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Chemotherapy

1. Introduction

1.1 MDT

Multidrug therapy (MDT) was first recommended by a WHO Study Group ([1]) in 1981. Its chief characteristics were the following:

- the regimens included several drugs acting by different mechanisms, in order to prevent the emergence of drug-resistance, and to be effective even for strains of *Mycobacterium leprae* resistant to dapsone;
- the duration of MDT was limited, in contrast to the life-long duration of dapsone monotherapy, in order to improve compliance of the patients. To make this possible, only bactericidal drugs were included as components;
- rifampicin (RMP) was included as a key component because of its powerful bactericidal effect against *M. leprae*. It was to be administered only once monthly under supervision, both to insure compliance and because of its high cost;
- the recommended regimens were the minimal effective regimens; there was no recommendation against the use of stronger or longer regimens.

1.2 Official regimens (1, 2)

To date, three regimens have been officially recommended: (i) WHO/MDT for paucibacillary (PB) leprosy; (ii) WHO/MDT for multibacillary (MB) leprosy; and (iii) a single dose of the combination RMP-ofloxacin-minocycline (ROM) for single-lesion PB leprosy, this last to be employed in those countries in which the proportion of single-lesion PB patients is large.

The composition of the first two regimens, which were recommended by a WHO Study Group ([1]), has remained unchanged. However, the definitions of PB and MB leprosy have been modified several times, and the cut-off point between PB and MB leprosy has been simplified from a bacterial index (BI) of ≥2+ in the initial skin smears at any site ([1]) to more than five skin lesions ([2]). Consequently, a larger proportion of newly detected patients are classified as MB leprosy than in the past. At the same time, the duration of MDT for MB leprosy has been gradually shortened, from "at least 2 years, and . . . whenever possible, until skin smears negativity" ([1]), to a total of 24 months ([3]). At its seventh meeting, the WHO Expert Committee on Leprosy stated that 24-month duration for MB leprosy remained valid, while suggesting that "it is possible that the duration of the current MDT regimen for multibacillary leprosy could be further shortened to 12 months" ([2]). This careful wording clearly indicates that the recommended duration of MDT for MB leprosy is either 24 or 12 months.

The third regimen, a single dose of ROM for the treatment of single-lesion PB leprosy, which possesses obvious operational advantages, was recommended as an alternative by the Expert Committee on Leprosy at its seventh meeting ([2]), and has subsequently been applied widely in India, Bangladesh and Brazil ([4]).

1.3 New MDT regimens

The need for new regimens that are more effective and operationally less demanding may be summarized as follows:

- from the operational point of view, the recommended duration of treatment, particularly for MB leprosy, is still too long;
- two of the components of the current regimen for MB leprosy—dapsone and clofazimine—are only weakly bactericidal against *M. leprae* ([5]). Because it is these weaker drugs that determine the minimal, effective duration of the current regimen, further shortening the duration of treatment by this regimen might result in higher relapse rates;
- administration of the daily components, dapsone and clofazimine, cannot be supervised, as a result of which the MDT regimen for MB leprosy is not resistance-proof, should patients fail to comply with treatment;
- patients who do not tolerate clofazimine because of its skin coloration, or who cannot take dapsone or RMP because of

allergy, or cannot benefit from RMP because of intercurrent disease or the emergence of RMP-resistance, require a safe and effective alternative;

The discovery of new drugs ([6]) that demonstrate very promising bactericidal activity against *M. leprae* has made possible the formulation of new MDT regimens. A highly desirable new regimen is one that would permit all of the components to be administered once monthly under supervision, significantly reducing the risk of emergence of RMP-resistance caused by irregular administration of the daily components. ROM is the first fully supervisable, monthly-administered regimen. The efficacy of multiple monthly doses of ROM for treatment of MB and PB leprosy has been tested in field trials in three different countries ([4]); however, two of the trials have been terminated prematurely. It is critically important that post-treatment follow-up of the patients treated in the only remaining trial be carried out as originally scheduled. Furthermore, because of the success of a single dose of ROM for the treatment of single-lesion PB leprosy, the treatment of multiple-lesion PB leprosy with a single dose of ROM should be evaluated. Should this treatment be successful, the chemotherapy of PB leprosy could be much simplified, saving significant resources that may be used for other important activities.

