ORIGINIAL ARTICLE J Pub Health Med Res 2015;3(1):39-43

Incidence of Ziduvidine Induced Anaemia in Correlation with CD4 Counts Among HIV Seropositives on Antiretroviral Therapy

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(Received:05/12/2014, Revised: 01/02/2015, Accepted: 12/03/2015)

Abstract :

Aims : To determine the incidence of Zidovudine(ZDV) induced anemia in correlation with CD4 counts and to compare the incidence proportion in patients initially treated with ZDV based regimen with that in patients initially treated with stavudine(d4T) based regimen. To estimate risk of developing ZDV induced anemia for the second time in patients rechallenged with ZDV based regimen.

Materials and Methods : Retrospective data was compiled from medical records of patients alive and on ART from April 2004 to July 2010 who developed anemia on ZDV based regimen.

Results : Among 2062 HIV seropositives, 1054(51%) were started on ZDV based regimen and 1008(49%) were started on d4T. The incidence proportion was 8% in patients initiating on ZDV based regimen whereas 3% in patients initiated on ZDV who had prior d4T experience. Median duration on ZDV before stop of the same was 103 days(IQR:73-220). Baseline CD4 count ≤ 200cells/μL was the strongest predictive factor for ZDV induced anemia. Of 39 patients rechallenged with ZDV for the second time, 13(33%) developed anemia within a median duration of 3months on ZDV based regimen while remaining 26(67%) did not develop anemia over median duration of 8 months on ZDV.

Conclusion : Patients initiating ZDV containing regimen are at greater risk of developing ZDV induced anaemia than patients initiating d4T and then substituted to ZDV based regimen. As two-third patients tolerated ZDV on second time substitution, this substitution strategy was observed to be effective as alternative drugs can be preserved for these patients for later use.

Introduction

Studies have consistently shown that the prevalence of anaemia is high in the HIV-infected population, particularly among those with AIDS[1,2]. Although highly active antiretroviral therapy (HAART) has been shown to reduce anaemia by inhibiting the progress of the disease[3], zidovudine (ZDV) 3'-Azido-3'-deoxythymidine (AZT), an inhibitor of the human immunodeficiency virus reverse transcriptase, an element of some HAART regimens, has been associated with hematological toxicity[1,4,5]. Zidovudine (ZDV) is one of the first-line antiretroviral drugs recommended by WHO for treating HIV infected adults in low resource countries[6]. ZDV is becoming increasingly affordable and available despite concerns about its short-term tolerability, especially the risk of anemia among patients with advanced disease, women, and individuals with low body mass index (BMI) [7,8].

ZDV is a wellknown cause of drug-induced haematotoxicity[9,10]. Both ZDV and d4T lead to macrocytosis but only ZDV causes anaemia. The reasons for this difference is not clear. Bone marrow cell lineages are markedly more sensitive to ZDV as compared with other nucleoside analogs. ZDV inhibits the proliferation of blood cell progenitor cells in a dose-dependent manner & can cause anaemia [11,12].

The anaemia associated with ZDV therapy is due to red cell hypoplasia or aplasia. Bone marrow examination may demonstrate pure red cell aplasia, erythroid maturation arrest, erythroid hypoplasia and megaloblastic erythropoiesis. ZDV has been found to inhibit hemoglobin synthesis and globin gene

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transcription[13]. ZDV specifically inhibits beta-globin gene expression in human erythroid progenitors leading to marked cell growth inhibition at clinically relevant concentrations (1mM)[14].The findings of Lewis et al.,-mitochondrial DNA is one of the intracellular targets involved in pathogenesis of ZDV-associated bone marrow progenitor cell toxicity[15]. Toxic metabolites may also be relevant for cytotoxicity.

In this retrospective study, we computed the incidence of ZDV-induced anaemia in HIV-seropositives alive and on ART, who are on regular follow-up at Bowring and lady curzon hospital. While ZDV has shown to be associated with anaemia in studies of patients with HIV infection [5,16,17–19], we report here the risk ratio of developing ZDV induced anaemia for patients started on ART regimens containing ZDV as part of their initial regimen compared with ART regimens not containing ZDV as part of their initial regimen as this has not been rigorously established. Among the ZDV-Induced anaemia patients we also estimate the percentage who developed ZDV induced anemia for the second time when rechallenged with ZDV-based regimen.

