therapy has become the standard treatment option for hormone-responsive BC patients.91 Other drugs that are used to manipulate the hormone environment in BC patients include aromatase inhibitors (e.g. anastrozole, exemestane) and gonadotropin-releasing hormone analogues (e.g. goserelin).
In WLWHA with estrogen receptor-positive (ER+) BC, treatment with hormone therapy has no significant side effects, and is very well tolerated.\textsuperscript{15,74,92}

**Chemotherapy**

Chemotherapeutic intervention remains a fundamental treatment strategy for the management of BC, either in the neoadjuvant or in adjuvant setting.

A few cases reports documented poor tolerance to chemotherapy while others demonstrated the contrary.\textsuperscript{10,83,93,94} Case series from the pre-HAART\textsuperscript{92} and early-HAART\textsuperscript{37} period noted that chemotherapy was poorly tolerated by PLWHA. Besides significant toxicity from chemotherapy, chemotherapy resulted in progression of HIV disease.\textsuperscript{82,95} HAART has been associated with better cancer outcomes as a result of maintaining reduced viral loads\textsuperscript{53} and improved immunity.\textsuperscript{96} This also seems to be the case for the treatment of BC in WLWHA.\textsuperscript{76}

Of their 10 HIV-infected patients who received chemotherapy for BC, Singh et al. observed that 60% completed adjuvant therapy, with 50% and 20% requiring treatment delay or dose reduction, respectively.\textsuperscript{78}

In the era of HAART, Parameswaran et al. reported that their HIV-infected cohort (n=52) experienced chemotherapy with more adverse effects than the non-HIV-infected cohort (55% vs 30%; P=0.03), leading to more chemotherapy dose reductions and/or delays. Eighty four percent of HIV-infected patients were on HAART. The most common toxicities necessitating the dose reduction and/or delay were anemia and neutropenia (with or without fever).\textsuperscript{81} They did not however find significant independent differences in outcome between HIV and non-HIV groups.

While anemia can easily be managed by a blood transfusion, neutropenia still remains a serious setback that can result in infection-related complications.\textsuperscript{97}

More recently Nigidi et al narrated that patients with HIV infection were almost two times more likely to develop neutropenia than their HIV-negative counterparts (hazard ratio 1.76, [95% CI 1.06-2.92]; P=0.029).\textsuperscript{77} Ninety five percent of patients were on HAART. It seems HAART did not prevent patients with HIV infection from experiencing neutropenia, but it did protect them from developing higher grades of neutropenia and more severe complications.\textsuperscript{77}

Intriguingly, Langenhoven et al. reported no difference in the rate of neutropenia between HIV-infected patients and HIV-non-infected patients, however she did note an increase rate of lymphopenia (26%) in HIV-infected patients compared to HIV-non-infected patients (0%).\textsuperscript{75} Eighty four percent of both HIV-positive and HIV-negative patients completed chemotherapy. All patients where receiving HAART.\textsuperscript{75}

These toxicities seem to be unrelated to CD4 count\textsuperscript{92} inferring that immuno-compromise and immune reconstitution does not sufficiently explain these findings, and that drug-drug interactions (DDI) may play a greater role than what was previously thought.\textsuperscript{81}

Protease inhibitors (PI, saquinavir, ritonavir, indinavir, fosamprenavir, lopinavir/ritonavir, atazanavir, darunavir, tipranavir) are a class of drugs that are infamous for causing DDI due to their close relationship with the cytochrome P450 system (CYP 450). In particular, PIs inhibit the CYP3A4 enzyme and may reduce the hepatic metabolism of alkylating agents (e.g., cyclophosphamide), anthracyclines (e.g., doxorubicin), and taxanes (e.g., paclitaxel) that are used in the treatment for BC. The resulting increased levels of these cytotoxic agents may potentiate the risk for myelosuppression.\textsuperscript{81,98} In contrast non-nucleoside reverse transcriptase inhibitors (NNRTI, nevirapine and efavirenz) are CYP3A4 inducers\textsuperscript{51} and may reduce efficacy of these chemotherapeutic agents.

Zidovudine, a nucleoside reverse transcriptase Inhibitors (NRTIs) is known to cause serve bone marrow suppression, which may be aggravated by chemotherapeutic drugs.\textsuperscript{51,99} Interestingly, zidovudine was first synthesized in 1964 as a treatment for cancer but had little anticancer activity and unacceptable toxicity.\textsuperscript{100} Nevertheless, in 1987 it was repurposed as the first drug against HIV.\textsuperscript{101}

Integrase inhibitors (raltegravir) and fusion inhibitors/CCR5 antagonist (maraviroc) are new classes of drugs for the treatment of HIV and are not inhibitors or inducers of cytochrome P450, therefore they are unlikely to interact with chemotherapeutic agents.\textsuperscript{98,102}

In an attempt to minimize chemotherapy-related complications, Gomez et al. adopted a number of strategies: i) use weekly chemotherapy rather than every 3 week therapy; ii) avoidance dose dense regimens; iii) the use of hormone therapy in women whose tumors are ER+ instead of chemotherapy; iv) avoidance of steroid premedication when possible and, v) the substitution Nab-Paclitaxel for Paclitaxel on occasion to avoid weekly steroid administration.\textsuperscript{74} The liberal use of haemopoietic growth factor support (granulocyte-colony stimulating factor, G-CSF) and prophylactic fluconazole, trimethoprim/sulfamethoxazole, and acyclovir to all HIV-infected women receiving chemotherapy was also advocated.\textsuperscript{74} In fact, a number of academics have endorsed the unrestrained use of G-CSF\textsuperscript{41,95,102} and that all patients should be started on HAART prior to chemotherapy.\textsuperscript{77,103}

SSA is an ideal setting in which to conduct studies exploring the DDI between HAART and chemotherapeutic drugs, because of its disproportionate burden of HIV.

