Miltefosine in Children with Visceral Leishmaniasis

Utpal Kant Singh*, Rajniti Prasad, Ranjeet Kumar** and Bir Prasad Jaiswal ****

*From the *Department of Pediatrics, Nalanda Medical College, Patna 800 020, India and **Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.*

Correspondence to: Dr. Utpal Kant Singh, 8, Rajendra Nagar, Patna 800 016, Bihar. India E-mail: patna@mapra.com

Manuscript received: December 5, 2005; Initial review completed: February 24, 2006; Revision accepted: August 29, 2006.

Sixty four children (38 boys and 26 girls), aged 1 yr to 14 yr, presenting with fever, splenomegaly and positive LD body in splenic smear examination, admitted to pediatric ward of Nalanda Medical college and Child care center between 1st July 03 to 30th June 04 were taken for study. Patients were categorized into two groups: 44 were in Group I (Patients who had not received prior anti-leishmanial drug) and 20 in Group II (Patients who had received 30 days course of SAG; 20 mg/kg/day). All patients were given Miltefosine in dose of 2.5 mg/kg /day od or bid per orally to a maximum of 100 mg and were followed at completion of therapy, 1 month and 6 months for clinical response, splenic size and parasite density. 63 patients had parasitological cure with relapse in one patient of Group I during follow up. One patient in Group II had no response with first course but became parasitologically negative with 2nd course of Miltefosine. In Group I, one patient had persistent splenomegaly and found to have associated portal hypertension. GI side effects i.e. diarrhea and vomiting were observed in 26 and 23 patients respectively. Majority of patients had pancytopenia. Elevated ALT (>3 times of normal) were seen in 28 and 11 patients of Group I and Group II respectively which returned to normal in subsequent follow up. The final cure rates were 93.2% and 95% in Groups I and II respectively.

Key words: *Miltefosine, SAG (Sodium antimony gluconate), Visceral leishmaniasis (VL).*

IN recent years, the treatment of visceral leishmaniasis (VL) is far from satisfactory(1,2). All anti-leishmanial drugs are toxic and most have to be used parenterally for prolonged period. The therapy has been further complicated by large number of infected children and declining effectiveness of pentavalent antimonial compounds. Although the lipid formulations of Amphotericin B are an important advancement in therapy, their high cost precludes their use.

Miltefosine is a phosphocholine analogue, originally developed as anti-malignant drug. Though it proved to be ineffective as antimalignant drug, it has been found to be highly active against leishmania in vitro and animal model(2,3). Unlike other chemotherapeutic agents, miltefosine lack bone marrow toxicity and even exerts growth-stimulating effects on hemopoitic progenitor cells(4). Very few studies have been conducted with miltefosine in children suffering from VL.We studied the efficacy, tolerance, safety and drug related adverse reactions of miltefosine in children with visceral leishmaniasis.

Subjects and Methods

We undertook a prospective, multicentric observational study of miltefosine therapy in children with visceral leishmaniasis. The study was conducted in parallel at two centers *i.e.*, children ward of Nalanda Medical College and Childcare Center, Patna from 1st July

2003 to 30th June 2004. Ethics committees of both centers approved study protocol and consent form. Written informed consent was taken from legal guardians of children.

Children aged 1 yr to 14 yr, presenting with fever, splenomegaly and positive LD body in splenic aspirates examination were included in the trial and segregated into two groups as follows.

Group I: Patients who had not received prior antileishmanial drug.

Group II: Patients who had received 30 days course of Sodium antimony gluconate (SAG),(20 mg/kg/day).

Children, who had received less than 30 days course of SAG, with bleeding diathesis, liver disorder (ALT & AST>3 times, serum bilirubin >2 times of normal), renal dysfunction (BUN and serum creatinine; 1.5 times of normal), co-existing malaria or HIV, neutrophil count less than 1000/cu mm and platelet count less than 40,000/cu mm were excluded from study.

Miltefosine (Impavido) was administered orally for 28 days at a dose of 2.5 mg/kg/day OD or bid to a maximum of 100 mg daily. During therapy, patients were monitored daily for vital signs, splenic size and adverse events. Adverse events were graded according to common toxicity criteria of National Cancer Institute(5). Hematological (CBC), biochemical (ALT, AST, BUN, Creatinine) and splenic size below left costal margin were monitored weekly during therapy, at completion, after one month and 6 months.

