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Assessment of Treatment Outcome in Visceral Leishmaniasis (VL) Patients with Reference to Efficacy and Safety – A Record-Based Observational Study in a Speciality Public Hospital

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Abstract
Background: *Study was done to assess the outcome of pharmacotherapy in visceral leishmaniasis (VL) patients in a specialty public hospital in Kolkata.*
Materials & Methods: *The hospital records of all consecutive VL patients admitted at Calcutta School of Tropical Medicine (CSTM), Kolkata during the last five years - 2010-2014, were reviewed and the relevant information inputs as documented studied to realize the noted objectives. Clinical presentation on admission including presence of co-infections (particularly HIV), trends and patterns of treatment regimens and rationale thereof, if available; treatment (anti-leishmaniasis) outcomes in reference to efficacy, safety and tolerability, fatality like serious complications and mortality and adverse drug reactions (for anti-leishmaninal drugs primarily), if any was noted.*
Results: *Commonest age group was from 18 to 45 years. Mean age was 30.02 ± 15.88 years and the range was 2 to 75 years. Fever was the presenting symptom of 85.4% of VL cases. In 2010 maximum (46.67%) cases got the combination regime of L-AmB and miltefosine followed by 26.67% L-AmB and 20% AmB.*
Conclusion: *VL was 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.*
Keywords: *Kala-azar, Visceral leishmaniasis, Anti-leishmaninal drugs, Liposomal AmB, Sodium Stibogluconate, Miltefosine, ADRs.*

Introduction

Kala-azar or visceral leishmaniasis 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 a growing concern.[1]

The traditional treatment is with pentavalent antimonials such as sodium stibogluconate 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.[2] The treatment of choice for visceral leishmaniasis acquired in India is now amphotericin B in its various liposomal preparations.[3,4] Miltefosine the first oral drug for this disease has received approval by the Indian regulatory authorities in 2002.[5, 6] Calcutta School of Tropical Medicine is a pioneer institute for treatment of VL and PKDL and it caters the people living in nearby endemic areas for years together since the period of Dr. U N Brahmachari.

So critical review of the hospital records of admitted VL patients of last five years from 2010 to 2014 may give us interesting knowledge of the treatment followed here under different clinical settings, their outcome and ADRs encountered. Also this hospital has been declared as a centre of excellence (COE) for the treatment of HIV patients. As the co-infection of HIV and VL is not uncommon, it may be worthy to see the presence of HIV among the admitted VL patients, and if response to treatment in such subgroups differ from those without it.

Aim

To assess the outcome of pharmacotherapy in visceral leishmaniasis (VL) patients in a specialty public hospital in Kolkata

Objectives

Primary Objectives

1) To explore the choice of treatment regimens in VL patients over the period under study
2) To assess the response to the different treatment regimens in VL patients
3) To study the safety and tolerability of anti-leishmanial drugs in such patients
4) To study the adverse drug reactions (for anti-leishmanial drugs primarily), if any, and how they were managed

Secondary Objectives

1) To explore the possibility of re-admission of VL within the period under study and probe for its reason, as far as practicable

Materials and Methods

Study area

The study was conducted in the department of clinical and experimental pharmacology at Calcutta School of Tropical Medicine, Kolkata.

Study population

The hospital records of all consecutive VL patients admitted at Calcutta School of Tropical Medicine (CSTM), Kolkata during the last five years - 2010-2014, were reviewed and the relevant information inputs as documented studied to realize the above-noted objectives.

Study design

Retrospective, record-based, observational study

Sample size

All in-patients of VL admitted during 2010-2014 at CSTM were considered. The total number of patients studied was 115.

Inclusion criteria

Case records or Bed Head Tickets (BHTs) of all consecutive VL patients admitted at Calcutta School of Tropical Medicine, Kolkata (CSTM), during the five years- 2010-2014, as available in the Hospital Records Section. No case was excluded.

