Needs and Challenges in Developing a New Treatment for Visceral Leishmaniasis

Shyam Sundar, MD
Professor of Medicine
Institute of Medical Sciences
Banaras Hindu University, India
TREATMENT OF VISCERAL LEISHMANIASIS
Efficacy of SSG 20mg/kg/d in Bihar, India during 1988-2002.
Amphotericin B

- Polyene antibiotic (Amphotericin B deoxycholate)
- Dose 0.75-1.0 mg daily or alternate days for 15-20 infusions
- Expensive & needs hospitalisation for 4-5 weeks
- Infusion reactions, thrombophlebitis common
- Hypokalemia, myocarditis & death are serious, but uncommon, toxicities
- High Cure rates ~100%
- Used as first line drug in Bihar with areas of Sb resistance
## Single Dose Liposomal Amphotericin B (AmBisome) in Indian Kala-azar

<table>
<thead>
<tr>
<th>Total Dose (mg/kg)</th>
<th>No. of Patients</th>
<th>Treat. Dur.</th>
<th>Cure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>46</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Sundar, BMJ, 2002)*</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>5</td>
<td>93</td>
</tr>
<tr>
<td>7.5</td>
<td>203*</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Sundar, CID, 2003)*</td>
</tr>
<tr>
<td>15</td>
<td>17</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Thakur, AAC, 2001)</td>
</tr>
</tbody>
</table>

* Multicenter
Liposomal Amphotericin B - AmBisome

• Total dose – most important determinant in the outcome – Total dose requirement
  • 20-24 mg/kg - for Brazil and Europe
  • 18-20 mg/kg – for Africa
  • 15 mg/kg – for Asia
  • 40 mg/kg for Immunosuppressed
• Even after a remarkable 90% decrease in the price of AmBisome, access remains a problem
• Problem of cold chain
Paramomycin (Aminosididine)

- An aminoglycoside (parenteral)
- Good antileishmanial activity, earlier used for bacterial & Parasitic infections
- In several phase II studies 16 mg/kg for 3 weeks cured 93% VL patients
- Has been licensed recently after results of Phase III trial became available (Cure rate 94.6%)
- Safe, Good alternative to antimony as first line Tt
- Produced in India, cheap (10 US$ per treatment course)
- Injectable (3 weeks)
- Being aminoglycoside, vulnerable for resistance
Miltefosine

- Hexadecylphosphocholine (alkylphospholipid analogue)
- Developed as an oral antineoplastic agent, but GI adverse events limited its use
- Excellent antileishmanial activity in experimental animals and in vitro
- A pilot dose escalating study conducted in 1997

(Sundar et al, Lancet, 1998)
Miltefosine

- **Dose**: 100 mg (>25 kg); 50 mg (<25 kg); Children 2.5mg/kg
- **Duration**: Four weeks, Oral administration - big advantage
- **Side – effects**:
  - Vomiting occurs in ~40%
  - diarrhea in ~20%.
  - Transient elevation of hepatic enzymes
  - Skin allergy, nephrotoxicity are occasionally seen
- **Long term cure rates 94%**
- **Cannot be used in pregnant females [teratogenic], and those refusing contraception (for the treatment period and another three months)** (Sundar et al, NEJM, 2002)
Summary

- In Indian subcontinent - Miltefosine as a therapeutic tool for ELIMINATION programme (by 2015)

- Pros and Cons
  - Orally administrable
  - Promising efficacy (Cures Sb refractory patients also)
  - However, there are challenges...

  There is a need to revisit the current strategy
Multidrug Treatment of VL - Rationale

- Every drug with the exception of amphotericin B is prone to development of resistance
- No new drug in pipeline
- The only way to protect the newly developed drugs is to develop combination chemotherapy
  - Shorten duration
  - Better compliance
  - Reduce cost
  - Less chances of development of drug resistance
  - Reduce drug pressure; mutual protection against resistance → prolong therapeutic life-span of effective use
Experimental Evidences of Combinations (Siefert & Croft, 2006)

- Activity enhancement index (AEI)
  - In vivo
    - Miltefosine + Ampho B – 11.3
    - Miltefosine + Paromomycin – 7.2
    - Miltefosine + SAG – 2.38
  - Thus, the three approved drugs for VL can be tried for multidrug therapy
    - AmBisome + Miltefosine
    - AmBisome + Paromomycin
    - Paromomycin + Miltefosine
VL Combination Toxicology

Combination drug administration (DNDi/Advinus Therapeutics, Bangalore)

Study groups
- Miltefosine alone
- AmBisome alone
- Paromomycin alone
- Paromomycin + Miltefosine
- AmBisome + Miltefosine (concomitant 5 days, milt alone 23 days)
- AmBisome + Paromomycin (concomitant 5 days, paromo alone 23 days)

Results
- No significant haematological changes: alone vs combined
- No significant clinical chemistry changes: alone vs combined
# Results of a Phase II combination trial in Indian VL (CID, In press)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Initial Cure Rate (%)</th>
<th>Final Cure Rate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBisome (5mg/kg)</td>
<td>45</td>
<td>100</td>
<td>91.1</td>
<td>78-97</td>
</tr>
<tr>
<td>AmBi 5 + Milt 14 days</td>
<td>45</td>
<td>100</td>
<td>95.6</td>
<td>84-98</td>
</tr>
<tr>
<td>AmBi 3.75 + Milt 14 days</td>
<td>45</td>
<td>100</td>
<td>95.6</td>
<td>84-98</td>
</tr>
<tr>
<td>AmBi 5 + Milt 10 days</td>
<td>46</td>
<td>100</td>
<td>97.8</td>
<td>87-100</td>
</tr>
<tr>
<td>AmBi 5 + Milt 7 days</td>
<td>45</td>
<td>100</td>
<td>97.8</td>
<td>87-100</td>
</tr>
</tbody>
</table>
Summary: What Are the Therapeutic Options?

- Use Antimony only in responsive regions, toxic drug, treatment related mortality in >5% patients, try and replace it quickly
- Amphotericin B – Use only as rescue/2nd line drug
- Liposomal AB – very attractive but cold chain?
- Miltefosine – Alone is a poor choice. DOT, lab monitoring, contraception
- Paromomycin – 21 daily injections, potential for resistance
- More drugs needed, nothing in clinical development

Combination Chemotherapy with short duration regimens?
Challenges to access

- Major challenge is to translate these research fruits into field setting
- For example miltefosine
  - Teratogenic (how to deal with women of child bearing age group),
  - Long half life (rapid emergence of resistance)
  - Uninterrupted availability?
  - Compliance in domiciliary care? (DOT)
  - Availability in private sector
  - In a recent evaluation we found 20-33% patients discontinued therapy
  - Real danger of losing this important drug in next few years
- Paromomycin
  - 21 daily injections (What can be done for compliance)
  - How to monitor the efficacy and adverse events