The bactericidal activities of both ofloxacin and minocycline are rather weak, compared with that of RMP; the combination ofloxacin-minocycline is significantly less active than is RMP alone, and ROM is no more bactericidal than is RMP alone ([7]). Replacing the components of ROM with more powerfully bactericidal drugs would make possible a fully supervisable, monthly-administered MDT regimen. Recent findings from experiments in mice indicate that rifapentine and moxifloxacin are significantly more bactericidal than are RMP and ofloxacin, respectively, and the combination rifapentine-moxifloxacin-minocycline (PMM) is far more bactericidal than is ROM ([8]). The efficacy of PMM is currently being measured in a short-term clinical trial among lepromatous leprosy patients. If the trial confirms the stronger bactericidal effect of PMM, a field trial to evaluate the efficacy and side-effects of PMM over the long term should be carried out.

1.4 A common regimen for both PB and MB leprosy

A common regimen for the treatment of both PB and MB leprosy is desirable. However, because PB and MB leprosy differ so greatly in terms of the size of the bacterial population and the underlying immunological response, the requirements for chemotherapy, especially in terms of the number of drugs and the duration of treatment, are bound to be very different. If a common regimen is formulated on the basis of the available drugs, it appears likely that it would overtreat PB or undertreat MB. The dream of a common regimen might be realized only if the new regimen contained several very powerful bactericidal drugs, which were capable of shortening the duration of treatment for MB leprosy to only a few doses or even to a single dose.

Recently, the WHO Technical Advisory Group (TAG), at its third meeting, recommended that all leprosy patients, both PB and MB, be treated by the MDT regimen for MB leprosy for a period of only six months ([9]) The TAG stated, in support of this recommendation, that:

- MDT has been proven to be robust in terms of treatment efficacy and safety;
- relapse rates are very low, less than one percent; and
- resistance to MDT has been virtually non-existent.

However, that a regimen is effective and safe is not sufficient to justify shortening its duration. A good example is THELEP regimen C, which was composed of a single dose of RMP *plus* daily dapsone administered for a period of two years; this regimen was highly effective and safe, but 20 per cent of the patients allocated to this regimen relapsed after an average of five years of follow-up ([10]) Since 1998, almost all MB patients have been treated with 12-months MDT; however, no information is available regarding the 5-year relapse-rate following 12-months MDT. Therefore, at least for the time being, there is no justification for further shortening of the duration of MB chemotherapy to 6 months. More-

over, it appears hazardous to state that resistance does not exist, because post-MDT surveillance has not been carried out in routine programs for almost 10 years ([3]). For these reasons, before any proposal to shorten further the duration of treatment for MB leprosy by the current MDT regimen or of a common regimen for both PB and MB leprosy may be implemented in control programs, these proposals must be studied by controlled trials, with relapse at the outcome.

2. Magnitude of MB Relapse After MDT and Possible Existence of a Higher Risk Subgroup of MB Leprosy

Among MB patients, the efficacy of MDT is best assessed by measuring the relapse rate after completion of treatment ([11]). The relapse rate was reported to be about 0.1% per annum among MB patients administered MDT for 24 months ([2, 12-17]). Because of the low relapse rates, post-MDT surveillance ([1]) has been discontinued ([3]). However, reports from the Institut Marchoux in Bamako and the Central JALMA Institute in Agra indicate the existence of a subgroup of MB patients who demonstrate a high frequency of relapse after 24-months MDT ([11])—as high as 4 to 7 per 100 patient-years among patients with initial mean BI $\geq$ 4.0, and far higher than that among patients with initial BI <4.0, suggesting that the high initial BI is a most important risk factor for relapse. In addition, relapse was observed to occur late—5 years after stopping treatment, on average ([11]), suggesting that follow-up of these patients may be important. Because there is no ready explanation of the discrepancy between the two estimates of the risk of the relapse among MB patients after 24-months MDT, and the possible existence of a subgroup of MB patients who are more prone to relapse, it is necessary to collect more information from the long-term follow-up of MB patients after completion of 24-months MDT. However, a number of difficulties are encountered in attempting to follow former MB patients after completion of MDT:

- in more and more routine programs, the patients are removed from the register as soon as they have completed MDT, and, very often, essential records—e.g., identity, address, initial BI and history of treatment—are lost, making it difficult to retrieve patients for follow-up and analysis;
- because of integration of the leprosy program into the general health services, responsibility for the detection of suspected relapse rests upon general health workers, many of whom do not possess the necessary skills. In addition, the general health services often lack the manpower and resources required to follow former patients who have already completed their treatment with MDT, because they are no longer considered "cases" ([2]); and,
- because of the poor quality of skin-smears in the past, and because a skin-smear service is no longer available in many programs, it is difficult to identify members of the higher-risk subgroup and to detect relapse.

Because no information exists with respect to the 5-year relapse rate among MB patients after 12-months MDT, determination of the relapse rate following 12-months MDT should be considered a high priority in those treatment centers in which post-treatment surveillance is possible. In addition, the results of ongoing trials, in which the relapse rates after treatment by various regimens, including the 12-month regimen, are compared ([4]), should be published as soon as they become available.

3. The Needs for Both Flexibility and Reliability of MDT Treatment

To guarantee that all newly detected leprosy patients receive treatment with MDT, the MDT services should be available and accessible to the patients. To accomplish this goal, a flexible, patient-friendly system for delivery of MDT must be implemented. However, at the same time, the principle that monthly RMP is to be administered under supervision ([1, 2]) should not be compromised, because RMP is the single, most important component of MDT, and non-compliance of leprosy patients with treatment has been well documented ([18]). In addition, the importance of regular contact between patient and health worker for the purpose of prevention of impairment must not be underestimated.

In areas in which the infrastructure is weak, there are patients who may find it difficult to visit the health center once monthly. Current policy states that, "in such cases, more than a month's supply of MDT blister-packs may be provided to the patient" [2], and that with "accompanied MDT", blister-packs for a full course of MDT should be provided at the time of diagnosis [19]. Consequently, in an increasing number of national programs, it has become the routine to provide the entire quantity of MDT blister-packs—i.e., a 6-months supply for PB and a 12-months supply for MB patients—to all newly detected patients. However, in many programs, those responsible for "accompanying" the patients' treatment either have not been recruited, or lack proper training, as a result of which many of them fail to carry out their mission. As a consequence, it is difficult to be certain that the MDT drugs are indeed self-administered by the patients, notwithstanding the fact that the success of MDT could be seriously jeopardized, should patients be non-compliant.

Because the monthly component was expected to be administered under supervision, studies of compliance with MDT undertaken since the introduction of MDT focused on regularity of self-administration of the daily component, chiefly dapsone, by urine testing. Whereas the results demonstrated better compliance with MDT than with dapsone monotherapy [20], only 70 to 80% of patients were found in compliance with the daily component [20–22], suggesting that the assumption that "patients who report for diagnosis and treatment may be considered as sufficiently motivated to take full responsibility for their own care" [2] may not be valid. Although one of the advantages of the blister-pack over the supply of MDT drugs in bulk was assumed to be improved patient compliance with the self-administered component [23], this assumption has been tested in only a few studies; these studies have demonstrated that blister-packs either did not improve compliance [24, 25], or improved it only marginally [26].