Study technique

With due permission of the hospital administration, the relevant hospital records were accessed and critically reviewed to look for

- Clinical presentation on admission including presence of co-infections (particularly HIV)
- Trends and patterns of treatment regimens and rationale thereof, if available
- Treatment (anti-leishmaniasis) outcomes in reference to efficacy, safety and tolerability, fatality like serious complications and mortality
- adverse drug reactions (for anti-leishmaninal drugs primarily), if any, and how they were managed
- Duration of hospital stay and advice on discharge if available.
- Any other information, if considered important

The Data Collection Form was designed based on the above critical review elements. While conducting the study it was found that the required information was incompletely available from the BHTs. So, it became necessary to consult with respective treating physicians to fill the gaps of information which may be regarded as source documents. Moreover, whenever possible patients were contacted by telephone which were available on BHTs, gave important information.

Statistical analysis

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

Ethics and Informed Consent

The study was undertaken only after the Institutional Ethics Committee approved the study protocol. This was a record-based retrospective, observational study.

Results

In the present study, the total number of BHTs accessed was 115, among them 96 patients had VL as the primary diagnosis. Total number of VL cases without HIV was 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 [Fig. 1]. 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 was 7.

Age distribution of VL cases

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 paediatric 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) [Table 1].

Sex distribution of VL cases

Present study shows the occurrence 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 [Table 2].

Geographical distribution of cases

Maximum number (80) of VL cases were from West Bengal, 10 cases from Bihar, 3 cases from Rajasthan and 1 case each from Jharkhnd, UP, Assam. Among those from West Bengal maximum (24) was from Kolkata, then north 24 Pargana district (13), Howrah (9), 7 cases each from Burdwan and Murshidabad, 5 cases from Maldah, 4 cases each from West Midnapore, South 24 Pargana and Hoogly, 1 case each from Nadia, Jalpaiguri and Darjeeling districts [Table 3, Fig. 2].

