

Duration to Surgery for Cancer and Comparative Dosage Efficacy of Chemo for infected with HIV Patients with carcinoma of the breast.

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Abstract

IMPORTANCE : Compared to other breast cancer patients, those who also have HIV had a greater death rate from breast cancer.

OBJECTIVE: to examine the duration between patients with HIV-positive and HIV-negative breast cancer, as well as the relative dosage intensity (RDI) of adjuvant and neoadjuvant chemotherapy.

DESIGN, SETTING, AND PARTICIPANTS : Participants in the retrospective, matched cohort analysis were women diagnosed with breast cancer between January 1, 2000, and December 31, 2018. We looked through the electronic medical records of three academic, urban cancer centres to find women who had been diagnosed with HIV either before or at the same time as stage I to III breast cancer. For every participant with HIV, two control patients with breast cancer who were HIV-negative were found using tumour registry data, which were then matched for study site, stage, and year of cancer diagnosis. The period of statistical analysis was December 2022–October 2023.

EXPOSURE HIV : infection found either 90 days or earlier after the subjects' breast cancer diagnosis.

MAIN OUTCOMES AND MEASURES : The time to first treatment for breast cancer, or the number of days from cancer diagnosis to first treatment, was the main outcome. Overall RDI for chemotherapy-treated individuals was the secondary endpoint. After correcting for confounding demographic and clinical characteristics, these outcomes were compared by HIV status using Cox proportional hazards regression and linear regression modelling, respectively. Fisher exact tests were used to compare the exploratory outcomes, which comprised

cases of anaemia, neutropenia, thrombocytopenia, and abnormal liver function test results following treatment.

RESULTS : 132 women with breast cancer alone (median age, 53.9 years [IQR, 47.0–62.5 years]) and 66 women with HIV and co-occurring breast cancer (median age, 51.1 years [IQR, 45.7–58.2 years]) were enrolled in the study. HIV-positive patients' median time to first cancer treatment was 48.5 days [IQR, 32.0–67.0 days] compared to 42.5 days [IQR, 25.0–59.0 days]; adjusted hazard ratio, 0.78, 95% CI, 0.55–1.12). This difference did not reach statistical significance. The median overall RDI was lower for the 36 women with HIV and the 62 women without HIV who had chemotherapy (0.87 [IQR, 0.74–0.97] versus 0.96 [IQR, 0.88–1.00]; adjusted $P = .01$). During chemotherapy, more HIV-positive women than HIV-negative women experienced grade 3 or higher neutropenia (13 of 36 [36.1%] vs 5 of 58 [8.6%]).

CONCLUSIONS AND RELEVANCE : According to this matched cohort analysis, patients with HIV and breast cancer may have had worse RDI for adjuvant chemotherapy, which could be attributed to more dosage reductions, delays, or discontinuations. It is essential to develop strategies for providing this susceptible group with support during chemotherapy.

INTRODUCTION

The life expectancy of HIV-positive individuals in the US increased from 10.5 years in 1996 to 28.9 years in 2011 with antiretroviral medication.^{1, 2} As a result, the number of HIV-positive individuals is rising. In the United States, 58% of HIV-positive individuals were 45 years of age or older in 2016.³ Elderly HIV-positive individuals are susceptible to non-AIDS-defining malignancies; among US HIV-positive individuals, the incidence of breast cancer increased tenfold between 1991 and 1995 and 2001 and 2005.

Breast cancer does not appear to be more common in women living with HIV (WLHIV).^{5, 6} WLHIV, on the other hand, experience worse outcomes when being diagnosed with breast cancer. Investigations into the National Cancer Database, Surveillance, Epidemiology and End Results (SEER)–Medicare, and the US-based HIV/AIDS Cancer Match Study registries show

that patients with HIV have much higher overall mortality (HR, 1.85–2.64) and cancer-specific mortality (hazard ratios [HRs], 1.85–2.64). It's possible that people with HIV who have breast cancer are more likely to receive subpar cancer care, but the reasons for these survival differences are probably complex. Racial and ethnic groups who have historically had less access to high-quality cancer care had higher prevalence rates of HIV.^{3, 10–15} On the other hand, in WLHIV, prolonged HIV infection and its treatment may be linked to a decreased tolerance for potent but hazardous cancer medications.

