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Outcomes and Chemotherapy-related Toxicity in HIV-infected Patients with Breast Cancer

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Keywords

HIV; AIDS; breast cancer; malignancy; African-American; chemotherapy toxicity

Introduction

In the era of combination antiretroviral therapy (ART), there has been a shift in the type of malignancies affecting patients with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS).¹ Incidence of the three AIDS-defining malignancies (ADCs) (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) has significantly declined. Non-AIDS defining malignancies (NADCs) now account for a larger fraction of malignancies compared with the pre-ART era.^{2,3} In a recent review of the cancer burden in the HIV-infected population in the United States between 1991 and 2005,⁴ certain NADCs, including breast cancer, had significantly increased in incidence over time. This increase likely reflects the aging of the HIV-infected population as well as an expansion of HIV/AIDS prevalence among women in the U.S.

From a global perspective, breast cancer is the most frequently diagnosed malignancy in women, representing 23% of all cancer cases and 14% of cancer deaths.⁵ It is the leading cause of cancer death in females in the developing world.⁵ In the past, the incidence of breast cancer has been lower in the AIDS population compared to the general population,^{6,7} with little variation in incidence by CD4 count or duration of HIV infection.⁸ However, the incidence of breast cancer in HIV-infected patients is increasing over time and now approaches the general population risk.⁹

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African-Americans account for nearly half of new HIV infections in the U.S. despite comprising a minority of the general U.S. population.¹⁰ Eighty-five percent of HIV/AIDS patients are African-American in Baltimore city.¹¹ For some cancers, including breast cancer, inferior treatment outcomes have been reported both for African-Americans^{12–15} and for HIV-infected patients.¹⁶ The impact of cancer on urban, predominantly African-American, HIV-infected patients in the late ART era is understudied. Given these shifts in cancer incidence and the changing face of the HIV epidemic in this country, we sought to better understand the characteristics and outcomes of breast cancer in HIV-infected patients at our large, urban, academic medical center in Baltimore, Maryland.

Patients and Methods

We searched the electronic and paper records of the University of Maryland and its affiliated HIV care clinics (approximately 5,000 patients per year) to identify all patients diagnosed with malignancy between January 1, 2000 and June 30, 2010.¹⁷ Inclusion criteria were age at least 18 years, HIV-infection, and diagnosis with breast cancer during the time of study. We identified 18 patients with a diagnosis of breast cancer (stage 0–III). Data was abstracted for demographics, risk factors for HIV, tumor and HIV characteristics, use of ART, cancer staging, treatment, and associated toxicities. Institutional tumor registry statistics were used for intra-institutional comparisons.

The date of cancer diagnosis was defined as the date of positive biopsy. Initial presentation was categorized by palpable breast mass, by screening mammography, or unknown. Hormone receptors (estrogen and progesterone) and HER-2 status were recorded. Patients were classified as alive, deceased, or lost to follow up on June 30, 2010. Initial CD4 count and viral load were defined as the value at the time of diagnosis with breast cancer. ART use was defined as use of combination ART at any time during the period of follow up. Family history was noted if there was a history of breast or ovarian cancer in a first-degree relative, regardless of age.

In patients receiving systemic chemotherapy, the first adjuvant chemotherapy regimen was evaluated for toxicity, with variables including type and grade of toxicity, number of treatment cycles before toxicity, need for treatment delay and/or dose reduction, treatment completion, and concurrent use of ART with chemotherapy. Associated toxicities were graded according to the CTCAE version 4.0.¹⁸

Overall survival (OS) and disease free survival (DFS) were estimated using the Kaplan-Meier method; survival curves were generated and compared using the log-rank test. Kaplan-Meier curves were stratified by study population, CD4 count and race. A univariate analysis for survival was performed using the Cox proportional hazards model. All data analyses were performed by SAS statistical software, version 9.2.0 (SAS Institute, Cary, NC). This study was approved by the University of Maryland Institutional Review Board.