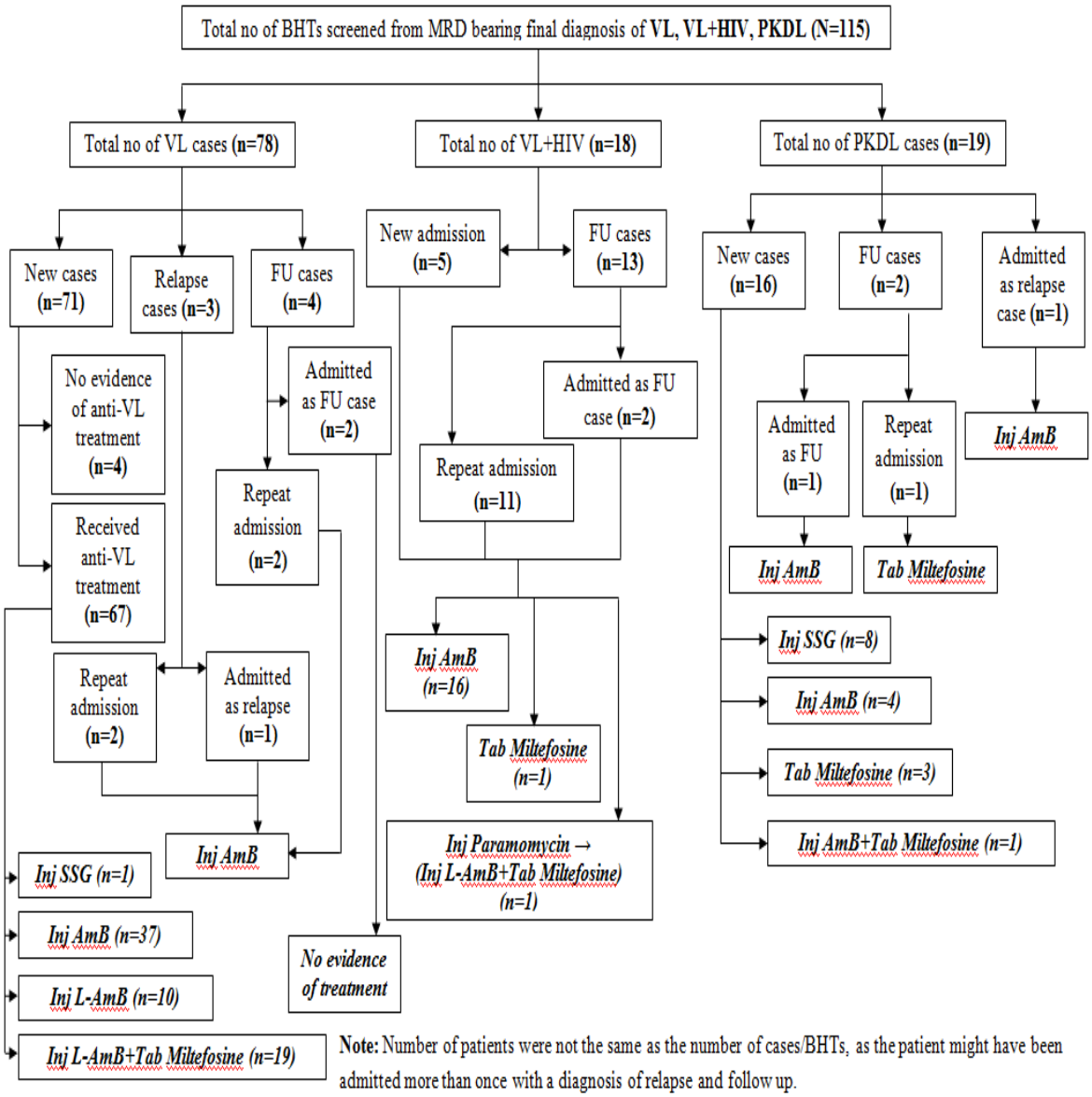

Figure 1: Flowchart of the study

Clinical features on admission

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 spleenomegaly very often huge [Table 4].

Trends and patterns of 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. 11 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

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.

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.

Year-wise preference of treatment regimen was variable

In 2010 maximum (46.67%) cases got the combination regime of L-AmB and miltefosine followed by 26.67% L-AmB and 20% AmB. But 6.67% cases did not get any treatment. In 2011 AmB was used in maximum no of cases (53.33%), followed by the combination group (26.67%) and L-AmB as sole therapy (6.67%). About 13.53% of cases did not receive any anti-leishmanial treatment.

In 2012, 88.46% cases received AmB and 3.84% (n=1) each got combination and SSG therapy and 1 case (3.84%) did not receive any anti leishmanial therapy. In 2013, 11(91.67%) out of 12 cases received AmB and 1 (8.33%) case did not receive any anti leishmanial therapy. In 2014, 10 (76.92%) out of 13 cases got AmB followed by 1(7.69%) case each received L-AmB, miltefosine and paromomycin followed by L-AmB and Miltefosine [Table 6, Fig 3].

Year-wise preference of treatment regimen was variable:

In 2010 maximum (67.67%) cases got SSG followed by 33.33% Miltefosine. In 2011 SSG was used in 2 cases (66.67%), followed by miltefosine in 1 case (33.33%). In 2012, 2 (50%) cases received SSG and 25% (n=1) each got AmB and miltefosine. In 2013, 1(50%) out of 2 cases received AmB and 1 (50%) received combination of AmB with miltefosine. In 2014, all 4 (100%) cases received were AmB [Table 7, Fig. 4].

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 was with L-AmB therapy.

Treatment outcomes

All VL cases presenting with fever became afebrile within one week of specific antileishmanial therapy commencement. With

ongoing therapy gradually the spleen size reduced, anemia getting corrected by increasing Hb%, appetite restored and the patients gained weight. There was overall wellbeing of all patients across all treatment regimens followed. Cases were discharged generally at the end of treatment where clinical cure been declared.

Accordingly clinical cure was achieved in all admitted cases of VL at the end of treatment. All regimens showed equivalent efficacy but definitely safety and tolerability were different. SSG was rather safe but tolerability 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 [Table 8].

Table 1: Age distribution of VL cases

Age group (years)	No of cases	Percentage (%)
0-17	23	24
18-45	60	63
46-60	10	10
>60	3	3

Commonest age group was from 18 to 45 years. Mean age was 30.02 ± 15.88 years and the range was 2 to 75 years [Table 1].

Table 2: Sex distribution of admitted VL cases during study period

Sex	No of cases	Percentage
Male	57	59
Female	39	41

Male female ratio in admitted VL cases was 1.46:1 [Table 2].

