EDITORIAL

THE RATIONALE FOR MULTIDRUG THERAPY (MDT)

In literature, the terms Multidrug Therapy (MDT) and Combination Therapy (CT) are used interchangeably and refer to concurrent use of 2 or more drugs in the management of diseases. In chemotherapy of cancer, malaria, HIV/AIDs, tuberculosis and leprosy Multiple Drug Therapy is the rule rather than exception. MDT is used to exploit synergistic and additive potential of individual drugs without increasing the toxicity of the combination. A tacit understanding is that such drugs will have different biochemical targets (different mechanism of action) and their toxicity will not be additive or complementary.

What has been the impetus behind MDT? There are several considerations but the most important ones are (a) resistance to chemotherapeutic agents by bacteria, virus, protozoa and cancer cells (b) the need to reduce acute and chronic toxicity (c) cutting down the cost of treatment by reducing the hospitalization period. The World Health Organization (WHO) has played a pivotal role in promotion of MDT in HIV/AIDS, tuberculosis, malaria and leprosy by providing financial resources and expertise. A brief review of some of the important factors which has helped to promote MDT are given below.

Development of resistance to chemotherapeutic agents is a common, almost predictable phenomenon when monotherapy is adopted. MDT is then seen as an answer to this problem since it helps to delay the development of resistance almost indefinitely. In the case of tuberculosis 3-4 drugs are commonly used. There are several acceptable dosage regimens but in nearly all cases treatment is in 2 phases. The first phase consists of intensive treatment with 3-4 drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) for approximately 8 weeks followed by a second phase of approximately 16 weeks, where the ambulient patient is discharged on 2 drugs, usually isoniazid and rifampicin. To cut down on hospitalization period, there are now “intermittent”dosage regimens where the patient is hospitalized for a shorter period and discharged on a very high dosage of isoniazid and rifampicin often taken twice a week for about 9 months.

Since the launch of Roll Back Malaria (RBM) initiative in 1998, WHO has promoted the use of Combination Therapy (CT) in malaria chemotherapy. Indeed promotion of CT started much earlier in the 1980s when plasmodium resistance to first line drug, chloroquine, was found to be very high in South East Asia, South America and Africa South of Sahara. The current combination for malaria consist of one artemisinin derivative (artemether, artesunate, dihydroartemisinin, arteether) and another 1-2 antimalarial drugs (piperaquine, lumefantrine, sulphadoxine/pyrimethamine, etc)

Over the years, cancer chemotherapy has evolved from the classical COPP (Cyclophosphamide/Vincristine/Procarbazine/Prednisone) combination to more than 12 combination regimens specific to different types of cancer. For example Adriamycin/Bleomycin/Vinblastine/Dacarbazine (ABVD) combination is used in Hodgkins disease while Bleomycin/Etoposide/Platinum (BEP) combination is used for testicular cancer.

In the case of HIV/AIDs, WHO guidelines on the choice of antiretroviral drugs have been adopted by many countries. The drugs include Nucleoside Reverse Transcriptase Inhibitors (NRTI) such as zidovudine, stavudine, lamivudine, zalcitabine; Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) such as nevirapine, efavirenz and protease Inhibitors (PI) such as Saquinavir, nelfinavir. Three common regimens are 3NRTI (one of which is abacavir), 2NRTI+1NNRTI, and 2NRTI+1PI.

For leprosy the combination regimen was introduced in 1982 following WHO recommendation. Dapsone, rifampicin and clofazimine are given daily in phase one for 6 months and the patient is discharged on Dapsone for 5 years.

More details regarding combination therapy for tuberculosis, leprosy, malaria, HIV/AIDS and cancer are available in literature. The combinations cited above were developed in response to growing resistance to the chemotherapeutic agents. The toxicity of individual drugs are not additive, except in the case of anticancer agents where bone marrow depression, alopecia, gastrointestinal disturbance are common to all drugs. A major benefit of combination therapy is the shortening of treatment period thus cutting down the cost considerably.

Multidrug therapy has attendant problems, which must be addressed. Among these is the patient non-compliance when taking several drugs. This is especially serious when different drugs are self-administered at different intervals by people who are not time conscious. The problem has been addressed by formulation of several drugs into a fixed-dose combination product. For example there are antituberculostatic agent in tablets form containing isoniazid, rifampicin and ethambutol. Similarly there are antiretroviral tablets containing stavudine, lamivudine and efivarenz (2NRTI+1NNRTI). The above two are examples of fixed dose combinations. In other cases, the drugs are separate but co-blister packed. There are arguments in favour and against fixed dose combinations. Whereas these combinations improve patient compliance, they limit the clinician's ability to alter the ratio of these drugs should the need arise. There is also the possibility that bioavailability of one drug may be influenced by another in the combination.

The elimination constant for one drug may be much shorter than that of the others making it impracticable to adopt same dosing interval without cumulation. This is especially important in tuberculosis, HIV, cancer and leprosy where treatment is continued over a long period.

When everything is considered, there is overwhelming evidence in favour of multidrug therapy in the above diseases. Indeed it can be stated emphatically that in the above diseases, there is no alternative to multidrug therapy.

Editorial-in-Chief