Comments from Pilar Aparicio, Leishmaniasis control program, IMT/NTD/CDS

Specific chemotherapy for VL

Treatment of VL should be under supervision. This is because of toxicity of drugs such as severe vomiting (chemical pancreatitis) sudden death due to cardiac arrhythmia, anaemia-associated heart failure, renal toxicity and procedures of some diagnostics (e.g. procedure to get splenic aspirate). For that the patient has to be admitted. Frequent monitoring of each VL patients' signs and symptoms as spleen size, Hgb, and body weight, is mandatory. After treatment, it is very important to follow up the patients periodically up to tree months to detect possible relapses.

First-line treatment: pentavalent antimonials (Sbv)

Generalities

Two different compounds of Sbv have been in use since the 1940's – sodium stibogluconate and Meglumine antimoniate. They are chemically different but are considered to be equal in effectiveness and toxicity. Treatment with Sbv drugs remains very efficient with one important exception in India where the resistance to the Sbv have increased over 60 per cent in some states (North Bihar). Three different drugs are currently available on the market:

- Generic sodium stibogluconate (SSG® – Albert David Ltd, India): 100 mg/ml, 1 vial = 30 ml (28 US$ full treatment course to a 35 kg patient)

- Meglumine antimoniate (Glucantime® - Sanofi-Aventis, France): 85 mg/ml, 1 ampoule = 5 ml (53US$ full treatment course to a 35 kg patient)

- Sodium stibogluconate (Pentostam® – Glaxo-Wellcome, UK): 100 mg/ml, 1 bottle= 100 ml (150 US$ full treatment course to a 35 kg patient)

Dose and Administration:

Sodium stibogluconate or Meglumine antimoniate: 20 mg/kg daily as a single daily dose either intramuscularly (in slow push) or intravenously (over 5 minutes) for 30 days. If the volume of injection exceeds 10 ml, it should be divided in 2 doses: one in each buttock or thigh.

In patients with severe ascites and/or edema, the dose of SSG should be decreased. The minimum dose is 2 ml (200 mg) for children weighing less than 10 kg.

Toxicity and adverse-effects:

Side effects of SSG are frequent, and can be severe especially in patients with cardiac disease (arrhythmia); renal failure; liver disease; severe

malnutrition/severely impaired general condition and advanced HIV infection.

The side effects/toxicities include: painful intra-muscular injection, thrombosis on intravenous administration; muscle and joint pain; loss of appetite, nausea and vomiting; biochemical (frequent) or overt (rare) pancreatitis and cardiac arrhythmia's including sudden death.

AmBisome® (liposomal Amphotericin B)

Generalities

Liposomal Amphotericin B circulates as particle, making Amphotericin B far less toxic. Thus higher doses can be given. Due to its excellent safety profile, AmBisome® (Gilead Pharma, USA) is considered by most VL experts as the drug of choice for VL treatment. It is used as first-line treatment in Europe. Its use in developing countries has been limited by its high price (market price in Europe: 2800 US$ per treatment). Recently, WHO has negotiated with Gilead a reduced price of 20 US$ per vial, which still results in a price of around 330 US$ per treatment course.

Dosage and administration

The total dose of AmBisome® is 20mg/kg intravenous given in split doses (e.g. 3 mg/kg/day for 6 days: days 1 to 5 and day 10 or days 1,2,3,5,10,15). For Indian subcontinent, 10-15 mg/kg given over 3-5 days is sufficient.

AmBisome® is infused in 300 to 500 ml of dextrose 5% infusion running in over 1 hour.

Toxicity and adverse-effects

The profile of adverse-effects are similar to conventional Amphotericin B but of milder intensity and lower frequency, chills and fever can be solved with paracetamol and do not suppose to stop the treatment"

Drug of choice for pregnant women.

Conventional Amphotericin B

Generalities

Conventional Amphotericin B (Fungizone®, Bristol Myers Squibb, USA; Sarabhai Piramal, India) is indicated for relapse cases, pregnant women and for patients who cannot tolerate (i.e. intractable vomiting, pancreatitis) or who do not respond to antimony compounds when there is no disponibility of Liposomal Amphotericin B.

Dosage and Administration:

Amphotericin B is given at 1 mg/kg every other day for 30 days (total 15 mg/kg).

Amphotericin B is infused in 1 liter of dextrose 5% infusion running in over 8 hours. Longer infusion time decreases infusion related adverse-effects (chills, fever).

Toxicity and adverse-effects:

The major adverse-effect is renal failure, usually reversible, which can be effectively prevented by providing adequate hydration with ORS or intravenous infusions if necessary. Avoid concomitant use of nephrotoxic drugs (e.g. Gentamicin, streptomycin).

Hypokalemia will be prevented by potassium supplementation with bananas (3x/day for adults) or, if bananas are not available in the market, with potassium tablets (1 banana = 8 mmol KCl = 1 tablet KCl).

A frequent but benign side effect is the occurrence of chills and fever during or after infusion. In the event of occurrence of chills and fever give Paracetamol and chlorpheniramine maleat one hour before the infusion, and go ahead with the Amphotericin B.

Miltefosine

Generalities

Miltefosine (Impavido®, Zentaris Pharma, Germany) is an antineoplastic agent which was registered for leishmaniasis treatment in India and Europe in 2003. Is the first oral drug for leishmaniasis, the cost of drug for a full treatment course (35kg patient) is 78 to 100 US$.

Due to its teratogenicity, its use is strictly contraindicated in pregnant women or in women who could become pregnant within 3 months after treatment.

Dosage and administration

Adults $\geq$ 25kg: 100mg/day for 28 days, < 25 kg: 50 mg/day for 28 days
Children < 12 years: 2.5mg/kg/day for 28 days (maximum 100mg/day)
The drug is provided as 10mg and 50mg capsules. Capsules should be taken after meals and the daily dosage should be divided in 2-3 intakes.

Toxicity and adverse-effects

Nausea and vomiting are frequent adverse-effects that are controllable with anti-emetics and usually self-limited, however, in about 1% patients these

can be severe and life threatening. Renal or liver toxicity have been observed in a low proportion of patients during clinical trials.

Paramomycin

Generalities

Paramomycin sulfate, formerly called Aminosidine, is an aminoglycoside antibiotic with good anti-leishmanial activity. Excellent efficacy and safety results have been obtained in India with a total dose of 15mg/kg/day im for 21 days (11 mg/kg of base).

The drug has been registered in India for VL use in 2006. In East Africa, it is being currently evaluated as monotherapy and in combination with SSG (given for 17 days). Low cost (10 US$/treatment).

Dosage and administration

The optimal dose schedule of Paramomycin, when given as monotherapy, remains to be determined except India where above mentioned dose as monotherapy cured 94.6% patients. In other parties of the world, the drug should be given only for compassionate use.

Toxicity and adverse-effects

No significant nephrotoxicity or ototoxicity has been reported. An1.6% of patients had audiometric evidence of reversible high-frequency hearing loss.