Table 3: Geographical distribution of VL cases

Geography	No of cases	Percentage
West Bengal	80	83
Bihar	10	11
Rajasthan	3	3
Jharkhand	1	1
Assam	1	1
Uttar Pradesh	1	1

Maximum number of VL cases was from Kolkata, West Bengal l1% cases were from Bihar, commonest among those out of West Bengal [Table 3].

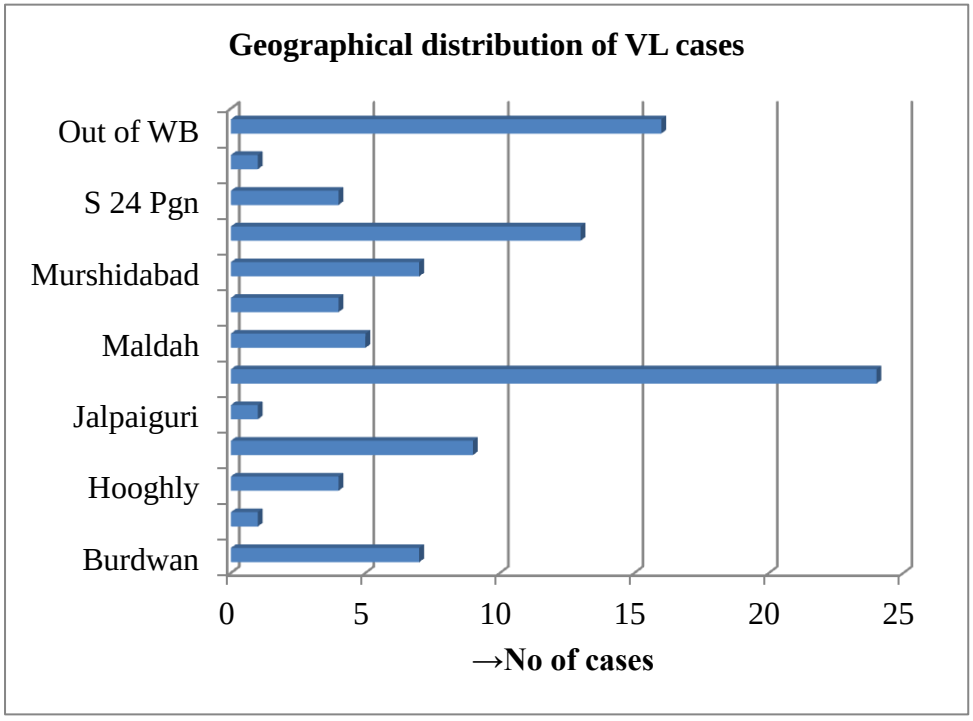

Fig. 2: Geographical distribution of VL cases

Table 4: Clinical features of VL cases at the time of admission

Clinical Feature	Present in number of cases	Percentage (%)
Fever	82	85.4
Anemia	96	100
Splenomegaly	96	100
Loss of appetite	65	67.7
Loss of weight	65	67.7

Table 5: VL cases according to final diagnosis on BHTs

Types of VL	No of cases	Percentage (%)
VL	71	74
VL (relapse)	3	3
VL (FU)	4	4
VL+HIV	5	5
VL+HIV (FU)	13	14
Total	96	100

Among 78 cases of VL without HIV total no patients were 74. Among 78 cases of VL with HIV total no patients 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 [Table 5].

Table 6: Year wise VL cases admitted

Year	No of cases	Percentage
2010	30	31
2011	15	16
2012	26	27
2013	12	12
2014	13	14

Maximum number of VL cases admitted in the year 2010 followed by 2012 [Table 6].