Methods :

This was a retrospective observational study, with the collation of data from medical records of 112 patients who developed ZDV-induced anaemia after screening for these patients from 2062 longitudinal medical reviews of patients enrolled for ART at A Tertiary care hospital attached to a medical college from April 2004 and alive till July 2010. Using standardized instrument information on patients demographic and clinical conditions, laboratory values and treatments were extracted from the existing records. Body mass index (BMI, weight in kilograms divided by height in meters squared) was used to assess nutritional status. Established cutoff values for BMI were used[19]: normal (BMI ≥ 18.5 kg/m2), mild malnutrition (BMI 17–18.4 kg/m2), moderate malnutrition (BMI 16–16.9 kg/m2), and severe malnutrition (BMI < 16 kg/m2). Permission was obtained from the institution to publish the study.For all analyses, anaemia was defined as a hemoglobin concentration of less than 10g/dL. Drug-related anemia was defined as a diagnosis of anemia for which the physician specified a drug-related cause in the medical record all other diagnoses were considered unrelated to drugs. Data analysis was performed in Epi Info™ Version 3.5.1 software.

Results :

From April 2004 to July 2010, 4290 HIV seropositives were commenced on ART at a tertiary care referral Hospital. Of these 1081 were transferred to other centers, 585 died and 562 were lost to follow-up, 2062 were alive and on ART. Of the 2062, 1054 were started ART with regimens containing ZDV and 1008 started with d4T based regimens but were substituted to ZDV based regimens consequent to any adverse drug reactions. Among 2062 patients, 112(5.43%) developed anaemia on ZDV based regimens for which the physician specification of drug-related (Zidovudine-related) cause in the medical record were documented. The overall incidence was 8 per person-years. Out of 1054 (51.11%) started on ZDV-based regimen, 84 (8%) patients developed ZDV induced anaemia and out of 1008 (48.88%) started on d4T based regimen 28 (3%) developed ZDV induced anaemia after substituting to ZDV-based regimen. Thus, the incidence proportion was 8% in patients initiating on ZDV based regimen whereas 3% in patients initiating on ZDV who had prior d4T experience. The main baseline and follow-up characteristics of 112 patients is shown in Table1.

In our study population, 52% were males and 48% were females. Baseline CD4 count was recorded for all the 112 patients, more than 80% had counts below 200 cells/µl. Previous (non-TB) AIDS-defining illnesses (ADIs) were documented in 13% of patients, prior TB in 14%, ADIs and TB in 8% and 24% respectively, at baseline or after commencement of ART. Baseline hemoglobin levels were noted for 112 patients, 19(17%) had grade 1 anaemia, 10(9%) had grade 2 anemia and 4(4%) had grade 3-4 anemia.

Median follow-up on ART was 3.25±1.28 years. The median time to stop ZDV-regimens was 103(IQR:73-220) days due to ZDV induced anemia.

Median hemoglobin(Hb) level was 11.0 g% (IQR: 10.6-13.0) at start of ZDV therapy. Distribution of hemoglobin levels at start of ZDV based regimen in the 112 patients is shown in Figure 1.

The median hemoglobin level at the time of diagnosis of anemia was 5.45 g% (IQR: 4.1-6.85) and its distribution is shown in Figure 2.

Seven patients required immediate blood transfusion to restore their hemoglobin levels. The bone marrow examination report of 9 patients showed hypocellular marrow in 5 patients.

The median duration on d4T-based regimen in patients who were started on d4T-based regimen and later substituted with ZDV-based regimen was 16 months.

In univariate analysis, reason to stop ZDV based regimens within a median duration of 3 months of commencement of ZDV as a result of ZDV-induced

anemia was significantly associated with age ≥ 40 years, CD4 count ≤ 200 cells/µl and BMI ≤ 18.0 in patients initiating on ZDV based regimens (Table 2).

Out of 112, 39(35%) were rechallenged with ZDV for the second time, of which 13(33%) developed anemia within a median duration of 3months on ZDV based regimen while remaining 26(67%) did not develop anemia over median duration of 8 months on ZDV.

