



AIDS-associated Cancers : An Emerging Challenge

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Abstract

Objectives: To study the incidence and effects of anti-retroviral therapy along with cancer chemotherapy on outcome of AIDS associated Cancers in Indian patients.

Method: 3832 cancers patients were investigated over a period of 5 years. 46 AIDS-associated cancers were identified. HIV status was evaluated by ELISA, Western Blot, viral load and CD4/CD8 counts. Patients were treated with different modalities of cancer management and anti-retroviral therapy was discussed with the patient and relatives. Patients were followed up 6 monthly.

Results: Incidence of AIDS-associated cancers was 1.2 percent. AIDS-Defining Cancers (ADC) were seen in 26 (54.35%) while non-AIDS-Defining Cancers (NADC) were observed in 21 (45.65%). Non Hodgkin Lymphoma was the commonest form of AIDS-defining cancers in 21 (84%) patients, cervical cancers in 4 (16%) women while there was not a single case of Kaposi's Sarcoma. AIDS associated cancers were common in males. Mean age was 38.5 years. Only 33.5% patients received treatment for HIV and cancers. Development of immune reconstitution syndrome was observed in 9.09% patients. Hepatitis B infection was seen in only one patient (2.17%).

Conclusions: AIDS-associated cancers are seen in advanced stage of HIV infection. Concurrent chemotherapy and anti-retroviral therapy for ARL is significantly effective. Cervical cancers and non-AIDS-defining cancers do not show predictable response to anti-retroviral therapy. Mortality in non-AIDS related cancers was significantly higher than AIDS related cancers.

Introduction

There are about 2.5 million HIV patients in India and the calculated prevalence in Maharashtra is around 0.62 per cent.¹ Survival of HIV patients improved significantly with better control of opportunistic infections and administration of Highly Active Anti-Retroviral Therapy (HAART).²

Real incidence of AIDS-associated cancers in Indians is not known. There are only few reports in Indian literature.³⁻⁵ It may be roughly 3-4 per cent in Indians while in developed countries; it may be 10-34 per cent.^{2,3} HIV associated cancers are mainly divided into two groups. AIDS-defining Cancers (ADCs) include Non-Hodgkin's Lymphoma, invasive cervical cancer and Kaposi's sarcoma. Other types of cancers in HIV patients are included in non-AIDS-defining Cancers (NADCs).²

We studied 3832 different types of cancers in Shri Siddhivinayak Ganapati Cancer Hospital, Miraj (Maharashtra) over a period of five years (January 2003-November 2008). Of them, 46 AIDS associated cancers were diagnosed. The present study focuses on these patients, their treatment effects of combination chemotherapy and antiretroviral therapy and overall outcome.

Patients and Method

Shri Siddhivinayak Ganapati Cancer Hospital is a dedicated cancer hospital in Miraj, District Sangli (Maharashtra), India. Number of cancer patients from Western Maharashtra, Konkan,

Northern Karnataka seek advice and treatment for oncological problems. During 2003-2008, 3832 cancer patients were enrolled in this study. All the cases were thoroughly investigated and hematological, biochemical and radiological investigations were performed. Histopathological study was performed by a team of pathologists and patients were classified according to ICD 10 code system. Treatment options like chemotherapy, surgery, or multimodality treatment were discussed with patients by respective specialists. Table 1 shows distribution of different cancers studied during last 5 years.

HIV infection is diagnosed by ELISA test and confirmed by Western blot test. Staging of HIV infection was done with CD4+/CD8+ counts. Viral load was estimated in these patients before administration of antiretroviral therapy and then 6 monthly to evaluate the response to HAART. Serum LDH was estimated for evaluation of disease activity. Patient and relatives were given complete information about the nature of both the diseases, further plan of management and expenses involved in this. Detail study of opportunistic infection was done and accordingly these conditions were managed. Different treatment options of highly active anti-retroviral therapy (HAART) were discussed with patients. Reverse transcriptase inhibitor (RTI) - or protease inhibitor (PI) based antiretroviral therapy, its monthly expenses, interaction between chemotherapeutic agents, their toxicities were discussed in detail with the patient and relatives.

All AIDS-associated cancer patients were evaluated monthly before next chemotherapy cycle and then every 3 or 6 monthly. Follow-up was continued after completion of chemotherapy or radiotherapy for status of HIV infection and evaluation for recurrence / relapses of cancers.

Results

3832 cancer patients were enrolled for this study. There

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Table 1 : Distribution of different cancers according to ICD10 coding system during 2003-08.