Results

Baseline Characteristics

Eighteen cases of invasive and non-invasive breast cancer were identified; all patients were African-American, and 17 were female. Demographic, HIV, and breast cancer characteristics are presented in Table 1. Median age at breast cancer diagnosis was 48 years, compared to 55 years in all breast cancer patients at our institution ($p < 0.01$) (Figure 1), and 56 years in all African-American patients with breast cancer at our institution ($p < 0.01$). A family history of breast or ovarian cancer in a first-degree relative was reported in 8 cases (44%). The predominant risk factor for HIV acquisition was heterosexual sex. Median CD4

count at cancer diagnosis was 437.5 cells/mm³. The majority of patients (83%) received ART during the follow up period; preserved CD4 count and poor adherence accounted for those patients not on ART. Most patients (89%) presented with a palpable breast mass, while the others (11%) were detected by screening mammogram. The majority of patients (72%) had early stage (I or II) disease at diagnosis. Estrogen receptor (cutoff > 1%) and HER-2 were positive in 72% and 44% of patients, respectively; there were 3 cases of triple-negative breast cancer (all African-American females under age 50). Multicentric breast cancer was found in 6 patients (33%); half of these patients had a family history of breast cancer.

Surgical Variables and Complications

All 18 patients underwent surgical resection. Nine patients (50%) had mastectomy, and 9 patients (50%) had breast-conserving surgery. Reasons for mastectomy included multicentric disease in 6 patients, locally advanced disease in 2 patients, and patient preference in one case. One patient also had a bilateral mastectomy for bilateral multicentric cancers. Clinically positive lymph nodes were identified in 6 patients (33%) preoperatively, and all 6 patients underwent complete axillary lymph node dissection at the time of surgery. Sentinel lymph node biopsy was successfully performed in 11 patients (61%), and complete axillary lymph node dissection was performed in 2 patients with positive axillary sentinel lymph nodes.

Surgical complications developed in 5 patients (28%); the median CD4 count in these patients was 588 (range 163–678) cells/mm³, and all patients were on ART. Three patients developed infections that required reoperation. Two patients who had temporary tissue expanders placed at the time of surgery developed surgical site infections that required removal of the tissue expander, and one patient developed an infected hematoma at a lumpectomy site that required operative drainage and debridement. The other two patients that developed wound infections were successfully treated with antibiotics alone.

Adjuvant Chemotherapy

Ten of the 18 patients received chemotherapy for breast cancer (Table 2); two of these 10 patients received neoadjuvant chemotherapy. Median time to initiation of adjuvant chemotherapy was 41 (range 21–126) days; all but one patient, who suffered a post-operative wound complication, received chemotherapy within 5 weeks of surgery. Four of the 8 patients with HER-2 positive breast cancer did not receive any adjuvant chemotherapy due to small tumor size (T1a/bN0). Two of the 4 HER-2 positive patients who did receive adjuvant chemotherapy were unable to receive intended trastuzumab due to significant decreases in left ventricular ejection fraction (LVEF), one after anthracycline-containing regimen and one after 39 weeks of maintenance trastuzumab. The other 2 patients were given chemotherapy before 2006 (prior to trastuzumab approval for adjuvant use).

Chemotherapy Toxicity

The most common Grade 3 toxicity was hematologic, occurring in 4 of 10 patients (40%), after an average of 2.25 cycles of chemotherapy; all had anthracycline chemotherapy, 2 were taking concurrent zidovudine-based ART, and 3 were taking protease-inhibitor based ART. Hematologic toxicities occurred in 4 patients, including symptomatic anemia requiring transfusion in one, and neutropenic fever in 3 cases. Grade 2 infectious toxicity was seen in 30%, and Grade 3 in 20%. Toxicities included mucositis, thrush requiring oral anti-infective agents, breast abscess, *Mycobacterium avium* pulmonary infection, and esophagitis requiring IV antibiotics. Grade 2 gastrointestinal toxicity occurred in 20%, and grade 3 in 10%. Toxicities included increased liver function tests requiring treatment delay and nausea/vomiting (in one case requiring hospitalization). Grade 3 cardiac toxicity occurred in 2

patients, and precluded planned administration of trastuzumab. Both patients with Grade 3 cardiac toxicity were on concurrent ART and chemotherapy; one of the ART regimens contained a protease-inhibitor which could have potentiated cardiac toxicity drug-drug interaction. Grade 2 neuropathy was seen in 30% and grade 1 neuropathy in 10% of patients receiving chemotherapy; all received taxanes.

