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Safety and Tolerability of Antileishmanial Therapy in Visceral Leishmaniasis – A Record Based Observational Study

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ABSTRACT

Background: Kala-azar or visceral leishmaniasis (VL) is the most severe form of leishmaniasis caused by protozoan parasite of the genus Leishmania. This disease is the second largest killer after malaria of parasitic diseases worldwide. **Methods:** This retrospective record based observational study was conducted to assess the outcome of pharmacotherapy in visceral leishmaniasis (VL) patients admitted in the period of 2010 to 2014 at Calcutta School of Tropical Medicine, Kolkata in reference to their safety and tolerability. **Results:** In this institute VL cases were treated with conventional and liposomal AmB as well as with SSG, Miltefosine and combination therapy. Among the regimens short course L-AmB was found to be the most efficacious and tolerable in respect to ADRs and hospital stay. ADRs were common with SSG, AmB, Miltefosine and almost absent with L-AmB. HIV co-infection was found to be the common cause for relapse and readmission of VL cases. AmB was least tolerable in respect to prolonged hospital stay (4 to 6 weeks) and ADRs encountered (100% with chill and rigor). **Conclusion:** Among the regimens short course L-AmB was found to be the most efficacious and tolerable in respect to ADRs and hospital stay.

Keywords: Visceral Leishmaniasis, Amphotericine B, Miltefosine, Tolerability.

INTRODUCTION

Kala-azar or visceral leishmaniasis (VL) is the most severe form of leishmaniasis caused by protozoan parasite of the genus Leishmania. This disease is the second largest killer after malaria of parasitic diseases worldwide, incidence being 200,000 to 400,000 each year. The parasite invades the internal organs such as liver, spleen and bone marrow and if left untreated is almost always fatal. Patients may present with fever, weight loss, fatigue, anemia and hepatosplenomegaly. According to WHO emerging problem of HIV/VL co-infection is of growing concern.[1-5]

The traditional treatment is with pentavalent antimonials such as sodium stibogluconet and meglumin antimoniate. Resistance is now common in India, and rates of resistance have been shown to be as high as 60% in parts of Bihar. The treatment of choice for visceral leishmaniasis acquired in India is now amphotericin B in its various liposomal preparations. Miltefosine the first oral drug for this disease has received approval by the Indian regulatory authorities in 2002.

Calcutta School of Tropical Medicine (CSTM) is a pioneer institute for treatment of VL and it caters the people living in nearby endemic areas for years together since the period of Dr. U N Brahmachari. VL patients are treated here after admission on diagnosis in the inpatient department of this hospital. So critical review of the hospital records of admitted VL patients may give interesting knowledge about the treatment followed here under different clinical settings.

The study was undertaken at CSTM to study the safety and tolerability of antileishmanial drugs in VL patients over the period under study.

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MATERIALS AND METHODS

This retrospective, record-based, observational study was conducted at CSTM. The hospital records (Bed Head Tickets or BHTs) of all consecutive VL patients admitted during the five years - 2010-2014, were reviewed and the relevant information inputs as documented were studied to realize the above-noted objectives.

The study was undertaken only after the Institutional Ethics Committee approved the bigger study Protocol of which it is a part and with due permission of the hospital administration, the relevant hospital records were accessed and critically

reviewed to look for treatment (antileishmaniasis) regimens in reference to efficacy, safety and tolerability.[2]

Sometimes it became necessary to consult with respective treating physicians to fill the gaps of informations which may be regarded as source documents. Moreover, whenever possible patients were contacted by telephone which were available on BHTs, gave important informations.

Data collected were compiled and analyzed using appropriate descriptive statistical methods.

RESULTS & DISCUSSION

In the present study, the total number of BHTs accessed were 96 with VL as the primary diagnosis. Total number of VL cases without HIV were 78. Among them 71 were admitted as new cases, 3 as relapse. Out of these 3 relapse cases one was admitted as relapse for the first time without prior admission in the study period and 2 were of repeated admission. Out of 4 cases recorded as follow ups (FU) in VL, 2 were admitted as FU without prior admission in study period whereas 2 of repeated admission within the study period. So altogether 74 patients were considered in VL group. But, again 4 newly admitted patients and 2 patients admitted as FU cases did not receive any anti leishmanial therapy. So out of 74 patients with VL 68 received anti VL treatment.

There were 18 BHTs with VL co-infected with HIV out of all VL cases. Among these 18 cases there were 5 new, 2 admitted as FU (follow up) and 11 were readmitted one or more times. So, actually the total number of patients considered in the VL with HIV group were 7. Number of patients were not the same as the number of cases / BHTs, as the patient might have been admitted more than once with a diagnosis of relapse and follow up. The mean age of VL cases in the study was 30.02 ± 15.88 years, the range was from 2 to 75 years. Maximum number (60 cases) belonged to the age group from 18 to 45 years, followed by pediatric age group of 0 to 17 years (23 cases), 46 to 60 years age group (10 cases) and the least was in the category of senior citizen above the age of 60 years (3 cases). Present study shows the occurance in male 59.37% (57 out of 96) and female 40.62% (39 out of 96) among VL cases, male female ratio was 1.46:1.