The relatively small number of patients with both diagnoses treated at any one cancer centre or the inherent constraints of bigger data sets, which lack granular treatment data, have restricted efforts to examine the quality of breast cancer care among WLHIV. According to an examination of the SEER-Medicare registry, patients with HIV-positive cancer had to wait longer between receiving their diagnosis and starting treatment (42.5 days as opposed to 36 days). However, the investigation only included women 65 years of age or older and 12 patients with HIV-positive breast cancer.¹⁹ There are conflicting reports out of South Africa and Botswana regarding whether or not WLHIV is less tolerant of the chemotherapy treatments used to treat breast cancer. However, even the non-HIV patients in those trials were given a lower dose of chemotherapy than is customary in the United States.^{20, 21} By combining retrospective data from three sizable urban cancer centres, we sought to address these issues in researching the relationships between concomitant HIV and breast cancer care. In particular, we examined relationships between HIV infection and two measures of the quality of care: the amount of time it took to start treatment after receiving a cancer diagnosis and the relative dose intensity (RDI) of neoadjuvant and adjuvant chemotherapy.

Methods

This study was approved and waivers of consent for the collection of retrospective, deidentified patient data were given by the institutional review boards of each participating university: Herbert Irving Comprehensive Cancer Centre of Columbia University, Abramson Cancer Centre of Penn Medicine, and Sylvester Comprehensive Cancer Centre of the University of Miami Miller Health System. All shared data were completely deidentified and used in accordance with the terms of the agreements that were established. The Strengthening the Reporting of Ob-

servational Studies in Epidemiology (STROBE) reporting guideline was adhered to in this study.

Study Sites and Participants

Three urban academic cancer systems were used to collect data on study participants: the Herbert Irving Comprehensive Cancer Centre of Columbia University in New York City; the Abramson Cancer Centre of Penn Medicine in Philadelphia, Pennsylvania; and the Sylvester Comprehensive Cancer Centre of the University of Miami Miller Health System in Miami, Florida, which includes women treated at Jackson Memorial Hospital.

Every case of breast cancer (eTable 1 in Supplement 1) and HIV (eTable 2 in Supplement 1) related to at least one International Classification of Diseases, Ninth Revision or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision code was found in the electronic medical record systems at each site. The investigators personally went over the list of possible participants that this approach produced in order to find people who satisfied the following eligibility requirements: (1) gender: female; (2) age: 18 years or older; (3) histological confirmation of invasive breast cancer initially detected between January 1, 2000, and December 31, 2018; (4) breast cancer stage: I to III at reporting; and (5) a verified diagnosis of HIV infection made no later than ninety days following the original diagnosis of breast cancer. The presence of a positive serology test result, a quantifiable HIV viral load, or an unambiguous reference to an HIV infection in a clinical record was considered confirmation of HIV infection for the purposes of this study. Patients were not required to have had all of their care at the study location in order to be eligible; however, women whose first cancer treatments took place during a clinical trial as well as those without data on the timing of cancer diagnosis or treatment initiation were excluded. Enrolled participants who satisfied the inclusion criteria made up the WLHIV group.

Following that, researchers at each site created a list of 12 additional breast cancer patients who were matched to each member of the WLHIV group by disease stage and year of diagnosis using information from their institutional cancer registries and the MatchIt package in R, version 3.3.0 (R Project for Statistical Computing). Additionally, 23 participants from Miami, Florida were matched according to whether they received treatment at the public hospital or in the university's clinics. To find two matching participants without HIV infection for each participant in the WLHIV group, investigators manually checked the medi-

cal records of the matched patients for women satisfying study inclusion and exclusion criteria other than concomitant HIV infection. The control group consisted of these extra individuals. We also identified a subcohort of participants in both groups who were enrolled at the research site and had undergone initial adjuvant or neoadjuvant chemotherapy for their breast cancer.

Data Collection and Outcomes

Participants' electronic health records from both groups were examined, and information was manually collected and stored in separate REDCap databases hosted by each institution.²⁴ Demographic information about the participants (age at the time of the diagnosis, self-reported race and ethnicity, relationship status, and country of birth), information about the breast cancer (stage, hormone receptor status, ERBB2 status, grade, and date of the first surgery, endocrine therapy, chemotherapy, and radiotherapy), information about the breast cancer (date of diagnosis and medication regimen at the time of the diagnosis), and information about HIV (if available) were also gathered. Data on the first-line regimen (i.e., specific drugs prescribed and dates and dose amounts of each drug actually received by the participants) and any available laboratory test data immediately before and during treatment (i.e., haemoglobin concentration, absolute neutrophil count, platelet count, alanine and aspartate transaminase concentrations, alkaline phosphatase concentrations, and total bilirubin concentrations) were also collected in the subset of participants who received chemotherapy at a study site. For those who were known to have passed away, the date of death was noted. The date of the participant's last recorded contact with the clinic was noted if their medical record had no entries after December 31, 2019. The number of days between the date of the histologically confirmed breast cancer diagnosis and the receipt of the first breast cancer-directed therapy, regardless of modality, was our primary outcome measure. This result was computed for each member of the two groups.