Outcomes in patients on chemotherapy

60% of patients completed intended adjuvant chemotherapy, while 40% discontinued treatment due to toxicity; the most common toxicity in patients discontinuing chemotherapy was infectious, while the most common overall Grade 3 toxicity was hematologic. Median baseline CD4 count in patients who discontinued chemotherapy was 205 (range 43–472) cells/mm³. Treatment delays occurred in 50% of patients, and dose reduction was required in 20% of patients; the majority had hematologic toxicity. At the end of follow up 70% of patients receiving chemotherapy were alive, 20% died from breast cancer, and 10% were lost to follow up. The 2 patients in the chemotherapy subgroup who died of breast cancer had stage II and III disease at presentation, widely divergent baseline CD4 counts (526 and 43), and were both on ART.

Use of ART while on chemotherapy

Most (70%) patients were on ART while undergoing chemotherapy treatment, and the majority of these patients completed chemotherapy. In those patients requiring a delay in chemotherapy, 4 of 5 were on ART during chemotherapy, and 3 of these 4 were on protease-inhibitor based regimens. In the 2 patients requiring chemotherapy dose reduction, one was on protease inhibitor-based ART.

Half of the patients receiving chemotherapy had concomitant HCV. All had normal baseline liver function. Three of 5 patients with HCV did not complete chemotherapy due to toxicity (neuropathy, symptomatic decline in ejection fraction, and patient discontinuation due to 'poor tolerance').

Clinical Outcomes

The median overall survival for the entire cohort was not reached; the overall survival curve is depicted in Figure 2. There were two breast cancer-related deaths, with breast cancer specific survival of 1.8 years (range 1.7–2.0). The one male in the study died of cardiovascular disease, unrelated to chemotherapy. Two patients were lost to follow-up. When survival was stratified by CD4 count ≥ 400 cells/mm³ or < 400 cells/mm³, no significant difference was seen ($p = 0.6$) (Figure 3).

Discussion

This study characterizes a large series of HIV-infected patients with breast cancer in the late HAART era. Other small studies have described institutional experiences with HIV and breast cancer, but largely from the pre-ART/early ART era.^{19–21} In our study population, patients with both HIV and breast cancer were African-American, predominantly female, and were diagnosed at a median age of 48 years. Patients generally presented with early stage disease; none presented with metastatic breast cancer. There was a high proportion (44%) with a family history of breast or ovarian cancer. Ten of eighteen total patients were given chemotherapy, and of these, 60% completed adjuvant therapy, with 50% and 20% requiring treatment delay or dose reduction, respectively. Overall survival was good and did not differ significantly by CD4 count.

The proportion of patients in this study with a family history of breast or ovarian cancer (44%) is markedly higher than that of the general population (12–20%).^{22,23} Our study is limited by small sample size and the potential for recall bias. However, if accurate, this finding suggests a possible influence of HIV on acceleration of oncogenesis and increased penetrance in patients who may already have a heritable risk. The triple-negative subtype, more common in young African-American females, was found in 3 (17%) of our patients, similar to the 12–15% prevalence in the general US population.²⁴ HER-2 positivity (44%) was higher than the prevalence in the general population (15–25%),²⁵ although this did not have a correlation with worse outcome. Both of these findings (high number with family history and with HER-2 positivity) should be confirmed or refuted in additional observations from other institutions and in different sociodemographic settings.

Surgical wound infection complications appear to be relatively common in this small group of HIV patients when compared to the general population undergoing surgical procedures for breast cancer. For example, a multi-center study²⁶ found a post-operative wound infection rate of 4.34% and 1.97% in patients undergoing mastectomy or breast-conservation therapy, respectively, as compared with our rates of 38% and 20%. A cautious approach to surgical management and reconstruction may be prudent since wound complications can delay systemic therapy which can ultimately worsen long-term outcomes.

