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CASE SERIES

Role of Antibiotic Prophylaxis and GCSF Support in Preventing Systemic Anticancer Therapy-Associated Toxicities in HIV Infected Cancer Patients: A Case Series

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SUMMARY

This is a case series report of five HIV-positive patients diagnosed with non-AIDS-defining cancer who received the combination of ART and chemotherapy. There is an increasing incidence of non-AIDS-defining cancers, such as breast cancer, lung cancer, hepatocellular carcinoma, prostate cancer, colorectal cancer, and Hodgkin's lymphoma. The purpose of this study is to see the impact of appropriate antibiotics prophylaxis and G-CSF Support in preventing the toxicities associated with systemic anti-cancer therapy (SACT) in HIV Patients.

Keywords: Human Immunodeficiency Virus, Acquired Immune Deficiency Syndrome, Anti-Retroviral Therapy, AIDS Defining Cancer, systemic anti-cancer therapy (SACT), Non-Aids Defining Cancer.

INTRODUCTION

The pandemic of HIV began during the early 1980s. Initially, HIV disease was always accompanied by the "AIDS-defining pathologies" which together with HIV infection, presented as Acquired Immuno-Deficiency Syndrome (AIDS). Among them, three neoplasms i.e. Kaposi's Sarcoma (KS), Non-Hodgkin Lymphoma (NHL), and HPV-related invasive cervical cancer were frequent and were labeled as AIDS-defining cancers (ADCs). After the introduction of the Anti-Retroviral Therapy (ART) HIV infection was no longer a death sentence, with the possibility of living an almost normal life. But ten years of the HIV epidemic the good news was soon followed by its downside: the increasing incidence of chronic pathologies and especially non-AIDS defining cancers (NADCs)[1]. Globally NADCs are a growing source of morbidity for people with HIV[2]. Epidemiological studies have recognized increasing incidence of carcinoma of the breast, anus, lung, skin, liver, and prostate; hematopoietic malignancies such as Hodgkin's lymphoma and other neoplasms like melanoma and leiomyosarcoma in HIV-positive patients[3]. Current guidelines highlight that people living with HIV with NADCs should receive standard, guideline-based treatment, and experts in infectious disease and oncologists should work closely to assess disease outcomes and address potential drug interactions between antiretroviral therapy and antineoplastic treatment.

Human immune deficiency virus (HIV) is a part of the lentivirus family that infects human immune cells specifically CD4 T cells weakening them and over some time, it leads to a condition called Acquired Immune deficiency syndrome (AIDS)[4]. Globally, 38.4 million people are living with HIV). In the past few decades, rapid advancements have been made in Antiretroviral therapy (ART) and its role in HIV infection[5]. Thanks to ART, people living with HIV have a longer life expectancy and decreased morbidity and mortality than untreated patients. ART preserves immune function and limits infectious complications in HIV patients. HIV is now considered a chronic disease, rather than a fatal one, in countries where ART is available.

The improved treatment options have increased the overall longevity of patients living with chronic HIV but it has also increased the incidence of malignancy in such patients[6]. Patients with HIV have seen a 4-fold decrease in AIDS and AIDS-defining illnesses (such as fungal infections, TB, and cancers associated with HIV) however on the other hand there has been a steady rise in non-AIDS-defining illnesses and cancer like lung, liver, kidney, head and neck and Hodgkin lymphoma[1]. People living with HIV have a higher risk of developing cancer due to immunosuppression and co-infections with oncogenic viruses. The exact etiology of these non-AIDS-defining cancer are poorly understood. Some researchers have postulated that HIV may activate a proto-oncogene[7] or suppress a tumor suppressor gene or lead to microsatellite instability[8]. Various studies published have shown a direct link between a low CD4 count and a high risk of developing AIDS-defining illness/ cancer and NADC, which suggests that starting ART and having a high CD4 count decreases such risk[9].

The use of ART in cancer patients with HIV has been shown to decrease the incidence of opportunistic infection and overall morbidity in such patients[4]. Therefore, initiation of ART is recommended in cancer patients with HIV. Several studies have shown that cancer patients with HIV receiving chemotherapy and ART have shown no toxic live threatening complication and their response and disease-free survival is comparable to that of cancer patients without HIV[10]. Still, other studies have mentioned that the simultaneous administration of ART and anticancer therapy is complicated. Unfortunately, patients with HIV used to be excluded from studies of cancer drug development, and the ideal ART regimen and possible complications of the combination of ART and anticancer drugs for HIV-infected cancer patients are still vague. Future studies are urgently needed to further define the safety profile/ toxic effects of combined chemotherapy and ART in HIV-positive NADC patients. Such studies should help in the development of guidelines for the treatment of the population.

