High Incidence of Zidovudine Induced Anaemia in HIV Infected Patients in Southern Odisha

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Abstract Zidovudine (AZT), a nucleoside reverse transcriptase inhibitor was the first breakthrough in AIDS therapy in 1990. This study was conducted with an aim to determine prevalence of AZT induced anaemia in HIV infected patients initiated on AZT containing anti retroviral therapy (ART) regimen and also to find out any risk factor for causing AZT induced anaemia. Study was carried out in ART centre, M.K.C.G, MCH, Berhampur between Jan 2009 and Dec 2011. HIV infected patients registered at ART centre were treated according to National AIDS Control Organisation (NACO) guidelines. Patients (n = 1221) with Hb >8 gm/dl were prescribed AZT based ART regimen. Patients having anaemia (<8 gm/dl) were excluded from the study. Correlation of baseline characteristics (age, sex, weight, Hb level, CD₄ count, World Health Organization (WHO) clinical stage) with risk of developing anaemia was also calculated. 178 (14.6 %) patients on AZT regimen developed anaemia. Patients with low CD₄ count were more prone to develop severe anaemia. Age, sex, weight, WHO clinical stage had no relation with development of anaemia. Incidence of AZT induced anaemia was very high and patients having low CD₄ count were more susceptible to develop anaemia.

Keywords Anaemia · HIV infection · Zidovudine

Introduction

Zidovudine (AZT), a nucleoside reverse transcriptase inhibitor was the first breakthrough in AIDS therapy in 1990. AZT is mandated in World Health Organization (WHO's) 'Essential Drug list'. As per the recent NACO (National AIDS Control Organisation) guidelines fixed dose combination of two NRTIs (AZT/stavudine+lamivudine) and one NNRTI (nevirapine/efavirenz) is recommended as the first line highly active antiretroviral therapy (HAARTs). Among them AZT is highly effective and the preferred NRTI in NACO sponsored anti retroviral therapy (ART) centers in India, but it is associated with several adverse effects like myelotoxicity, mitochondrial toxicity, myopathy and among them myelotoxicity is a major side effect [1]. The prevalence and incidence of AZT induced anaemia varies widely in different parts of the world [2, 3] and also in different parts of India ranging from 5.42 % to 16.20 %.

Our study was conducted with an aim to determine incidence of AZT induced anaemia in HIV infected patients and also to find out any risk factor for causing or precipitating AZT induced anemia.

Materials and Methods

This study was conducted at ART Center, Department of General Medicine, M.K.C.G. MCH, Berhampur, Odisha from Jan 2009 to Dec 2011. HIV/AIDS was diagnosed as per NACO guidelines. All newly registered HIV patients above 16 years having hemoglobin (Hb) more than 8 gm/dl on AZT containing HAART therapy were included in the study.

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Demographic details, occupation details, education, CD₄ Count, weight, WHO Clinical stage [4] and baseline investigations like Hb, differential count(DC), total leukocyte count (TLC), erythrocyte sedimentation rate (ESR), liver function test(LFT) and kidney function test(KFT) were done. Patients were followed for a minimum period of 12 months and Hb estimation was done in a periodic interval just before starting ART, after 2 weeks then at monthly interval for 6 months, then at an interval of 2 months for next 6 months. Patients having Hb <8 gm% were put on stavudine based HAART. Among these patients for whom therapy later changed to AZT based regimen due to adverse effects of stavudine (peripheral neuropathy, lipodystrophy, mitochondrial toxicity) [5], rate of development of anaemia was noted and was compared with patients initiated on AZT based regimen. In our study “AZT induced anaemia” was considered, when Hb falls <8 gm/dl in patients taking AZT based HAART and on stopping the AZT, Hb level rises subsequently. Bone marrow study was done in patients developing anaemia. All patients developing anaemia due to AZT based regimen was shifted to stavudine based HAART. Patients on AZT based HAART developing anaemia, other causes of anaemia were also searched for, like Fe deficiency anaemia, opportunistic intestinal infestation and GI bleeding, hematological disorder, B₁₂ and folic acid deficiency anaemia, Hemorrhoid, H/O NSAID intake or menstrual disturbances in women were excluded from “AZT induced anaemia” group. Then incidence of AZT induced anaemia and its Correlation to Age, Sex, Weight, Hb level, CD₄ count, WHO clinical stage were determined. Mean decline in Hb and mean duration of fall in Hb were noted. After stopping AZT based therapy, mean recovery of Hb was also noted. All statistical calculations were performed using SPSS (version 16) Software. Unpaired ‘t’ test was used to find out differences in mean values of numerical variables at baseline between patients who developed AZT induced anaemia (group -1) with those who did not develop anaemia (group -2). Chisquare test used to find out significant association for qualitative variables used. Both tests were done using graph pad software. Multivariate analysis was done to know the risk factor for developing anaemia among baseline characteristics. A p value <0.05 was considered as statistically significant.