Parasitological analyses of splenic aspirates were performed at completion of therapy, 1 month and at 6 months. The density of parasites was graded from 0 (no parasite/ 10000 high power field) to 6 (>100 parasites/ field). Cure was defined as an absence of parasites at the end of therapy and no relapse during six months of follow up. Relapse was defined by appearance of symptoms and signs suggestive of leishmaniasis with demonstrable LD bodies in splenic aspirates after initial cure. Treatment failure was defined as either the lack of initial cure or relapse.

The two groups were compared by Student's t-tests to test the significance and 95% confidence limit of final cure.

Results

There were 64 children in the study: 44 in Group I; and 20 in Group II. Their baseline characteristics (clinical and laboratory parameters) are summarized in *Table I.* The baseline characteristics were similar in both groups except platelet count in Group II; which may be due to associated hypersplenism and prior sodium stibogluconate therapy.

At the completion of miltefosine therapy splenic aspirates were done in all patients. All patients were parasitologically negative except one patient in Group II who required repeat course of miltefosine. In Group I, one patient had persistent splenomegaly and USG of hepatobillary system showed cavernous transformation of portal vein with portal vein diameter of 14 mm *i.e.* portal hypertension. Hence initial cure rate in both groups were 100%. In both groups, the mean splenic size had decreased to 1.5 cm below costal margin. Two patients in Group I and one patient in Group II were lost in follow up, hence a total of 61 were followed at 6 month *i.e.*, 42 in Group I and 19 in Group II. Majority of patients had persisting anemia but only one patient in Group I had clinical and parasitological relapse. The patient who relapsed during follow up had no difference from cured patients in baseline characteristics. The final cure rates on per protocol basis, in which all patients who could be followed for trial period

are analyzed, were 93.2% and 95% in Groups I and II respectively.

Adverse events related to miltefosine therapy are mentioned in *Table-II.* Diarrhea was mild, self limiting and controlled in 2-3 days and did not require discontinuation of miltefosine therapy. Vomiting was also mild and gets controlled with oral antiemetics.

ALT and AST started to rise during second week of therapy and remained elevated till end of treatment and declined to base level after 2 weeks of completion. Blood Urea Nitrogen returned to normal after one week of completion of therapy. Electrocardiogram and ophthalmologic examination in both did not reveal any abnormalities at completion, one month and 6 months of therapy.

Discussion

This study shows that Miltefosine is an effective drug for treatment of visceral leishmaniasis in children older than one year. Of 64 children who presented to us with clinical features suggestive of VL were treated with Miltefosine for 28 days (dose: 2.5 mg/kg/day). At end of therapy all patients except one, who required repeat course, had parasitologcal cure. At 6 month follow up; cure rate was 93.2% and 95% in Groups I and II respectively.

Miltefosine was well tolerated in children and may be compared with other therapeutic agents in terms of efficacy, side effects, tolerance and cost of administration(6,7). The standard therapy till date for VL is pentavalent antimonials *i.e.*, sodium stibogluconate or in regions with a high prevalence of antimony resistance, amphotericin B. Sodium stibogluconate has the disadvantage of both toxicity and clinical resistance in approximately 40% of patients in certain regions of Bihar(8), where it has been used for long period. Liposomal amphotericin B is highly effective and well tolerated, but its high cost,

TABLE I–*Baseline Characteristics of Children with Visceral Leishmaniasis*

	Group I (n = 44)	Group II (n = 20)	P value
Age-years (mean ± S.D)	8.4 ± 3.2	7.5 ± 2.6	0.17
Sex (M : F)	26: 18	12: 8	
Weight (kg)	18.7 ± 3.8	16.6 ± 3.6	0.01
Spleen (cm)	6.3 ± 3.8	7.2 ± 2.8	0.23
Hb(g/dL)	7.4 ± 1.8	6.4 ± 2.8	0.05
Leukocyte count/cu mm	3260 ± 1420	2980 ± 1124	0.33
Platelet count/cu mm	88,000 ± 10, 000	72,000 ± 8000	<0.001
ALT (IU/L)	31.2 ± 20.8	28.8 ± 12.6	0.54
AST (IU/L)	34.6 ± 18.2	31.4 ± 13.6	0.37
Creatinine (mg/dL)	0.58 ± 0.10	0.48 ± 0.11	<0.001
BUN (mg/dL)	10 ± 4	18.2 ± 4.6	<0.001
Parasitological density	2.8 ± 1.2	3.2 ± 1.4	0.17

Group I: Patients who had not received prior anti-leishmanial drug and received Miltefosine.
Group II: Patients who had received 30 days course of SAG (20 mg/kg/day) and received Miltefosine.