The only subcohort of participants who had their first chemotherapy at any of the three hospital systems involved in this study had their overall chemotherapy RDI evaluated, which was our secondary endpoint. Using the usual formula²⁵ (total number of days to deliver all doses given / total number of delivered doses)/(total standard dose / total number of days to deliver full standard dose) was used to determine the RDI of each prescribed medicine separately.

Any information found in the prescribing clinicians' notes was the primary source of information for the standard dose quantities and time. In the event that such notes yielded no information, standards were established using published recommendations and descriptions of the various regimens in use. The unweighted mean of each drug's RDI in the participant's initial regimen was the overall RDI. The same method was used to calculate the relative dose intensities for each medication class, including taxanes, cyclophosphamide, fluorouracil, platinum, and anthracyclines. Use of a delivered dose of 0.0 mg and a typical delivery interval allowed for the inclusion of doses that were entirely missed because of early cessation or treatment abandonment in the numerator.

Statistical Analysis

The period of statistical analysis was December 2022–October 2023. In the chemotherapeutic RDI analysis, the features of both the entire cohort and the subcohort of participants were presented using numbers, percentages, and median (IQR) values. Employing a univariable Cox proportional hazards regression model, we examined the number of days to breast cancer therapy beginning between women with and without concomitant HIV infection. We also created a multivariable Cox proportional hazards regression model of time to treatment initiation with covariates for HIV status, the matching factors of stage and year of diagnosis, and any other characteristic that was associated with the number of days to treatment initiation in order to control for demographic or clinical differences based on HIV status that might confound those results. denoted in individual univariable Cox proportional hazards regression models as a Wald test $P \leq .10$. Since Black and Hispanic women are more likely than White women to receive subpar breast cancer treatment, as evidenced by previous research, we used non-Hispanic White race as the standard reference value when assessing the relationship between self-reported race and ethnicity and the number of days until treatment initiation in our regression models. Using the Fisher exact test, we compared the percentage of each group in the chemotherapy subcohort that received each drug class and the percentage of each group that received an overall RDI of 0.85 or above (a dosage intensity threshold that has been linked to better survival).^{25, 27, and 28} Using Wilcoxon rank sum testing, we compared the median RDI of each pharmacological class as well as the median RDI overall. We created a linear regression model of the individuals' continuous RDI values with covariates for HIV status, stage, year of

diagnosis, and other parameters related with RDI in individual univariable logistic regression models ($P \leq .10$) for the multivariable analysis of the total RDI.

The proportion of participants in each arm experiencing grade 3 or higher neutropenia, grade 3 or higher anaemia, grade 1 or higher thrombocytopenia, and grade 1 or higher hepatic toxic effects (transaminitis, alkaline phosphatase elevation, or hyperbilirubinemia) during chemotherapy were recorded, and arms were compared using Fisher exact tests in order to investigate the causes of differences in RDI. We also used Kaplan-Meier curves and log-rank testing to evaluate overall survival from the time of breast cancer diagnosis as an exploratory analysis. Thirty participants who were not officially recorded as deceased were administratively censored on December 31, 2019, if they were still in follow-up, or on the date of their last recorded contact with the clinic. Every test had two sides. For the primary and secondary outcomes, a regression-adjusted $P \leq .025$ was deemed significant, and a straightforward Bonferroni correction was employed to account for multiple comparisons. Every other comparison and analysis is regarded as exploratory. Statistical testing was conducted using SAS, version 9.4 (SAS Institute Inc.).