It is recommended that after initiation of antiretroviral therapy in patients infected with HIV, monitoring should be based on CD4 T-lymphocyte cell counts and plasma HIV RNA levels[11]. Likewise, in cancer patients (ADC or NADC) with HIV undergoing chemotherapy periodic follow-up and monitoring of CD4 count and viral load is required.

1st patient: Thirty eight years old gentleman diagnosed case of HIV in 2015 on ART. He presented to the oncology unit in the Autumn of 2018, with a diagnosis of stage IVB Hodgkin's lymphoma on liver biopsy. On presentation, he was unwell with loose stools, fever, weight loss, grade III anemia requiring multiple transfusions, hyperbilirubinemia, and coagulopathy. His baseline CD4 count was 92 and a viral load of 38 copies. His past medical history included HCV, which was diagnosed and treated in 2013. Past history also showed tuberculosis which was successfully treated in 2014. Since his presentation was in clinically full-blown AIDS, He was managed in-house. He was started on supportive care, transfusion support, Fluid resuscitation and appropriate antibiotics, and Vitamin K supplements. His antiretroviral drugs (tenofovir, lamivudine, and efavirenz) were optimized. He was also

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maintained on trimethoprim-sulfamethoxazole (due to low CD4 count) prophylaxis throughout the treatment course. Because of frailty and deranged liver function tests, he was given dose-adjusted chemotherapy with ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). He started showing signs of improvement. And by the second cycle of chemotherapy, his condition stabilized. He was then escalated to standard-dose chemotherapy, which he completed in 2019. The rest of the chemo course went uneventfully with a one-time EAR visit for loose stool and diarrhea. To rule out either HIV-related causes, colonoscopy, and stool studies were done and turned out unremarkable. He achieved a complete metabolic response in 2019 and has been in remission ever since then.

He had a regular follow-up with the Infectious disease team with CD4 count and viral load. His viral load in February 2019 was undetectable but in October 2019 his regimen was switched to tenofovir, lamivudine, and doultegravir because of the detectable viral load on PCR. His last PCR viral load since then has been undetectable.

2nd patient: Twenty seven years old gentleman diagnosed case of HIV in 2015 on ART. In 2021, he was diagnosed with Stage IVBS classical Hodgkin's lymphoma. He presented with B-Symptoms, and bilateral cervical and axillary lymphadenopathy. His baseline viral load was undetectable and his CD Count was 96. Since diagnosis, he was in full-blown AIDS. He was using ritonavir, efavirenz, lamivudine and zidovudine. He had fair compliance with AIDS medications. He was treated with 6 cycles of ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine). His Course of chemotherapy was complicated with febrile neutropenia, for which he was admitted after the first cycle of chemotherapy where he had received supportive care, transfusion support, fluid resuscitation, and appropriate antibiotics and G-CSF cover. His Anti-HIV medications were optimized rest of the cycles were managed with appropriate antibiotics, anti-viral, and G-CSF cover. He completed 6 cycles of chemotherapy uneventfully and has been in remission ever since with regular follow-ups. His last viral load done in April 2022 was 46 copies with a CD4 count of 265.

3rd patient: Forty five years old gentleman diagnosed case of resectable peri-ampullary adenocarcinoma. He presented in the medical oncology department with pain right hypochondrium and weight loss. During a routine screening work up before chemotherapy, he turned out to be HIV positive. His baseline viral load was 194000 copies. He was in full-blown AIDS. Examination revealed he had anal warts. The patient underwent Whipple surgery for periampullary cancer in March 2021 followed by adjuvant chemotherapy for 8 cycles. He received chemotherapy under the cover of TMP/SMX, acyclovir, G-CSF, and ciprofloxacin He was started on ART regimen consisting of tenofovir, lamivudine, and dolutegravir. The course of chemotherapy was complicated with frequent emergency visits with an acute febrile illness which were managed well with supportive medications, appropriate antibiotics, acyclovir, and G-CSF Cover. Later on, he had disease progression with liver metastasis and lung opacities. Bronchoalveolar lavage was negative for infectious etiology..His metastatic disease was managed with palliative chemotherapy and anti-HIV medications were optimized. Unfortunately, he passed away in November 2022 from his advanced d and incurable disease. His last viral load was undetectable and his CD4 count was 320 in September 2022.