Type of Cancer	ICD10 Code	Male	Females	Total	HIV associated Cancers	Percent
Head and Neck	C00-14	836	319	1155	4	0.35
Gut	C16-18,C21	243	148	391	3	0.77
Uterus, tubes, adnexa	C51-52,C54-55	0	357	357	2	0.56
Metastases	C 97	224	117	341	3	0.88
Breast Cancer	C50	0	269	269	1	0.37
Other Blood Cancers	C90-95	157	96	253	0	0.00
Genitourinary Cancers	C64-68	198	42	240	1	0.42
Cervical Cancer	C53	0	173	173	4	2.31
NHL	C82-85,C96	108	60	168	21	12.50
Lung and Mediastinum	C34	60	27	87	1	1.15
Brain Tumors	C70-72	66	16	82	2	2.44
Prostate	C61	72	0	72	0	0.0
Ovary	C56	0	52	52	2	3.85
Soft Tissue Sarcoma	C49	31	18	49	1	0.09
Bone Tumors	C40-41	20	16	36	0	0.00
Liver, GB, Pancreas	C22-25	24	10	34	1	2.95
Thyroid and Endocrine	C73-74	12	13	25	0	0.00
Hodgkin's Lymphoma	C81	13	10	23	0	0.00
Skin Cancers	C43-44	5	8	13	0	0.00
Eye & Orbit	C69	8	4	12	0	0.00
Total		2077	1755	3832	46	1.20

Table 2 : Clinicopathological details of 46 HIV associated cancers

Number of cancer patients in this study	Number	Percentage
Male	2077	54.20
Females	1755	45.80
HIV Associated Cancers	46	1.20
HIV Associated Cancers in males	32	1.61
HIV Associated Cancers in females	14	0.76
Mean age of AIDS related Lymphoma (ARL)	40.8 years	
Mean age of non AIDS-related cancers	41.2 years	
Pediatric AIDS-associated cancers	03	6.52
Adult AIDS-associated cancers	43	93.48
HBV positive AIDS related Cancers	01	2.17
Median CD4+ count	162.8 /mm ³	
HAART started for AIDS related cancers	11	23.91
HAART not started for patients AIDS related cancers	35	76.09
Reconstitution syndrome following HAART	01	9.09
Types of Non-Hodgkin's Lymphoma	21	
Diffuse large B cell Lymphoma	18	85.71
Primary Central Nervous system Lymphoma	1	4.76
T cell Non-Hodgkin's Lymphoma	1	4.76
Lymphoblastic Lymphoma	1	4.76

were 2077 were males and 1755 females. Male-to-female ratio was 1.18:1. Head and neck cancer was the most common type followed by cancers in females (breast cancers and gynecological cancers), gastrointestinal cancers and other types. There were 46 (1.20%) AIDS-associated cancers. Of these 21 had non-AIDS related cancers and 25 AIDS related cancers. The latter comprised of, Non-Hodgkin's Lymphoma in 21 patients (84%) and 4 (16%) of invasive cervical cancers. There was no case of Kaposi's sarcoma in our study.

In this study, AIDS-related cancers (ARL) were more common in males than females, with a ratio of 2.29:1. Pediatric AIDS-associated cancers were seen in only 6.52 per cent of patients. Median CD4 count was 162.8/mm³ indicating advanced stage

of HIV infection while viral load ranged between 50,000 to 393,000/ml. Of 46 cases of AIDS-related cancers, only 11 (23.91%) received antiretroviral therapy. One patient (9.09%) developed reconstitution syndrome characterized by sudden aggravation of tubercular lymphadenopathy and hyperlipidemia due to protease inhibitor based HAART. In NHL group, diffuse large B cell lymphoma was found in 85.71% patients while 14.61% had other forms of NHL. At the end of 2008, 11 (23.91%) patients are alive, 31 (67.39%) dead and remaining 4 (8.7%) lost to follow up.

Discussion

Pattern of AIDS-associated cancers in Indian patients differed significantly from developed countries where there were cases of Kaposi's sarcoma. In developed countries, Kaposi's sarcoma was the commonest cancer followed by non-Hodgkin's lymphoma.² We and Dhir et al did not find a single case of Kaposi's sarcoma in our studies.⁴ Only one case of Kaposi's sarcoma was found in an autopsy study of 162 AIDS patients in another Indian study.⁵

AIDS related lymphoma (ARL) was the commonest cancer in our study. All these patients had advanced stage, B symptoms, extranodal involvement such as bone marrow, central nervous system etc at the time of presentation. Mortality in AIDS-associated cancers was higher when these patients had low CD4 count and Karnofsky performance score, presence of extranodal disease, an advanced clinical stage, presence of bone marrow involvement, an age more than 35 years and a high serum lactate dehydrogenase concentration.⁷ Risk of development of NHL in HIV patients is almost 100-300 times higher than general population when they have low CD4 count, high viral load and not receiving anti-retroviral therapy.⁸