Results

66 suitable women with comorbid HIV and breast cancer were found throughout the three institutions: 38 (57.6%) from the University of Miami, 17 (25.8%) from the University of Pennsylvania, and 11 (16.7%) from Columbia University. We included 132 control patients with breast cancer who were HIV-negative, with two matched controls for every woman living with HIV (Table 1). Compared to the matched controls, the WLHIV had a somewhat lower median age at breast cancer diagnosis (51.1 years [IQR, 45.7-58.2 years] vs 53.9 years [IQR, 47.0-62.5 years]). Among the WLHIV, a greater percentage identified as non-Hispanic Black (43 of 66 [65.2%] vs. 26 of 132 [19.7%]) and 48 of 66 [72.7%] vs. 72 of 132 [54.6%] reported being single, divorced, or separated. Among WLHIV, hormone receptor-positive cancer was less common (45 of 66 [68.2%] vs 114 of 132 [86.4%]). Within the chemotherapy subcohort, racial and relationship status disparities continued; 36 WLHIV and 62 women without HIV were included.

Patients without HIV waited a median of 42.5 days (IQR, 25.0-59.0 days) (unadjusted HR, 0.73 [95% CI, 0.54-0.99]) from diagnosis for their first breast cancer treatment, whereas patients with breast cancer and comorbid HIV infection waited a median

of 48.5 days (IQR, 32.0-67.0 days) (Table 2). After controlling for variations in race and ethnicity, stage, grade, primary surgery received, and year of cancer diagnosis between patients with and without HIV, there was no significant correlation found between HIV status and a longer time to start breast cancer treatment (HR, 0.78 [95% CI, 0.55-1.12]). Treatment beginning delays were still linked to non-Hispanic Black race and Hispanic ethnicity (HR, 0.50 [95% CI, 0.33-0.77] and HR, 0.67 [95% CI, 0.45-0.99], respectively). Fewer WLHIV were treated with a taxane in the subcohort of patients undergoing chemotherapy (30 of 36 [83.3%] vs 61 of 62 [98.4%]) (Table 3). Both the median overall chemotherapy RDI and the percentage of patients getting an RDI of 0.85 or above (21 of 36 [58.3%] vs 51 of 62 [82.3%]; $P = .02$) were lower in WLHIV patients compared to HIV-negative patients (0.87 [IQR, 0.74-0.97] vs 0.96 [IQR, 0.88-1.00]; unadjusted $P = .01$). When WLHIV was compared to other medication types, the documented RDIs for anthracycline and taxane chemotherapies were lower. White race satisfied the requirements to be included as a covariate in our multivariable analysis, along with HIV status and the initial matching criteria (i.e., stage and year of diagnosis). While stage and year of diagnosis were not related with lower overall RDI, HIV status was nevertheless linked to lower overall RDI (β , -0.09 [95% CI, -0.15 to -0.03]; $P = .01$) (Table 4). Interestingly, Black race exhibited a small correlation with greater total RDI (β , 0.09 [95% CI, 0.004-0.18]; $P = .04$), even after adjusting for HIV status and other variables. Autocorrelation was a problem when the linear regression assumptions for this model were tested; however, autocorrelation was eliminated by our model by including a first-order autoregressive error correction parameter, which had no effect on the significance or strength of HIV's link with RDI. There were also more myelotoxic effects observed in WLHIV, as evidenced by elevations in neutropenia of grade 3 or above (13 of 36 [36.1%] vs 5 of 58 [8.6%]; $P = .002$) (Table 5).

The 5-year overall survival was 90.9% for patients without HIV and 81.8% for WLHIV, with a maximum follow-up of 190.6 months and a median follow-up of 69.4 months (IQR, 38.2-104.1 months) (eFigure in Supplement 1). In this small sample, the difference was not statistically significant (HR, 1.73 [95% CI, 0.78-3.80]; log-rank $P = .17$).

Discussion

After controlling for non-Hispanic Black race and other covariates that varied based on HIV status, we found no significant

differences in the time from breast cancer diagnosis to the start of cancer treatment in this multi-institutional cohort study of 66 patients with stage I to III breast cancer living with HIV and 132 matched patients with breast cancer without HIV. In the subcohort of patients who underwent chemotherapy, we did discover, however, that the group of patients with HIV infection had a lower overall chemotherapy RDI, and that fewer than 60% of those women had an RDI of 0.85 or higher—a clinically significant cutoff that has previously been linked to survival. This correlation was particularly strong at the individual medication level for taxane agents. Neutropenia incidence was higher when chemotherapeutic dosage intensity was reduced. This tiny study did not find any statistically significant differences in overall survival; nevertheless, the 73% increase in death among breast cancer patients who also had HIV is generally in line with bigger registry-based and cohort studies from the US and sub-Saharan Africa.