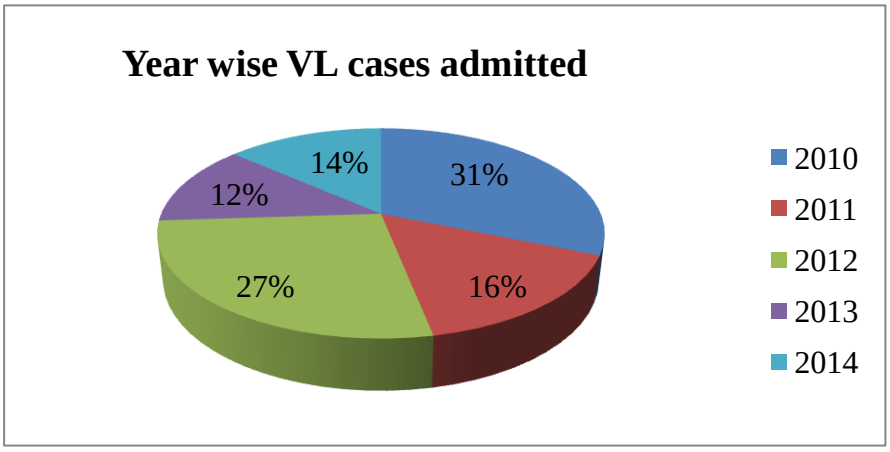

Fig. 3: Year wise VL cases admitted

Table 7: VL cases treated with different regimens

Treatment regimens	No of cases	Percentage
AmB	58	60
L-AmB+ Miltefosine	20	21
L-AmB	10	10
SSG	1	1
Miltefosine	1	1
Paramomycin → (L-AmB+ Miltefosine)	1	1
Treatment NA	6	6

Commonest drug prescribed was AmB. About 6 cases did not receive any antileishmanial therapy though admitted as VL [Table 7].

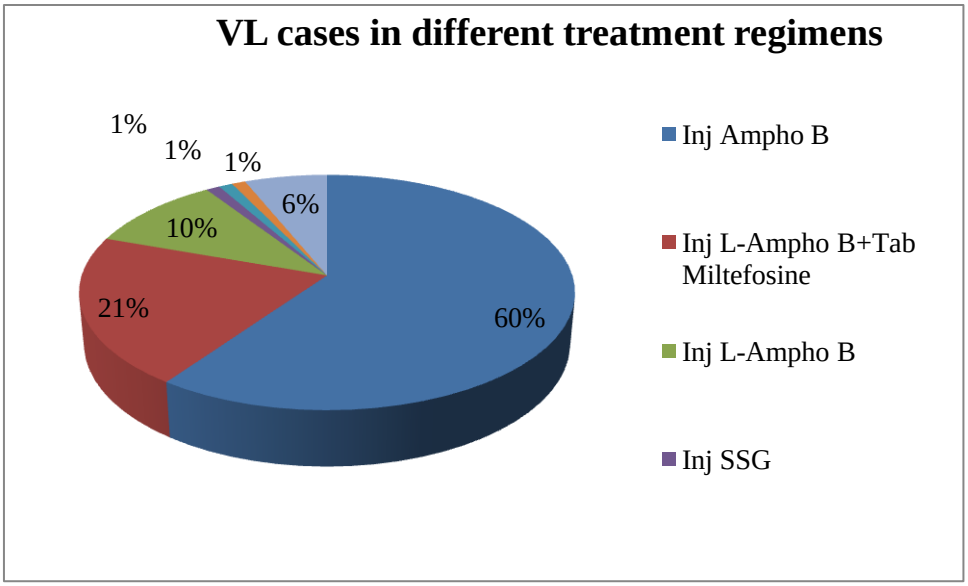

Fig 4: VL cases treated in different regimens

Table 8: ADRs encountered in treatment of VL cases

ADRs	No of cases	Percentage (%) approximately
Chill & Rigor	58	60
Nausea & Vomiting	13	13.5
Hypokalemia	8	8.33
Increase creatinine	1	1
Pruritus	1	1
Febrile convulsion	1	1
Vertigo	1	1
No ADR	27	28

Maximum number of ADRs was chill and rigor encountered in 58 cases (60%). There was no ADR detected in 27 cases (28%) [Table 8/Fig. 5].