---

**BC screening in PLWHA**

Lack of resources and infrastructure in the South African public healthcare system\textsuperscript{104} and other LMIC\textsuperscript{5} renders screening mammography (MMG) untenable.\textsuperscript{38} Presently MMGs are performed on asymptomatic and identifiable high-risk patients at specialist breast units.\textsuperscript{104}

Current United States Preventive Service Task Force (USPSTF) screening guidelines recommend, for the general population, a biennial MMG for women age 50-74.\textsuperscript{52,55} There are currently no approved guidelines or recommendations for screening WLWHA for BC\textsuperscript{55} and most authorities believe that application of national guidelines is appropriate for WLWHA.\textsuperscript{52,53,55} Other advocates have suggested that because WLWHA at risk of developing BC at a younger age, they should be considered for an earlier screening MMG exam than the general population.\textsuperscript{3,8,73} As to the most appropriate way to screen WLWHA, especially those in LMIC is debatable\textsuperscript{105,106} and beyond the scope of this article.

However, given the increase in HIV care and treatment expenditure in SSA, and increased number of PLWHA having access to clinical care and stricter medical follow up, leveraging this infrastructure to increase cancer screening and referral is a promising and likely cost-effective method to diagnose cancer at an earlier stage in PLWHA.\textsuperscript{107} This is certainly applicable to BC awareness and screening in WLWHA\textsuperscript{15,36} given the greater opportunity of patients to interact with healthcare providers.\textsuperscript{9}
Future developments and potential areas of clinical research

HIV as a vaccine for BC

It has been established that numerous BC lines express CXCR4 receptors however do not express CD4 molecules on the cell surface. With the emergence of RSX4 and X4 HIV-1 viruses, and the fact that they kill cancer cells in vitro, it can be theorized that the virus can be altered to kill BC cells exclusively.

Instead of using the virus as a whole, the development of an altered virus-like particle or peptide may have the potential as a new therapy for CXCR4-related BC. It was proposed as a treatment for HAART-induced gynecomastia, after other instigates have been ruled out.60

HAART as new chemotherapy for BC

Identification and characterization of new pharmacological activities from existing drugs represents an effective way to accelerate the translation of discoveries at the bench to the bedside.109,110 PIs have emerged as a potential anticancer drug for several cancers111 including BC,109,112 Nelfinavir successfully inhibited the growth of HER2-positive breast cancer cells both in the lab and in mice. It seems that PIs may have the ability to cooperate with or sensitize BC to other chemotherapeutic drugs or cancer treatment options.91

The chemokine receptors CCR5 and CXCR4 are the co-receptors for the cellular entry of HIV-1. Maraviroc (CCR5 Antagonist) binds specifically and selectively to CCR5 on the surface of the CD4 cells and blocks HIV-1 binding. It conferred little or no virologic benefit in patients with X4 HIV-1 strains.113 Microarray analysis of human BC specimens found increased expression of CCL5 and its receptor CCR5, in the basal and HER-2 genetic subtypes of BC114 and that CCR5+ cells favor migration and invasion of these cancer cells. In in vivo studies, Maraviroc displayed anti-metastatic outcomes on basal subtype BC cell lines,114 giving rise to the possibility of its use as therapeutic intervention or prevention of metastatic BC.115 Results from clinical trials are keenly anticipated.109,116

Tamoxifen and its role in HIV treatment

Tamoxifen may serve as an antiviral agent, causing inhibition of HIV virion production, as well as preventing the spontaneous apoptosis of CD4-positive T cells and facilitating the regeneration of lymphocyte populations.66 It was proposed as a treatment for HIV prior to the development of antiretroviral drugs117 and recently there has been renewed interest in tamoxifen in the setting of HIV.110

With HAART, breast enlargement has emerged as a problem in the treatment of MLWHA. Tamoxifen and other anti-estrogen drugs are proving to be increasingly useful in the treatment of HAART-induced gynecostasia, after other instigates have been ruled out.60

The way forward

All cancer patients should be screened for HIV prior to commencement of cancer treatment as it is not uncommon to diagnose these conditions simultaneously. With an increasing incidence of BC in WLWHA, it seems plausible to screen for this malady at facilities that provide care to HIV-infected individuals and to offer them, at medicum, a clinical breast exam. Research exploring DDI between HAART and chemotherapy is urgently needed. In HIV-infected patients with cancer, adjusting the HAART regimen, to reduce toxicity and enhance efficacy of chemotherapy, should be considered. Another forethought is the permissible use of G-CSF as primary prophylaxis for myelosuppression, especially when the CD4 count is low. Repurposing antiretroviral drugs as the treatment of cancer needs to be validated in clinical trials. A significant portion of health resources in SSA countries are used for the prevention and treatment of HIV/AIDS, often at the expense of cancer services.99 With the increasing incidence of cancer, including BC, in PLWHA and the general population, development and maintenance of oncology services is now obligatory in the region.

References


References continued...