Of the 26 who tolerated ZDV on rechallenging for the second time, 10(38%) were males and 16(62%) were females.

Discussion :

It was observed that patients initiated on ZDV based regimens were most likely to develop ZDV induced anaemia within median duration of 3 months when compared to those initiated on ZDV who had prior d4T experience. Our findings were consistent with the findings of Huffam et al, whose study suggested that Prior HAART experience was protective for development of ZDV induced anaemia. This suggests that immune reconstitution, as may be achieved by a period of d4T-containing ART prior to commencement of ZDV, may reduce the rate of subsequent ZDV related anaemia[20]. In an open study of the use of zidovudine, Cohen et al (1989)found 10 out of a total of 81 patients developed a severe anaemia within the first 3 months of treatment[21]. In our study we found 61% of patients developing anaemia within 3 months of start of Zidovudine regimen. However we found 19% of patients developing anaemia after one year of start of ZDV based regimen. The possible reason could have been the plasma accumulation of toxic metabolities of zidovudine which after reaching a particular high concentration have caused anaemia in these patients.

Risk factors for human immunodeficiency virus (HIV)–related anemia reported in the literature include advanced HIV disease, female sex, African origin, low BMI, and older Age [22-27]. In contrast our study population had more males than females who developed anaemia on ZDV, however it was found that in patients who commenced on ZDV based regimen, the reason for stopping as a result of ZDV induced anaemia was significantly associated with age ≥ 40 years, CD4 count ≤ 200 cells/µl and BMI ≤ 18.0.

A study from rural Cambodia aimed at Evaluation of a systematic substitution of zidovudine for stavudine showed that the duration on d4T-based regimen before switch was not associated with the occurrence of anemia. The timing of a switch is still in question and suggests that choosing the optimum timing requires balancing the d4T toxicity avoided by the switch against the increased rate of ZDV-induced anemia and the extra burdens for patients and the programs [28].

Our study found that two-third patients tolerated ZDV on second time substitution, this substitution strategy was observed to be effective as alternative drugs can be preserved for these patients for later use. Maximum were females who tolerated ZDV when rechallenged for the second time. However, if a routine second time switch to ZDV is to be widely considered, further studies of the longer term efficacy and toxicities of ART switch strategies are needed, including investigation of the impact on adherence, tolerability, and virological and clinical outcomes.

Acknowldgements :

We would like to thank National AIDS Control Organisation (NACO) and Karnataka State AIDS Prevention Society (KSAPS) for their support and encouragement in conducting this study.