Key Message

- Miltefosine is safe, well tolerable and highly effective in newly diagnosed and SAG resistant children with visceral leishmaniasis

TABLE II–*Adverse Effects Associated with Miltefosine*

	Group I (44)		Group II (20)	
	No.	%	No.	%
Vomiting **	16	36.36	7	35
Diarrhea**	18	40.9	8	40
Anorexia	4	9.09	3	15
↑ALT*	28	63.63	11	55
↑AST*	21	47.95	10	50
↑Blood Urea Nitrogen	6	13.6	2	10
↑Creatinine	0	0	0	0
Rashes***	1	2.2	1	5

*↑ ALT (Alanine aminotransferase), AST (Aspartate aminotransferase): >3 times of normal.
** Self limiting and disappeared in 2 -3 days.
*** Transient for 6-8 hrs only.

associated renal dysfunction and febrile reactions with each dose of Amphotericin B is a barrier for wide spread use in developing countries like India. Pentamidine has been used in SAG resistant cases, but tolerance is a great problem and resistance is now evident(9,10).

Oral Miltefosine was safe and effective in children in this study. The efficacy is comparable with amphotericin B. Furthermore it is also effective in SAG resistant patients. This drug is now registered in India and freely available in endemic regions. A large clinical study is required to evaluate further efficacy, relapse and future resistance to this drug.

Acknowledgements

We acknowledge patients and parent for giving consent for study and all laboratory staff for doing biochemical, hematological and parasitological workup.

Contributors: UKS conceived and designed the study along with RP. UKS, RP and RK were also involved in acquisition, analysis and interpretation of data along with BPJ. All authors were involved in drafting the manuscript. UKS shall serve as guarantor.

Funding: None.

Competing interest: None stated.

REFERENCES

1. Desjeux P. Leishmaniasis: public health aspects and control. Clin Dermatol 1996; 14: 417-423.
2. Croft SL, Neal RA, Pendergast W, Chan JH. The activity of alkylphosphocholines and related derivatives against Leishmania donovani. Biochemical Parasitol 1987; 42: 2633-2636.
3. Kuhlencord A, Maniera T, Eibl H, Unger C. Hexadecyl phosphocholine: oral treatment of

visceral leishmaniasis in mice. Antimicrobial agents Chemotherapy 1992; 36: 1630-1634.

4. Jendrossek V, Handrick R. Membrane targeted anticancer drugs: potent inducer of apoptosis and putative radiosensitisers. Curr Med Chem Anti-Canc Agents 2003; 3: 343-353.
5. Cancer therapy Evaluation Program. Common toxicity criteria.Rockville.Md:National cancer Institute. 2002(accessed April 4,2006,at:// ctep.cancer.gov/reporting/index.html.)
6. Sundar S, Jha TK, Thakur CP, Engel J, Sindermann H, Fischer C *et al*. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002; 347: 1739-1746.
7. Sundar S, Jha TK, Sindermann H, Junge K, Bachmann P, Berman J. Oral miltefosine in children with mild to moderate Indian visceral leishmanisis. Pediatr Infect Dis J 2003; 22: 434-438.
8. Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug resistance. Trop Med Int Health 2001; 6: 928-934.
9. Jha SN, Singh NKP, Jha TK. Changing response to diamidine compounds in cases of kala-azar unresponsive to antimonial. J Assoc Physicians India 1991; 39: 314-316.
10. Thakur CP, Kumar M, Pandey AK. Comparison of regimes of treatment of antimony resistant kala-azar patients: a randomized controlled study .Am J Trop Med Hyg 1991; 45: 435-441.