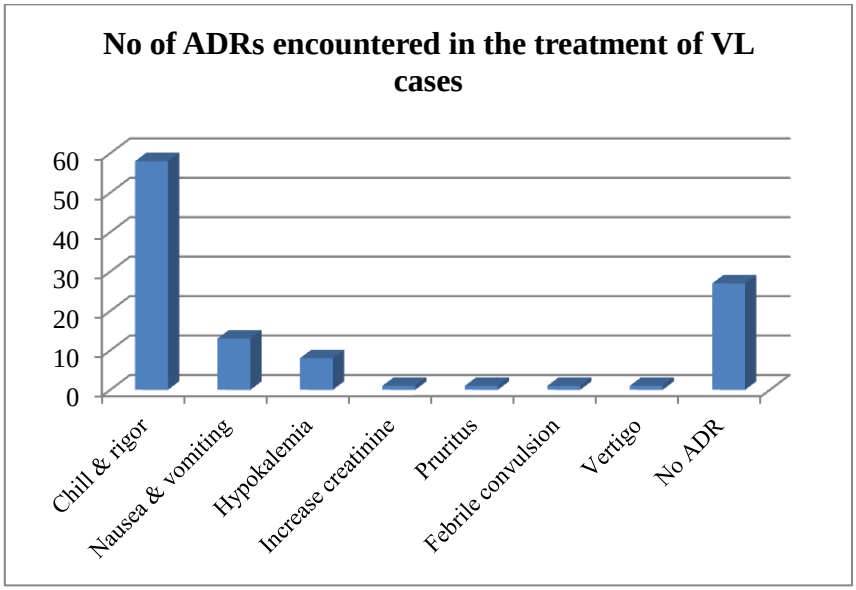

Figure 5: No of ADRs encountered in treatment of VL cases

Table 9: Treatment regimen for VL cases followed in different years

Years	AmB	L-AmB	L-AmB+ Miltefosine	SSG	Miltefosine	Paromomycin- L-AmB+ Miltefosine	No treatment
2010	6	8	14	0	0	0	2
2011	8	1	4	0	0	0	2
2012	23	0	1	1	0	0	1
2013	11	0	0	0	0	0	1
2014	10	1	0	0	1	1	0
Total in 5 years	58	10	19	1	1	1	6

The most preferred regimen across the study years was AmB. In the year 2010 maximum number of regimen followed was with combination therapy of L-AmB+ miltefosine [Table 9].

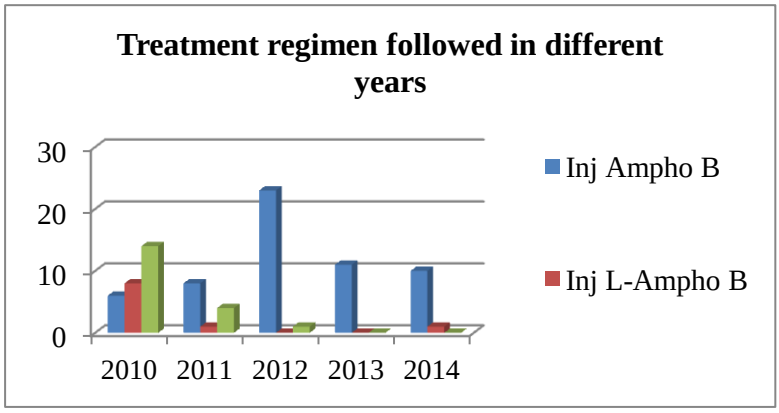

Figure 6: Treatment regimen followed in different years (only 3 major treatment groups considered)

Table 10: Treatment outcome in diferrent regimens for VL cases

Drug regimen	Efficacy/ clinical cure rate (%)	ADRs encountered	Average days of hospital stay	Tolerability
AmB	100	58 (100%)	29.63 ± 18.76	Least
L-AmB+ Miltefosine	100	11 (57.89%)	23 ± 7.47	Moderate
L-AmB	100	0	16.7 ± 7.97	well
SSG	100	0	15	well
Miltefosine	100	0	3	well
Paramomycin → (L-AmB+ Miltefosine)	100	1	77	moderate

Clinical cure was achieved in all admitted cases of VL at the end of treatment. All regimens showed equivalent efficacy but safety and tolerability were different [Table 10].