Results

Total patients registered at ART center during study period (January 2009 to December 2011) were 1738. AZT based HAART was started in 1221 (70.2 %) patients (Hb >8 gm/dl). Among them 887 (72.6 %) were male, 334 (27.4 %) were female. Remaining 517 (29.8 %) had <8 gm/dl and were put on stavudine based regimen. Among all patients on AZT based HAART, developing anaemia, eight patients

Table 1 Incidence of AZT induced anaemia in relation to duration of therapy

Months	n (%)	Cumulative n (%)
½	12 (6.8)	12 (6.8)
1	34 (19.2)	46 (26.0)
3	80 (44.8)	126 (70.8)
6	39 (22.3)	165 (93.1)
9	7 (3.8)	172 (96.9)
12	4 (2.1)	176 (99.0)
>12	2 (1)	178 (100)

Table 2 Bone marrow examination results

Bone marrow finding	Patients (%)
Total BM Examination	34
Normocellular	21 (62)
Dysplastic changes in erythroid line	7 (20)
Dysplastic changes in myeloid line	6 (18)

had evidence of intestinal infestation, three patients had hemorrhoids, seven patients had excessive menstrual bleeding, six patients had features suggestive of Fe deficiency anaemia and all of them were excluded from study. Among 1221 patients on AZT based regimen 178 patients (14.6 %) developed AZT induced anaemia (Hb <8 gm/dl). In 126 patients (70.8 %) AZT induced anaemia occurred within 3 months of therapy and 165 patients (93.1 %) within 6 months of therapy (Table 1).

Nature of anaemia was Normocytic - Normochromic in 48.7 % and Macrocytic in rest of the patients in peripheral smear. Mean decline in Hb was 6.4 ± 1.2 gm/dl. On stopping AZT therapy Hb level increased to a mean of 9.8 ± 1.4 gm/dl. Mean duration for fall of Hb was 3.56 ± 2.43 months. After substitution of stavudine mean duration for increase in Hb level was 1.34 ± 0.67 months. Bone marrow examination was done in 34 patients (Table 2). It was normocellular in 21 patients (62 %). Dysplastic changes in erythroid line was present in seven patients (20 %) and dysplastic changes in myeloid line was present in six patients (18 %).

On comparison of baseline characteristics (Table 3), it is evident that patients having low CD₄ count were more prone to develop anaemia ($p = 0.0001$). Age, sex, weight, Hb, WHO clinical stage did not show any correlation with occurrence of anaemia. Among 517 patients (Hb <8 gm/dl) who were on stavudine based HAART, stavudine was stopped in 97 patients due to side effect like peripheral neuropathy at mean duration of 13.7 ± 4.4 months and was substituted with AZT based regimen. At the time of change from stavudine to AZT parameters like wt, Hb,

Table 3 Comparison of baseline characteristics of patients on AZT therapy who on follow up developed anaemia (Group -1) to those who did not develop anaemia (Group -2)

Variables	Group -1 (n = 178)	Group -2 (n = 1043)
Age, Year (mean $\pm$ SD)	33.46 $\pm$ 7.06	34.43 $\pm$ 7.49
Gender (M/F)	129/49	658/285
Hb (gm/dl) mean $\pm$ SD	10.14 $\pm$ 1.78	10.37 $\pm$ 1.64
Weight (Kg) mean $\pm$ SD	45.6 $\pm$ 9.23	47.01 $\pm$ 9.74
WHO Clinical Stage		
II	56 (31 %)	357 (34.2 %)
III	76 (43.2 %)	413 (39.6 %)
IV	46 (23.6 %)	273 (26.2 %)
CD4 count (μ l)	106.2 $\pm$ 83.2	128.3 $\pm$ 78.6
<50	67 (37.6 %)	177 (16.97 %)
50 – 100	51 (28.6 %)	209 (20.03 %)
101 – 200	37 (20.8 %)	324 (31.06 %)
>200	23(13 %)	333 (31.94 %)

CD₄ count, stage of disease were significantly improved as compared to patients initially put on AZT based HAART. At the time of substitution, mean wt. -53.42 ± 8.04 kg, Mean Hb -11.78 ± 3.56 gm/dl, Mean CD₄ count $-254 \pm 93.4/\mu$ l. 68 patients were in clinical stage-I and stage-II. Among these patients, who were shifted from stavudine to AZT, only six patients (6.18 %) developed AZT induced anaemia after a mean duration of 3.46 ± 1.58 months. This is significantly lower ($p < 0.01$) as compared to those initiated on AZT based HAART.

Discussion

In our study 14.6 % patients developed AZT induced anaemia as compared to other studies where incidence of AZT induced anaemia were 5.42–16.2 % In majority of patients (93.1 %) meantime for development of anaemia was within 6 months [6], comparable to other studies [7, 8]. Two patterns of anaemia development were noted in our study. (i) 68 % patients had progressive fall in Hb (ii) 32 % had an abrupt fall in Hb. In most of the patients (84 %) after stopping AZT there was recovery in Hb level within 1 month. In ten patients recovery took as long as 6 months and may be due to the fact that Myelotoxic effect of AZT can persists as long as 3 months [6]. The factors having correlation with AZT induced anaemia like age, sex, wt., Hb level [9, 10], CD₄ count, stage of disease [11] was present in various studies We found only significant association of low CD₄ count with increased risk of developing AZT induced anaemia ($p = 0.0001$). Incidence of anaemia was much lower (6.18 %) in patients initiated

on stavudine based regimen and then substituted with AZT as compared to those initiated on AZT therapy (14.6 %) and may be due to improvement of wt., Hb, CD₄ count with stavudine based HAART.

Similar study was done by ART centre institute of medical science, Banaras from 2005 to 2007, their study was conducted on 1257 patients of which 16.2 % developed AZT induced anaemia [12].

In our study, incidence of AZT induced anaemia was 14.6 % and patients having lower baseline CD₄ count were more susceptible to develop anaemia. Development of AZT induced anaemia was found to have no relation with age, sex, weight haemoglobin and WHO Staging. This anaemia was observed within 3 – 6 months of therapy and was reversible on discontinuation of AZT. There was rise in Hb level after an average period of 1 month.

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