Report of a WHO informal consultation on liposomal amphotericin B in the treatment of visceral leishmaniasis

Rome, Italy, 16 April 2005

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Executive summary

Liposomal amphotericin B is commonly used to treat visceral leishmaniasis (VL). The World Health Organization (WHO) convened an informal consultation in Rome, Italy, on 16 April 2005 to update the background on and define guidelines for the use of liposomal amphotericin B. In Europe, this formulation is widely used to treat VL in immunocompetent and immunodepressed patients. The VL disease burden is much higher in Africa and Asia than in Europe, and levels of drug availability are low. Public sector agencies can, however, purchase liposomal amphotericin B for distribution through the public sector of developing countries at a preferential price (in July 2007, US$ 20 per vial of 50 mg). Liposomal amphotericin B (total dose 20 mg/kg) administered in one or two injections has proved to be of high efficacy and low toxicity in immunocompetent VL patients in East Africa, the Mediterranean Basin and Brazil. Results of some controlled trials indicate that a total dose of 10 to 15 mg/kg in South-East Asia may be sufficient to achieve an equally high cure rate. Recommendations on the use of liposomal amphotericin B, either alone or in combination, have been provided for different forms such as zoonotic and anthroponotic VL as well as for patients infected with human immunodeficiency virus (HIV) and visceral leishmaniasis (HIV-VL coinfection).

Introduction

Over the past decade, liposomal amphotericin B has been increasingly used as both a first-line drug to treat patients diagnosed with VL in some endemic regions and as a second-line drug to treat VL patients who fail to benefit from conventional therapy. Liposomal amphotericin B has the highest therapeutic index of existing antileishmanial drugs, a moderately long serum half-life (7 hours) and sustained presence in the tissues for several weeks post-treatment. Historically, the major obstacle to its wider use for VL treatment was its high cost, which has now been reduced to US$ 20 per vial for public sector agencies wishing to purchase the product for distribution through the public sector of developing countries. WHO policy precludes the recommendation of therapies based on affordability. However, the convergence of recent successful clinical trials in determining the minimum effective total dose and the current preferential pricing provided by the manufacturer for VL patients treated in the public sector means that liposomal amphotericin B may become affordable as a first-line therapy even in resource-constrained settings. Moreover, few new antileishmanial drugs are currently in the development pipeline, and drug resistance is on the rise. Therapy using fixed-dose combinations of drugs is now the standard of care for patients with diseases such as malaria and tuberculosis, and drug resistance is a serious challenge. For these reasons, there is also growing interest in combined regimens of drugs in current use for VL.

Objectives of the Meeting

WHO convened an informal consultation at the Istituto Superiore di Sanitá in Rome, Italy, on 16 April 2005. The objectives of the meeting were (i) to discuss current expert knowledge of, and experience with, liposomal amphotericin B in the treatment of VL and (ii) to produce a consensus document with clear guidelines for dosage and clinical use of liposomal amphotericin B for VL. The participants, who represented a wide variety of VL-endemic regions, were experts in specialties ranging from basic research to clinical medicine and access to drugs.

Epidemiology of visceral leishmaniasis

Visceral leishmaniasis, or kala-azar, causes an estimated 500 000 new cases of disease and more than 50 000 deaths every year; 90% of cases occur in just five countries: India, Bangladesh, Brazil, Nepal and Sudan [1]. In South Asia and the Horn of Africa, the predominant mode of transmission is anthroponotic (AVL) [2]. In these areas, humans with kala-azar or post-kala-azar dermal leishmaniasis (PKDL) provide the principal reservoir for ongoing transmission [3, 4], and incomplete or irregular treatment of human VL leads to drug pressure and the rapid development of resistant parasites [5]. In the Mediterranean, the Middle East and Brazil, the disease is zoonotic (ZVL): the domestic dog is the principal reservoir host sustaining transmission to humans [2]. In these regions, most human VL disease occurs in children or immunocompromised adults.

In addition to the distinction between the epidemiology of AVL and that of ZVL, key factors that influence the ability to control VL include the following: poverty and its many effects; poor nutritional status of the population; armed conflict and population movements; ecological changes that alter human contact with the sandfly vector; the prevalence of HIV infection; parasite resistance to antileishmanial drugs; and poor access to health care and antileishmanial drug treatment [6]. In nearly all resource-poor endemic regions, access to antileishmanial drugs is constrained by the economic burden that VL care imposes.