PROBLEMS IN MANAGEMENT OF KALA AZAR : EXPERIENCE FROM BIHAR

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ABSTRACT

35 cases of Kala-Azar were managed at 200 bedded peripheral hospital, Bihar from Jan 1994 to Jan 1998. Patients presenting with history of fever for more than 3 weeks duration with splenomegaly or hepatosplenomegaly were investigated for Kala-Azar. A confirmative diagnosis of Kala-Azar was made in all cases by demonstrating *Leishmania amastigote* (LD body) in bone marrow or splenic aspirate. All patients were initially treated by sodium stibogluconate (SSG) 20 mg/kg body wt daily for 20 to 40 days depending on response. SSG induced cardiac toxicity was seen in 6 cases (VT-2, ST-T changes-2, QTc Prolongation-2) out of which 1 patient died of refractory ventricular tachycardia. 9 patients were unresponsive to SSG, 8 patients were treated with pentamidine isoethionate (4 mg/kg body wt IV alternate day) 10-15 dosage. 1 patient was treated with amphotericin-B. All the patients showed clinical and parasitological improvement and no relapse was noted at 6 month follow up. 6 patients had associated tuberculosis (Disseminated TB-2, Miliary TB-1, Pulmonary TB-1. Pleural TB-2). 2 patients had associated pneumonia, 1 patient had HIV infection and 1 patient had erythema nodosum leperosum.

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KEY WORDS :Kala-Azar; Pentamidine isoethionate; Sodium Stibogluconate.

Introduction

Resurgence of Kala-Azar in India has posed many problems. It has assumed epidemic proportions in North Bihar. As per WHO estimates there are 1.2 million cases of Kala-Azar in India out of which 1 million infected persons are from Bihar. As per unofficial estimates there are 2.5 million cases in Bihar, out of which approximately 0.25 million are unresponsive to pentavalent antimonials (SSG) [1] requiring costly and toxic second line drugs like pentamidine or amphotericin-B. To counter the problem of drug unresponsiveness and relapse different workers tried different regimens of pentavalent antimonials by increasing doses and duration of treatment [2,3].

Material and Methods

All cases of Kala-Azar, who were admitted at 200 bedded peripheral hospital in Bihar from Jan 1994 to Jan 1998 were included in the study. Patients presenting with history of fever of more than 3 weeks duration with splenomegaly or hepatosplenomegaly were investigated for Kala-Azar. A confirmative diagnosis of kala-azar was made in all cases by demonstrating *Leishmania amastigote* (LD body) in bone-marrow or splenic aspirate. A thorough clinical assessment was made before starting treatment. All patients were treated by sodium stibogluconate (SSG) 20 mg/kg body weight daily for 30 to 40 days depending on response. Bone marrow or splenic aspiration was repeated on 20th day for LD bodies. If found positive it was repeated on 30th and 40th day. SSG unresponsive patients were treated with pentamidine as it was available through Govt sources. Bone marrow/splenic aspiration was repeated after 10 inj of pentamidine. Repeat bone marrow/splenic

aspiration was done on completion of treatment. All cases were followed up for six months for relapse.

Definition of Cure :Indicated by afebrile condition, weight gain, haematological improvement, regression of spleen size and absence of LD bodies in bone marrow or splenic aspirate at the end of treatment.

Definition of relapse :In responsive patients reappearance of clinical features of Kala-Azar along with parasites in bone marrow or splenic aspirate.

Results

35 cases of Kala-Azar were managed during this period. Age ranged from 4 to 60 years, majority were in the age range of 20 to 30 years. Males were 28 (half were serving soldiers) and females were 7. LD bodies were demonstrated in bone marrow in 21 patients and in splenic aspirate in 14 patients. 4 patients were of relapse after SSG. Fever, anaemia and splenomegaly were present in all patients. Two third of patients had fever for 1 to 2 months. Mean duration was 1.6 month with a range of 10 days to 6 months. Aldehyde test was positive in 28 patients.