Treatment delays and dose reductions in adjuvant chemotherapy were common (50% and 20%, respectively), a rate that is much higher than expected for breast cancer patients receiving standard adjuvant chemotherapy. For instance, in one large trial,²⁷ only 31% of patients experienced treatment delays, and 3–7% had dose reductions. In total 60% of patients prescribed chemotherapy in our cohort completed their intended course. Baseline CD4 count did not have an obvious impact on chemotherapy-related toxicities or on survival. The concomitant use of ART, particularly zidovudine, and protease-inhibitor based combinations, with chemotherapy appeared to be associated with dose reduction and/or treatment delay and grade 3 hematologic toxicity, the most common high-grade toxicity found in the group. This is similar to trends observed in a recent study of chemotherapy tolerance in HIV-infected patients with lung cancer.²⁸ Zidovudine is a myelosuppressive antiretroviral drug originally developed as a chemotherapeutic agent for cancer. Protease inhibitors inhibit hepatic cytochrome p450 metabolism of many drugs and may potentiate chemotherapy drug levels and associated toxicities.²⁹ In HIV-infected patients with cancer, particular attention must be paid to overlapping toxicities and to drug-drug interactions of ART and chemotherapy.

As more patients with HIV are included in cancer clinical trials, experience with concurrent chemotherapy and ART will improve. Because of small sample size and homogenous racial distribution of cases (i.e. all African-American), our findings may not be generalizable to all patients with HIV and breast cancer. However, they do illustrate the importance of close collaboration between medical and surgical oncologists and infectious diseases physicians in optimizing treatment outcomes. Linking HIV and cancer care in a multi-disciplinary setting is critical to reduce morbidity and mortality associated with surgery, radiation, and chemotherapy in breast cancer patients with HIV.

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Clinical Practice Points

- Non-AIDS defining cancers (NADC), including breast cancer, have been increasing in the HIV-infected population since the advent of combination antiretroviral therapy (ART). Aging and increased numbers of women infected with HIV have led to increased breast cancer incidence in this population.
- In this case series, we report survival and chemotherapy-related outcomes of 18 African-American, HIV-infected patients with breast cancer at our urban, academic institution.
- HIV-infected patients presented with early stage disease and had a high prevalence of family history of breast cancer, raising the possibility of accelerated oncogenesis in the setting of HIV.
- Treatment discontinuation and delay were higher than expected and occurred more often in those with hepatitis C virus co-infection and use of zidovudine and protease-inhibitor based ART regimens.
- In HIV-infected patients with breast cancer, particular attention must be paid to overlapping toxicities and drug-drug interactions of chemotherapy with ART.

Figure 1. Median age at breast cancer diagnosis: Group 1= Study Population, Group 2 = Institutional Population ($p < 0.01$)

Figure 2.
Overall survival probability for all cases (n = 18).

Figure 3.
Median overall survival by CD4 < 400 (Group 1) or ≥ 400 (Group 2) (p = 0.6).

Table 1

Characteristics of subjects with HIV and breast cancer.

Characteristic	Total (N = 18)
Female Sex [N (%)]	17 (94)
African-American Race [N (%)]	18 (100)
Median age [years (range)]	48 (37–74)
ECOG Performance Status [N (%)]	
0	13 (72)
1	4 (22)
2	1 (6)
HIV transmission risk factor [N (%)]	
Heterosexual	13 (72)
Injection drug use	4 (22)
MSM	1 (6)
Hepatitis C infection [N (%)]*	7 (39)
Smoker [N (%)]	14 (78)
Median CD4 cell count (cells/mm ³) at cancer diagnosis, (range)	437.5 (43–678)
HIV-1 RNA viral load 75 (copies/ml) at cancer diagnosis [N (%)]*	7 (39)
Antiretroviral therapy at time of cancer diagnosis *	9 (50)
Family history of breast/ovarian cancer [N (%)]	8 (44)
Breast	7 (38)
Ovarian	1 (6)
Mode of breast cancer detection [N (%)]	
Palpable Mass	16 (89)
Screening Mammography	2 (11)
Receptor positivity [N (%)]	
Estrogen	13 (72)
Progesterone	11 (61)
HER-2*	8 (44)
Triple negative (ER-/PR-/Her-2-)	3 (17)
Multicentric	6 (33)
Stage at diagnosis	
I	7 (39)
II	6 (33)