Discussion

This retrospective record based study was conducted to assess the outcome of pharmacotherapy in visceral leishmaniasis (VL) patients admitted in the period of 2010 to 2014 in Calcutta School of Tropical Medicine, Kolkata. This hospital caters a vast population from all over West Bengal as well as the adjoining states, so, demographic profiles of the cases admitted here may differ from what are obtained in field study. In Operational Guidelines in Kala-Azar (Visceral Leishmaniasis) Elimination in India - 2015, by NVBDCP, the commonlly affected age group was in children of 5 to 9 years with male female ratio of 2:1, whereas in present study the commonest age group was 18 to 45 years both in VL and PKDL cases, with male female ratio of 1.46:1 in VL and 3.75:1 in PKDL.[7]

Amphotericin B deoxycholate (AmB) is recommended for the treatment of refractory VL in India and used in doses of 0.75–1.0 mg/kg for 15–20 intravenous infusions with high cure rates (CR) ~ 100% [15]. It was concluded by Thakur et al,

that the dosage of amphotericin B used was an effective and well-tolerated regimen and achieved 99% cure. Toxicity could be minimized with some precautions. All unresponsive and relapsed patients responded to more amphotericin and no resistance to the drug was seen.[8]

Adverse effects associated with AmB require close monitoring with increased hospital stays, which increase the cost of therapy. All cases have experienced the adverse drug reaction as chill and rigor with or without fever. To combat this ADR antihistamine tablets or injection along with paracetamol tablets had to be given. In some instances these were started even before starting the infusion as prophylaxis. Other measures taken were slowing of the drip rate, temporarily stopping the drip for few hours, totally stopping the infusion for that day and advising further to infuse on alternate day basis according to severity of the reaction. Shyam Sunder,H. Mehta et al have shown in their study similar findings.[9]

Another important ADR was hypokalemia. It increases the risk of an abnormal cardiac rhythm such as bradycardia and cardiac arrest. Though it is an important finding only in 8.33% of cases showed mild to moderate hypokalemia. Mild hypokalemia was treated with oral potassium chloride syrup, where as in other cases they were managed by intravenous administration of potassium chloride in doses as required. One of the treating physicians administered routinely Inj.potassium chloride with the IV infusion bottle prophylactically thereby avoiding this complication to a large extent.

In literature search it was found that AmB cause renal impairment in the form of increased serum creatinine level. But in present study 58 cases serum creatinine reports were avilable out of them only 2 cases of increased level obtained, one of them got L-AmB other one conventional preparation. This important finding may indicate that renal toxicity is less common than those obtained in African or Latin American cases. The drug has high efficacy; however, prolonged hospitalization, adverse reactions like high fever with rigor and chills, and the need to close monitoring of renal functions and electrolyte levels are well-recognized drawbacks of AmB treatment.[10]

To combat this, various lipid formulations have been introduced. In lipid formulations of AmB, deoxycholate is replaced with other lipids leading to less exposure of the free drug to organs. These formulations are based on the concept of targeted drug delivery to macrophages in the liver, spleen and bone marrow: the cells and organs affected in VL. Thus the tolerance is greatly improved and adverse effects including hypokalemia and nephrotoxicity are greatly reduced. By using these formulations it is possible to deliver larger doses of the drug over short periods of time. There is geographical variation in the total dose requirements of lipid formulations for the treatment of VL. In India, a total dose of 10 mg/kg results in a CR of >95% is given.[11] L-AmB was used in 10 cases as sole therapy at 7.5 mg /kg body weight two doses as intravenous infusion. 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. A large phase IV study showed CR of 95%.[12] Its efficacy, ease of use and applicability in the control program made this drug the backbone of the elimination program in India, Nepal and Bangladesh. However, relapse rate doubled and efficacy reduced after a decade of use of the drug in the Indian subcontinent.[13, 14] Injection sodium stibogluconate (SSG) which was the most frequently prescribed drug in the past, had only been used in single case of VL. The dose of SSG was 20 mg/kg as a single daily dose intravenously (over 5 minutes) for 30 days. This patient did not encounter any ADR. 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 outpatient department.