4th patient: Thirty three years -old female diagnosed case of HIV in 2017. Her baseline viral load was 15483 and her CD4 count was 236. She was in blown AIDS. She was using ART therapy consisting of tenofovir, lamivudine, and dolutegravir. She presented to the medical oncology unit with a lump in the left breast in 2022.Biopsy of the left breast lump shows Invasive ductal Carcinoma grade III ER 90%, PR 70%, H2N 3+ve, proliferation index (Ki67 20-25%). The staging workup was negative for distant metastasis. She had locally advanced stage IIIB disease. As per institutional guidelines, she was offered anti Her 2 Targeted therapy in combination with chemotherapy under the cover of antibiotics prophylaxis namely ciprofloxacin, TMP/SMX, acyclovir, and G-CSF. She has completed her course of treatment uneventfully. During treatment, the patient had not experienced any major complications either from chemotherapy- or HIV exacerbation that required inpatient treatment or postponement of chemotherapy. Her last viral load on September 22 was 426.

5th patient: A 32-year-old male presented with Stage IVBSX Mixed cellularity classic Hodgkin's lymphoma with bone marrow and hepato-splenic involvement in 2022. His international prognostic score (IPS) was 5/7 with 5 years of Freedom from progression at 42% and overall survival at 56%. He was tall and thin with unusually long arms and legs, suggesting Marfan's syndrome. His Echo showed aortic root dilatation and mitral valve prolapse. On baseline screening, he was found to be HIV positive. His baseline viral load was 182,000 and his CD4 count was 58. He was started on ART consisting of tenofovir, lamivudine, and dolutegravir. He was started on Losartan potassium for his cardiac condition and echocardiography was performed on alternate cycles. After optimization of his comorbid conditions, he was started on chemotherapy with ABVD regimen for 6 cycles followed by radiotherapy to the site of bulky disease. Given low CD4 counts, his chemotherapy was administered under the cover of G-CSF, ciprofloxacin, trimethoprim-sulfamethoxazole, and acyclovir. His treatment course went remarkably uneventful, without experiencing any grave chemotherapy or HIV-related complications. His interim and end-of-treatment PET scan showed a complete metabolic response.

He remains on regular Oncology and Infectious disease follow-up. On the follow-up, his latest viral CD4 count is 327 and the viral load was undetectable. He remains in remission from Hodgkin's disease point of view.

RESULTS

This case series of five patients with HIV and NADC (HIV diagnosed at the time of presentation of cancer or earlier) highlights the treatment of these patients with antiretroviral therapy (ART), anticancer drugs along with GCSF, and antibiotics prophylaxis. Out of seven six individuals had shown biochemical and radiographic responses to this combination treatment. Four patients had shown insignificant immune-related adverse events and suppression of their HIV infection. One patient is in palliative treatment for disease progression.

DISCUSSION

HIV/AIDS increases the propensity of HIV-associated infections due to suppression in CD4-positive cell lineage. After the introduction of ART, there has been a decrease in the frequency of AIDS-defining illnesses and cancer and an increase in the frequency of NADCs. Therefore, cancer screening schedules need to be followed regularly. As we are all aware that diagnosis and treatment of cancer is associated with significant morbidity and mortality, oncologists must tailor the treatment according to comorbid conditions. If these patients continue aggressive regimens, their chances of developing grade III to IV chemotherapy associated toxicities are significantly increased and they can sometimes have fatal outcomes during the process of this treatment. Therefore, managing patients with HIV/AIDS and cancer is not a typical and straightforward condition faced by the oncologist. Through our knowledge of the pathophysiology of HIV/AIDS and cancer and the pharmacodynamics of chemotherapeutic agents, we are aware that significant immune suppression is associated with both the diagnosis and treatment. Toxicity can also negatively affect antiretroviral therapy compliance, favoring the emergence of resistant HIV strains[12].

Therefore, great care is required in the management of cancer patients with HIV/ AIDS, who are predisposed to multi-lineage compromise in the immune system. According to National Cancer Care Network (NCCN) guidelines on the management of

patients with HIV, those being treated with highly immune suppressive regimens should be given appropriate prophylaxis with myeloid growth factor support and appropriate antibiotics, antiviral or in some cases antifungal prophylaxis[13]. The cornerstone of management is an optimization of ART with resultant optimal CD 4 counts. Therefore, in patients with a new diagnosis of HIV or those with poor compliance to ART, patients are started on ART at least 2 weeks before starting SACT. To combat the drop in granulocytic lineage associated with SACT, prophylactic GCSF support is deemed beneficial. Additionally, proper antibiotics prophylaxis with gram-negative, antiviral, and atypical organism coverage minimizes the chances of infection and resultant SACT-associated toxicity. Therefore, all patients were managed according to the above rationale. Consequently, we observed that the SACT course of these patients sailed smoothly or with minimal complications. With this approach, we did not see any rise in the toxicities as can be expected in patients with immune-compromised status.

CONCLUSIONS

Based on the above case report, we strongly recommend compliance with ART, the use of prophylactic myeloid factor support, and antibiotics in HIV patients with cancer. Further multicenter studies are warranted to develop more experience in the management of cancer patients with HIV.

Conflict of interest: Nil

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