Characteristic	Total (N = 18)
III	4 (22)
0/non-invasive	1 (6)
Tumor histology	
Invasive Ductal Carcinoma	14 (77)
Invasive Lobular Carcinoma	1 (6)
Ductal Carcinoma in Situ	2 (11)
Other (mucinous)	1 (6)
Treatment	
Chemotherapy	10 (56)
Hormonal therapy	12 (67)
Mastectomy	9 (50)
Breast Conserving Surgery	9 (50)
Radiation	11 (61)

* Missing observations: hepatitis C infection (3), HIV-1 viral load (5), antiretroviral therapy (1), HER-2 receptor (1)

Table 2

Types of chemotherapy and toxicity outcomes of 10 patients receiving chemotherapy.

Patient	Chemotherapy	Concurrent ART with chemotherapy	Cycles before toxicity	Type of toxicity	Toxicity grade	Treatment delay	Dose reduction	Status of chemotherapy
1	Paclitaxel	No	1	Neurologic	1	No	No	Completed
2	<i>Adriamycin + Taxotere</i> Paclitaxel (weekly)	No No	n/a 5 2 2	n/a Infectious Gastrointestinal Neurologic	n/a 2 2 2	No Yes	No Yes	Completed Discontinued due to toxicity after 8 of 12 intended weeks
3	Cyclophosphamide + methotrexate + 5-fluorouracil (CMF)	No	1	Not specified	n/a	n/a	n/a	Discontinued due to toxicity
4	Adriamycin + cyclophosphamide	Yes Zidovudine Lamivudine Efavirenz	4 4	Hematologic Cardiac	3 3	Yes	No	Completed
5	Docetaxel + adriamycin + cyclophosphamide <u>Capecitabine</u>	Yes Tenofovir Emtricitabine Efavirenz Yes Tenofovir Emtricitabine Efavirenz	n/a n/a	None None	None None	No No	No No	Completed To hospice with metastatic disease progression
6	Dose-dense adriamycin + cyclophosphamide then paclitaxel + trastuzumab	Yes Abacavir Lamivudine Ritonavir-boosted Atazanavir	3 3 39/52 weeks	Hematologic Infectious Cardiac	3 2 3	Yes	Yes	Discontinued due to toxicity from trastuzumab (other drugs completed with switch of paclitaxel from weekly to q2 week due to toxicity)

Patient	Chemotherapy	Concurrent ART with chemotherapy	Cycles before toxicity	Type of toxicity	Toxicity grade	Treatment delay	Dose reduction	Status of chemotherapy
7	Adriamycin + cyclophosphamide	Yes Nevirapine Saquinavir Nelfinavir	1	Infectious	2	No	No	Completed
8	Docetaxel + adriamycin + cyclophosphamide	Yes Tenofovir Emtricitabine Efavirenz	5 3	Gastrointestinal Neurologic	2 2	No	No	Completed
9	<i>Docetaxel</i> Liposomal Doxorubicin <u>Navelbine, then Capecitabine</u>	Yes Abacavir Lamivudine Ritonavir-boosted lopinavir Yes Abacavir Lamivudine Ritonavir-boosted lopinavir	1 1	Hematologic Infectious	3 3	Yes Yes with navelbine due to thrombocytopenia	No	Completed (suboptimal response) Discontinued due to toxicity Died while on 3 rd line treatment
10	Taxotere + adriamycin + cyclophosphamide (TAC) × 1, then cyclophosphamide + methotrexate + 5-fluorouracil (CMF)	Yes Zidovudine Tenofovir Ritonavir-boosted lopinavir	1 1 1 1	Hematologic Infectious Gastrointestinal Neurologic	3 3 3 2	Yes	No	Completed

Neoadjuvant chemotherapy indicated by italics; adjuvant chemotherapy regular font; second line chemotherapy underlined.