There are no specific guidelines for the treatment of ARL. Patients with ARL do not tolerate conventional chemotherapy. They develop severe myelosuppression and opportunistic infections. When low-dose chemotherapy was administered, results were suboptimal.⁹ Addition of HAART to standard chemotherapy with support of different growth factors, improved the outcome of AIDS related Non-Hodgkin lymphoma

patients. Different chemotherapy regimes such as infusional CDE, m-BACOD with G-CSF, EPOCH, CHOP and chemotherapy with Rituximab were tried for the management of these patients.^{7,9} German ARL study group investigated concurrent administration of HAART and CHOP regime in 72 patients with ARL. They reported 79 per cent complete remission and longevity up to 47 months. Toxicities were not very severe. Now combined modality is considered standard-of-care ARL.¹⁰ In HAART era, goal of treatment of ARL is complete remission, not palliation.¹¹

We managed ARL with standard CHOP regime along with Reverse Transcriptase inhibitor (RTI) based antiretroviral therapy (HAART). Patients tolerated chemotherapy and HAART well and could complete chemotherapy without any interruption. Patients were treated with different anti-retroviral regimes such as Emtricitabine, Lamivudine, Efavirenz or Zidovudine, Lamivudine, Efavirenz or Loponavir/Ritonavir-based antiretroviral therapy. Zidovudine was omitted if patients developed myelosuppression. Similarly, Didanosine was not used as it causes peripheral neuropathy or exacerbates chemotherapy induced peripheral neuropathy. PI-based antiretroviral therapy is very expensive, can cause or worsen chemotherapy induced neutropenia by inhibiting cytochrome P450/CYP3A enzyme system.¹² Some protease inhibitors may reduce the hepatic metabolism of cyclophosphamide or anthracycline.¹³ There has been some concern about tumorigenesis with Protease inhibitors like Nelfinavir. Nelfinavir was tumorigenic in animal studies but not in clinical studies in humans so far.¹⁹ Ritonavir caused significant regression of cancers like head and neck cancers. Its Inhibitory effect was boosted by ionizing radiation in animal studies with minimal toxicity.¹⁵

Epstein-Barr virus, human papilloma virus or Human Herpes Sarcoma virus induced AIDS-defining cancers, while "non-viral" theory is proposed in the pathogenesis of non-AIDS-defining cancers.^{7, 15, 20}

Immune reconstitution inflammatory syndrome (IRIS) following HAART was seen in ARL after receiving chemotherapy and antiretroviral therapy. Few AIDS-associated cancer patients on HAART develop exacerbation of inflammatory condition. This could be due to persistence of immunodeficiency in spite of chemotherapy and HAART. Development of IRIS indicated improvement in immunity and over all prognosis of such patients may be better.¹⁴

In this study, all cervical cancers had advanced stage at the time of presentation with significant complications. Though, cervical cancer is an AIDS-defining Cancer, there could be variable response to anti-retroviral therapy. If HIV-infected women receive HAART in early stage, there could be regression of malignant lesions. Surprisingly, there was no correlation with CD4 count and clinical response to HAART in different clinical studies.^{16, 17}

Patients with non-AIDS related cancer had aggressive malignancies and poor performance status. Mortality was significantly higher in this group. Response to HAART and cancer management was not uniform and predictable when treated with antiretroviral therapy.¹⁸ Recent study showed that with the use of antiretroviral therapy for HIV infection, there was a decline in AIDS-defining Cancers and an increase in non-AIDS-defining Cancers. It was attributed to development of skin cancers in white population.²

CD4 count was considered as a surrogate marker and correlated with the disease activity and prognosis in some

types of malignancies. Thus median survival was only 4 months when CD4 count was less than 100/mm³, but 11 months if more than 100/mm³ in the absence of HAART. CD4 count correlates well with progress of Kaposi's Sarcoma and Non-Hodgkin's Lymphoma but not with cervical cancers.¹⁷

Although AIDS-related cancers improved significantly with HAART, and mortality reduced by 70 per cent, the same results were not seen in non-AIDS-related cancers.⁷

Conclusion

Number of HIV associated cancers is increasing due to increased survival rates and the age of HIV positive patients. Pattern of AIDS related cancers in Indian patients differs significantly from developed countries. Non-Hodgkin's lymphoma is the commonest type of AIDS related cancer, followed by non-AIDS-related cancers. Kaposi's sarcoma is not found in our study. AIDS-defining cancers respond to combined treatment with chemotherapy and antiretroviral therapy but in non-AIDS-related cancers, outcome is poor. Concomitant chemotherapy and HAART is considered as the standard-of-care for ARLs.

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