We postulated that WLHIV may face significant delays in receiving cancer care due to the necessity for more thorough pre-treatment evaluation or structural access hurdles. These delays were noteworthy among patients in the SEER-Medicare database and, should they be present here, might potentially lead to lower survival rates.^{19, 33, 34} WLHIV, on the other hand, only required an extra 5.5 days to begin cancer treatment. This difference vanished when the larger percentage of Black and Hispanic women in the group who are HIV positive was taken into account, indicating that any real difference may be the result of well-established racial disparities in access to breast cancer care.^{35–39} Furthermore, it seems improbable that the slight variation seen here significantly adds to survival inequalities.

Additionally, we predicted that WLHIV would experience more frequent dosage delays or reductions in chemotherapy due to either a decreased tolerance to the harmful effects of chemotherapy or inconsistent adherence to the recommended treatment regimen. Sub-Saharan Africa is the source of the majority of the literature currently available on chemotherapy dose intensity in HIV-positive breast cancer patients. The mean RDI for all patients was only 0.78.²⁰ However, Botswanan breast cancer patients did show a decrease in chemotherapy RDI linked to concomitant HIV infection. Divergent findings originate from South Africa, where a sizable cohort study of breast cancer revealed a median RDI of 0.88 for all women and parity in RDI by HIV status. We discovered HIV-positive breast cancer patients in US academic settings who had median RDIs that were comparable to those of South African WLHIV. In contrast, there

was a difference in the US between this same dose intensity and the almost ideal amount observed in HIV-negative breast cancer patients. The most frequent cause of decreased RDI is myelosuppression, and some of the reduction shown here may be explained by the rise in neutropenia among WLHIV despite their access to granulocyte colony stimulating agents. Forty Chemotherapy-induced myelosuppression may not only impact longevity by lowering RDI; declines in the amount of circulating CD4 cells following cancer treatment have been found to be independently linked to a higher death rate among HIV-positive cancer patients.

The biggest variations in RDI occurred when taxane chemotherapy was being administered. It is challenging to determine whether these variations result from WLHIV's innate intolerance to taxanes or from the fact that taxanes are usually administered in the second part of more aggressive regimens, when the overall myelosuppressive effects have started to build up. With numerous popular antiretroviral medications (such as efavirenz, elvitegravir, and boosted protease inhibitors), overlapping metabolic pathways imply a potential risk of drug-drug interactions; nevertheless, this is also the case with cyclophosphamide, for which RDI did not change.⁴² Another coexisting consequence of long-term HIV infection is peripheral neuropathy. On the other hand, we are unable to say whether patients with WLHIV or those without HIV reported more dose-limiting neuropathy.

Limitations

The limited cohort size, instances of missing data, and potential for certain data mistakes resulting from manual data extraction are some of the limitations of our study. These drawbacks resulted from the study's retrospective design and the requirement to combine data from several medical record systems in order to examine a group that is still uncommon in the US. Even in this small sample, however, the correlation between HIV infection and chemotherapy tolerance approached statistical significance, and our results are both tenable and in line with bigger cohort studies from sub-Saharan Africa. Analysis of potential associations between HIV control and breast cancer care was hindered by the fact that participants living with HIV commonly obtained their infectious disease care at other institutions and that data on CD4 counts, viral loads, past opportunistic infections, and current medicines were frequently lacking. Although the fact that all participants received their cancer treatment at sizable academic cancer centres may restrict the applicability

of the findings, it is more likely that community practices will merely exacerbate the differences in cancer care observed at centres with experience treating patients with difficult cancer.

Conclusions

This cohort study is the first to demonstrate variations in chemotherapy tolerance among patients with breast cancer, with or without HIV, who were treated in a high-resource setting. To the best of our knowledge, it also contains the largest collection of comprehensive cancer treatment data from US-based patients with comorbid HIV. More information on the timing and harmful effects of cancer treatments was accessible with access to complete medical record data than with tumour registries. The well-established higher risk of death for breast cancer patients with concomitant HIV infection may be attributed to dose-limiting toxic effects and inadequate receipt of neoadjuvant and adjuvant treatment in this population. HIV coinfection may also make it more difficult to administer other harmful but effective treatments for breast cancer properly. To effectively serve this expanding demographic, strategies for assisting breast cancer patients who are also HIV positive throughout hazardous therapy are required.

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