Tuberculosis was commonest coinfection seen in 6 patients. 2 of these patients had unilateral minimal pleural effusion. Pleural aspirate was exudative, lymphocyte predominant. Mantoux was positive in both patients. 1 patient had miliary opacity in lung. 1 patient had paratracheal and cervical lymphadenopathy. Cervical lymphnode biopsy showed caseating granuloma. 2 patients had minimal infiltration in chest x-ray with positive Mantoux. AFB smear was negative in all these patients. AFB culture could not be done due to lack of facility. Basis of diagnosis was histological in 1 case, exudative lymphocyte predominant pleural effusion in 2 cases and radiological opacity suggestive of pulmonary tuberculosis in 3 patients. All these patients showed satisfactory response with ATT (2 EHRZ+4RH). 1 patient was found HIV positive.

1 patient had erythema nodosum leprosum. In addition to fever, hepatosplenomegaly and inguinal lymphadenopathy he had

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TABLE 1
Investigation (n=35)

Investigation	
WBC count	
Leucopenia (< 4000)	11
Normal	24
Hb (g/dl)	
< 7	7
7-10	22
> 10	6
LD bodies in bone marrow	21
LD bodies in splenic aspiration	14
Aldehyde test :	
Positive	28
Negative	7

multiple painful subcutaneous nodules all over the body. His skin smear was positive for *Mycobacterium lepre* and skin biopsy confirmed Hansens disease B.T.

TABLE - 2
Associated Diseases

Associated Diseases	No.
Tuberculosis	
Disseminated	2
Miliary	1
Pulmonary	1
Pleural	2
Pneumonia	2
HIV infection	1
Erythema Nodosum Leprosum	1

All cases of Kala-Azar were treated with SSG 20 mg/kg body weight with no upper limit, for a minimum of 30 days. LD bodies became negative on 21st day in 23 patients. 18 patients showed symptomatic improvement within 1st week of treatment with abatement of fever, haematological improvement and regression of spleen size. LD bodies became negative after 30 days of SSG in another 5 patients out of these 3 patients relapsed within 1 month.

SSG induced cardiac toxicity was noted in 6 patients, QTc prolongation was noted in 2 patients, ST-T changes in 2 patients and VT was noted in 2 patients, out of which one patient died of refractory ventricular tachycardia. Only one patient developed cardiac toxicity after 8 days while the rest developed cardiac toxicity after 18 days of SSG.

Of 9 patients who were unresponsive to SSG, 8 were treated with pentamidine isoethionate 4 mg/kg body weight IV alternate day 15 doses. 1 patient was treated with amphotericin - B 1 mg/kg body weight (total dose - 1.5 gm). All these patients responded satisfactorily with abatement of fever within a week. Patient started gaining weight and showed improvement in blood count from 2nd week and parasitological cure. No relapse was noted in 6 months follow up. In pentamidine treated group, 1 patient developed transient hypoglycaemia and 1 patient had deterioration requiring insulin for diabetes control.

Discussion

In endemic area Kala-Azar patient may have co-in-

fection with tuberculosis and leprosy. A common intramacrophage niche for leishmanial and mycobacterial pathogens, and a similar spectrum of immune response and disease phenotypes, also lead to the prediction that the same genes/candidate gene regions might be responsible for genetic susceptibility to mycobacterial antigens such as tuberculosis and leprosy [13].

In the current epidemic of Kala-Azar in India the most outstanding feature has been increasing unresponsiveness to antimony. In vitro sensitivity of antimony for *Leishmania donovani* strain DD-8, isolated from different areas in Bihar shows increasing unresponsiveness where ED 50 dosage are 3 to 4 times higher [4] which is not possible because of toxicity and problem of unresponsiveness is increasing because of suboptimal doses.