FIG.1

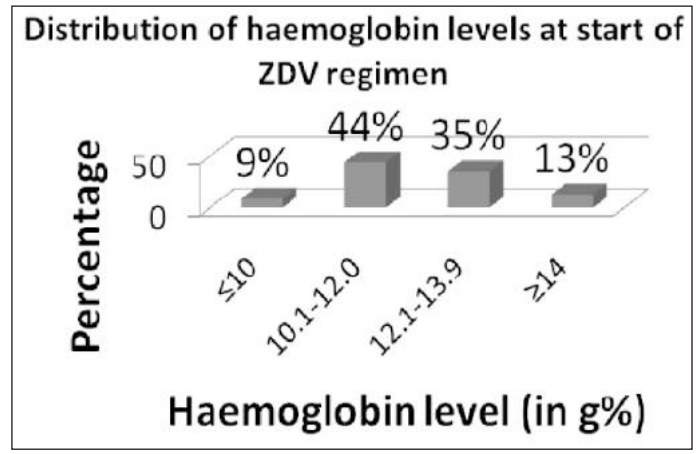

FIG 2

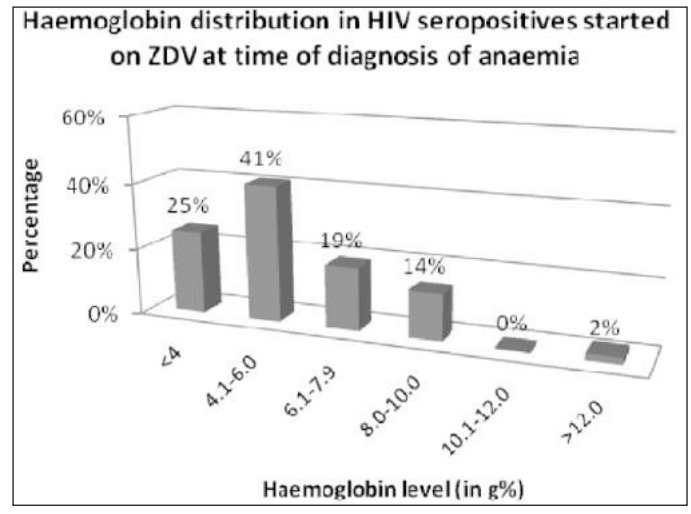

TABLE 1: Baseline and Follow-up Characteristics of HIV-Positive Patients who developed ZDV induced anaemia

	Patients initiated on ZDV (n=84)	Patients initiated on ZDV with prior d4T experience n=28	Total, n=112
Male/Female n(%)	45/39 (54/46)	13/15(46/54)	58/54 (52/48)
Age,yrs			
<19	-	1(4)	1(1)
20-29	21(25)	7(25)	33(29)
30-39	37(44)	4(14)	25(22)
>40	26(31)	16(57)	53(49)
On CTX on ART			51(46)
CD4 count, mm3			
<50	12(14)	9(32)	20(18)
50-100	24(29)	6(21)	30(27)
100-150	20(24)	5(18)	24(21)
150-200	15(18)	5(18)	20(18)
>200	13(15)	3(11)	18(16)
CD4 count, mm3,at baseline,median (IQR)	113.5(70-172)	97.5(43.5-176)	106(64-173)
WHO clinical stage,at baseline,n(%)			
I	15(18)	5(18)	20(18)
II	46(55)	15(54)	65(58)
III	19(23)	6(21)	16(14)
IV	4(5)	2(7)	11(10)
Body mass index,kg/m2,n(%), at start of ZDV			
<16.0 severe malnutrition	11(13)	3(11)	15(13)
16.0–16.9 moderate malnutrition	9(11)	2(7)	13(12)
17.0–18.0 mild malnutrition	12(14)	2(7)	21(19)
>18.0 normal nutrition	52(62)	21(75)	63(56)
HAART regimen,n(%)	-	-	
d4T+3TC+NVP	-	24(86)	24(21)
ZDV+3TC+NVP	79(94)	-	79(71)
d4T+3TC+EFV	-	4(14)	4(4)
ZDV+3TC+EFV	5(6)	-	5(5)
Haemoglobin level (in g/dl) at Start of ZDV	n=84	n=19 missing=9	n=103
≤10	5(6)	4(21)	9(9)
10.1-12.0	40(48)	5(26)	45(44)
12.1-13.9	32(38)	4(21)	36(35)
≥14	7(8)	6(32)	13(13)
No.years on HAART,median(IQR)(range)	3(2.0-3.57)(0.38-5.33)	5(4-5)(1.8-6.0)	3.25(2.35-4)(0.38-6.0)
No.days on ZDV before first episode of anaemia,median(IQR)(range)	104(74-215)(23-1136)	115(77-397)(43-1428)	103(73-220)(23-1409)
Challenged with ZDV based regimen,n(%)	30(36)	9(32)	39(35)
Second episode of ZDV induced anaemia in <6 months,n(%)	11(37)	2(22)	13(33)
No. of days on ZDV before second episode of anaemia,median(IQR)(range)	121(66-319)(10-741)	102(87-312)(82-39)	120(73-312)(10-741)
Tolerated ZDV for >6months	19(63)	7(78)	26(67)

TABLE 2:

	Number	%	p-value
Age(yrs)			
≤40	61	73	-
≥40	23	27	0.5
CD4 count			
≥200	13	15	-
≤200	71	85	0.007
BMI			
≥18	57	68	-
≤18	27	32	0.01

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How to Cite this article :
Asima Banu, Huilgol BGK, B Prabhakar, Vidyashankar, Incidence of Ziduvidine Induced Anaemia in Correlation with CD4 Counts Among HIV Seropositives on Antiretroviral Therapy. J Pub Health Med Res, 2015;3(1):39-43

Funding: Declared none
Conflict of interest: Declared none