In Bihar (India) and to some extent in adjoining Nepal there has been increasing resistance to SSG and this has led to implementation of alternative treatment regimens for these regions. However its efficacy remains high in other parts of world.[11, 15] Arthralgia, myalgia, elevated hepatic and pancreatic enzymes are other common associated toxicities. Response to SSG in patients with HIV–VL co-infection, however, has shown less efficacy and been associated with increased mortality as compared to HIV-negative VL cases. Some adverse effects especially chemical pancreatitis is more common in HIV co-infected patients.[16, 17]

In a subsequent large phase III study in the Indian subcontinent, three drug combinations (single injection of 5 mg/kg L-AmB and 7-day 50 mg oral miltefosine or 10-day 11 mg/kg intramuscular PM; or 10 days each of miltefosine and PM) showed an excellent CR (>97%) in treatment of VL.[18] Another combination trial in India where single dose of L-AmB 5 mg/kg and miltefosine 2.5 mg/kg/day for 14 days, showed a CR of 91.9% by intention to treat and 97.6% by per protocol analysis.[19]

One case needs special mentioning who was suffering from VL with IC and had the history of repeated admission. In one occasion he was give Injection paramomycin for 20 days then the combination therapy of L-AmB for 5 doses followed by miltefosine tablets for 28 days was given. Patient tolerated the therapy well. 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.

So the patterns of treatment regimens showed that the most preferred regimen was AmB over the years from 2010 to2014. The reason is obvious, as SSG was out of favour due to its increasing resistance in this part of the country and the then guideline clearly puts it as first line drug for the treatment of VL with or without HIV even considering potential toxicities. Though it was in the process of evolution of next guideline where L-AmB has been chosen as the first line therapy, here it was used as preferred therapy in the year of 2010 and 2011 which was part of a similar study. L-AmB is costlier than conventional AmB, but shorter duration of therapy least hospital bed occupancy, less loss of wages of patients along with much better tolerability, fewer side effects keeps it ahead of AmB. Now the latest guideline by National Vector Born Disease Control Programme (NVBDCP) clearly states L-AmB as the first line therapy for VL.[7]

All VL cases presenting with fever became afebrile within one week of specific antileishmanial therapy commencement. With ongoing therapy gradually the spleen size reduced, anemia getting corrected by increasing Hb%, appetite restored and the patients gained weight. There was overall wellbeing of all patients across all treatment regimens followed. Cases were discharged generally at the end of treatment where clinical cure been declared. Advice on discharge was not available from BHTs, but usually patients were advised to attend OPD on monthly follow up for six months. If the patient remained asymptomatic till 6 months, they were declared cured. Accordingly clinical cure was achieved in all admitted cases of VL at the end of treatment. But due to lack of proper documentation in follow up visits the outcome as final cure could not be deduced.

To comment on efficacy from the BHTs all regimens showed equivalent efficacy but definitely safety and tolerability were different. SSG was rather safe but tolerability not much as it was given by IM injections on both buttocks repeatedly. So many a times patients did not come to OPD for further therapy leading to irregular and incomplete treatment. This might lead to emergence of resistance.

AmB was highly efficacious but not safe, as 100% occurrence of transfusion reactions in the form of fever, chill and rigor. Hypokalemia, nephro-

toxicity in the form of increasd creatinine level were serious ADRs encountered which required close monitoring of patients. Tolerability was also poor as cases were admitted for long time with all those ADRs. 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.

Major limitations of the study were small sample size and it's retrospective and record based nature. In most of the cases documentations were incomplete in terms of history, investigations, ADRs and outcomes. So, information had to be collected from the patients and treating physicians that might have a lot of recall bias. Computerized documentation in future will be helpful for this kind of studies.

Conclusion

The 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. Total number of patient's records (BHTs) accessed were 115, among them 96 had VL as primary diagnosis and 19 had PKDL as the primary diagnosis. As there were readmissions and/or FU admissions of the same patients, actually 74 VL patients were admitted during this period and 68 VL patients received anti VL treatment for the first time. Other 7 VL patients were found to be co-infected with HIV, although they were admitted 18 times in the same institute due to relapse and prophylactic therapy. Total 18 patients with PKDL were analyzed in this study. The mean age of VL patients in the study was 30.02 ± 15.88 years. Male: female ratio was 3:2 approximately. 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). Commonest ADRs encountered 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.

VL–HIV co-infected patients were treated with AmB with dose and duration as usual with mono infected VL patients. Initial cure rate was found to be 100%, but relapse was common. Secondary prophylaxis with 1 mg /kg AmB every month prevented relapse. ADRs found were not excessive in co-infected group. Treatment outcome of VL was determined as clinical cure at the end of treatment, as records of follow-up after end of treatment were not available in most 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 was 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.

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