TABLE -3
In vitro sensitivity of antimony

Area	ED 50
Patna	17.5 µg/ml
Vaishali	18.7 µg/ml
Muzaffarpur	22.4 µg/ml
Calcutta	4.8 µg/ml
U P	7.1 µg/ml

We found the efficacy of SSG in the dose of 20 mg/kg for 30 days to be 74%. Thakur et al found the cure rate 81% [5], Jha et al 64% [6] and Sunder et al reported a cure rate of 60% [7]. Better response in our patients is possible because half of our patients were from central Bihar where SSG unresponsiveness is comparatively less than North Bihar [8]. WHO recommended a ceiling of 850 mg of SSG but current recommendations do not favour this [9]. Increase in the duration of SSG treatment has also increased the incidence of drug induced cardiotoxicity. In India SSG induced cardiac toxicity had been reported in about 10% patients [10]. We observed cardiac toxicity in 18%, out of which one died of ventricular tachycardia. After cumulative dose of 400 mg/kg body weight, the risk of cardiac toxicity increases and ECG should be monitored weekly. Drug should be stopped on QTc prolongation or ST-T changes, which might be the signs of impending fatal arrhythmias [9]. Thakur et al reported cure rate of 77% in SSG unresponsive patients, with, 15 inj of pentamidine [11]. Jha et al reported 75.2% cure rate [12]. We were lucky that all our 8 patients treated with pentamidine improved. Patients became afebrile in 8-10 days and LD bodies became negative in all cases after 10 inj of pentamidine. High cure rate in our patients was possible be-

cause out of 8 we put 6 patients on pentamidine after 21 days of SSG if LD bodies were still demonstrated in bone marrow/splenic aspirate.

Of the 4 patients with relapse, 3 were unresponsive to SSG. They improved with pentamidine. All relapsed patients had shown slow response during earlier course of SSG. Although recent studies indicate constant decline in response rate of pentamidine, we found it to be still a good drug and relatively less toxic than amphotericin-B. The newer liposomal preparations of amphotericin are very costly and should be used as 3rd line drugs.

We recommend that fresh cases of Kala Azar should be treated with SSG 20 mg/kg body weight with no upper limit for 30 days and regular ECG monitoring should be done to detect early cardiac toxicity. Patients showing partial responsiveness to SSG (slow clinical and parasitological response) should be treated with 2nd line drugs early to prevent unnecessary drug toxicities and relapses, rather than prolonging the treatment by 40 to 60 days.

References

1. Jha TK. Management of Kala-Azar. *API Postgraduate medicine* 1992;13-8.
2. Thakur CP, Kumar M, Singh SK, Bharna D, Prasad US, Singh RP, Dhawan PS & Achari V. Comparison of regimen of treatment with sodium stibogluconate in Kala Azar. *BMJ* 1984;228;395-7.
3. Jha TK, Sharma VK. Prolonged Sodium Stibogluconate therapy in Indian Kala-Azar. *J Assoc Physicians India* 1985;34;9:469-71.
4. Nealra, Sen S. *Trans Roy Soc Trop Med & Hyg* 1990.
5. Thakur CP, Kumar M, Kumar P, Mishra BN, Pandey AK. Rationalisation of regimens of treatment of Kala-Azar with sodium stibogluconate in India. A randomized study. *BMJ* 1988;26:21-5.
6. Jha TK, Singh NKP, Jha S. Therapeutic use of sodium stibogluconate in Kala-Azar from some hyperendemic districts of N. Bihar, India (abstr). *J Assoc Physicians India* 1992;42:868.
7. Sundar S, Rosenkaimer F, Murray HW. Immunochemotherapy for a systemic intracellular infection : Accelerated response using interferon in visceral leishmaniasis. *J Infect Dis* 1995;171:992-6.
8. World Health Organisation. The leishmaniasis : Report of a WHO Expert Committee. *WHO Tech Rep Ser* 1984;701.
9. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg* 1992;46:296-306.
10. Singh NKP, Sharma D, Jha TK. Kala-Azar mortality in hospitalised cases in North Bihar, India. *J Assoc Physicians India* 1989;37:514-6.
11. Thakur CP, Kumar M, Pandey AK. Comparison of regimens of treatment of antimony-resistant kala-azar patients : A randomized study. *Am J Trop Med Hyg* 1991;45:435-41.
12. Jha SN, Singh NKP, Jha TK. Changing response to diamidine compounds in cases of Kala-Azar unresponsive to antimonials. *J Assoc Physicians India* 1991;39:314-6.
13. Blackwell JM. Genetics of host resistance and susceptibility to intramacrophage pathogens : a study of multigene families of tuberculosis, leprosy and leishmaniasis in North-Eastern Brazil. *Int J for Parasitol.* 1998;28(1):21-8.