Fever was the presenting symptom of 85.4% of VL cases Most of the cases had history of insidious onset. Duration of fever varied from few days to months and even low grade fever upto 2 years. 67.7% of VL cases presented with loss of appetite and weight loss which were gradual. All cases were suffering from anemia some of them were grossly anemic needing blood transfusion. All cases also had splenomegaly very often huge.[3]

Treatment regimens in VL patients

By thorough scrutiny of all the BHTs, the treatment regimens followed in this institute from 2010 to 2014 for the treatment of VL patients were as follows:

Injection Amphotericine B Deoxycholate (AmB) - administered in the dose of 1mg/kg body weight dissolving in 5% Dextrose solution to be infused slowly taking about 6 hours for 1 bottle infusion 15 to 20 doses either daily or on alternate day basis was the commonest prescribed regimen. Out of 96 VL cases 58 (60.41%) cases received AmB including 16 (88.88%) out of 18 VL with HIV cases. Eleven out of 18 VL with HIV cases received monthly prophylaxis with single dose of AmB. Before starting the full daily dose a test dose was initially administered on routine basis. This was to safeguard for any feature of hypersensitivity which might arise. Some of the treating physicians have given the gradual escalating doses on daily dosing to reach the target dose, however those test doses were considered while calculating the total dose to be administered.

Combination chemotherapy of L-AmB followed by Miltefosine - this regimen was the second in frequency of use, 19 cases out of the total of 96 VL cases studied. In this regimen single dose of L-AmB at 7.5 mg/kg body weight was infused slowly followed by 14 days of oral Miltefosine in the dose of 50 mg tablet twice daily for those patients over 25 kg weight and once daily for body weight less than 25 kg.[4]

Liposomal preparation of AmB (L-AmB) was used in 10 out of 96 cases as sole therapy at 7.5 mg /kg body weight two doses. This regimen was very well tolerated with no significant recorded ADR.

Miltefosine as monotherapy was given in one patient who was suffering from VL with HIV and had the history of previous treatment with conventional AmB. This particular patient was given Tab Miltefosine in the dose of 50 mg tablet twice daily for 28 days as per the recommendation and there was no reported adverse reaction.

Injection Sodium Stibogluconate (SSG) had only been used in single case of VL. This patient did not encounter any ADR and 30 doses were prescribed. During hospital stay the patient was given the drug by I/V route but on discharge he was advised to take rest of the injections by I/M route from OPD.[6]

One patient was suffering from VL with HIV and had the history of repeated admission. In one occasion he was given Injection Paromomycin for 20 days then the combination therapy of L-AmB for 5 doses followed by Miltefosine tablets for 28 days. This particular patient was also suffering from Hepatitis B. He was getting additional anti-retroviral therapy in the form of Tenofovir, Lamivudin, Lopinavir and Ritonavir.

Over the five years the most preferred regimen was AmB (60%), followed by combination regimen of L-

AmB and Miltefosine (21%), L-AmB (10%), no treatment in 6% cases and 1% each of SSG, Miltefosine and Paramomycin followed by combination therapy of L-AmB and Miltefosine.

Duration of hospital stay: average hospital stay of VL patients with AmB therapy was 29.63 ± 18.76 days, whereas with L-AmB therapy it was 16.7 ± 7.97 days and with combination therapy it was 23 ± 7.47 days. So, least duration of stay with L-AmB therapy.

Treatment outcomes

Clinical cure was achieved in all admitted cases of VL at the end of teatment. All regimens showed equivalent efficacy but definitely safety and tolerability were different. SSG was rather safe but tolerbility not much as it was given by IM injections on both buttocks repeatedly. AmB was highly efficacious but not safe, as 100% occurrence of transfusion reactions in the form of fever, chill and rigor. Hypokalemia often encountered which required close monitoring of patients. Tolerability was also poor as cases were admitted for long time.

L-AmB and combination of L-AmB with Miltefosine both regimens were efficacious at the same time ADRs were negligible except few cases of nausea and vomiting associated with Miltefosine. Most importantly they were well tolerated as short duration of hospital stay and oral formulation.

CONCLUSION

This retrospective record based observational study was conducted to assess the outcome of pharmacotherapy in visceral leishmaniasis (VL) patients admitted in the period of 2010 to 2014 at Calcutta School of Tropical Medicine, Kolkata in reference to their safety and tolerability.

Majority (60%) of VL patients were treated with AmB, only 10% of VL cases were treated with L-AmB and 20% with combination therapy (L-AmB with Miltefosine). Miltefosine, Paromomycin and SSG were given to single patient each.

Commonest ADRs encounterd in the treatment of VL patients were chill and rigor with or without fever (50%). This was almost universal in AmB and least in L-AmB. Nausea and vomiting were reported in 12% of cases, almost all in Miltefosine group. Hypokalemia was noted in 7% of cases treated with AmB or L-AmB. No ADR was recorded in about ¼ th (24%) of the cases.

Clinical cure was defined as subsidence of fever, anaemia and splenomegaly. Though clinical cure rate was 100% with all the regimens but short course L-AmB stood out to be far better regimen in respect to ADRs encountered (almost nil) and average hospital stay (2 days to 2 weeks). Next was combination therapy where average hospital stay was 3 to 4 weeks and ADRs were encountered in about 60% of cases. AmB was least tolerable in respect to prolonged hospital stay (4 to 6 weeks) and ADRs encountered (100% with chill and rigor).

So, it can be concluded from this study that in this institute VL cases were treated with conventional and liposomal AmB as well as with SSG, Miltefosine and combination therapy. Among the regimens short course L-AmB was found to be the most efficacious and tolerable in respect to ADRs and hospital stay. ADRs were common with SSG, AmB, Miltefosine and almost absent with L-AmB. HIV co-infection was found to be the common cause for relapse and readmission of VL cases.

Limitations

Major limitations of the study were small sample size, retrospective and record based nature. In most of the cases documentations were incomplete in terms of history, investigations, ADRs and outcomes. Information collected from the patients and treating physicians might have some recall bias.

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