Because the monthly component is no longer administered under supervision to a significant proportion of patients [19, 27], it appears very likely that reduction of the frequency of contact between patients and health workers will affect the regularity of drug administration; therefore, compliance with both the monthly and daily components of MDT is certainly an issue far more important and complicated than before. It is important to measure the degree of non-compliance among those who are treated under the policy of flexible drug delivery with both the daily and the monthly components of the MDT blister-pack. This may have significant impact on MDT delivery policy, and even on the strategy of the chemotherapy of leprosy.

"Accompanied MDT" is the term applied to a program in which a family or a community member supervises the monthly administration of drugs to the patient [27]. This concept appears reasonable, but before its wide implementation, this approach should be tested under field conditions, to identify the requirements for its success. However, even with the best program of accompanied MDT, the justification for providing the total quantity of MDT drugs to the patient may be disputed, because the family or community member cannot replace the health worker.

4. Absenteeism and Default

A defaulter has been defined as a patient who has not collected MDT treatment for 12 consecutive months [28]. It has been recommended that defaulters who cannot be retrieved be removed from the register [28], and that the register be updated at least annually [27, 28]. In a number of national programs, as many as 40% of newly detected patients have been considered defaulters [29]. Since introduction of the "flexible MDT delivery" strategy, increasing numbers of patients have received the entire quantity of MDT drugs at the time of the first dose of treatment. Although it has been stated that the percentage of defaulters has declined dramatically as a result of this approach, it is difficult to assess the actual rate of completion of treatment.

Whatever the reason for default, every effort should be made to prevent it. A serious attempt should be made to trace absentees beginning at the time of their first absence. Absentees who return to treatment should be treated according to WHO recommendations: six doses of MDT within nine months for PB; and 12 doses within 18 months for MB. In

addition, tracing and persuading the defaulters to return for treatment is most important.

For those patients who have become defaulters, those who have died or migrated from the country should be removed from the register, whereas those who have moved out of the district or are taking treatment elsewhere should be transferred rather than simply removed from register. As long as the defaulters continue to live in the district and have yet to complete the full course of MDT treatment, they remain, by definition, "cases" [2], and may continue to represent sources of transmission. Instead of removing these defaulters from the register, health workers should be encouraged to retrieve them actively, with assistance from the community. A new course of MDT should be given to every defaulter after his retrieval or return.

5. Drug Resistance

To date, all of the official MDT regimens contain RMP, which is significantly more bactericidal than any other antileprosy drug or any combination of ofloxacin, clarithromycin and minocycline [7, 30]. Emergence of RMP-resistance would create tremendous difficulty for the treatment of individual patient, and its widespread dissemination would pose a serious threat to the achievement of leprosy control.

RMP-resistant leprosy was first documented in the 1970s [31]. It was rare [31, 32], probably because, in that era, RMP was seldom employed for the treatment of leprosy. Later, it was reported that, among a total of 404 MB patients who had been treated with various RMP-containing regimens, 39 relapsed and 22 were found to harbor organisms resistant to RMP, as proven by the mouse footpad technique [33]. Virtually all of the resistant strains were isolated from patients who had been treated with RMP only after they had relapsed after long-term monotherapy with dapsone or other sulfones, and almost all of the strains were also resistant to dapsone, indicating that these patients had in effect been receiving RMP monotherapy. Because many of the 22 patients developed RMP-resistance in the decade after beginning treatment with RMP [33], it appeared that RMP-resistance could emerge rather rapidly among patients whose treatment regimens were inappropriate.

Although more than 10 million leprosy patients in the world have completed treatment with MDT, and RMP-resistant leprosy has not been reported among these patients [2], one must be cautious in interpreting the findings. First, post-MDT surveillance for relapse is no longer carried out in most routine programs. Second, the standard means of diagnosing drug-resistant leprosy has required use of the mouse footpad technique; however, the great majority of the mouse footpad laboratories established for surveys of dapsone-resistance have disappeared during the last decade, which coincided with intensive implementation of MDT. As a result, RMP-susceptibility testing is rarely carried out, and the results are not always reliable. In fact, one cannot exclude the possibility that a number of RMP-resistant leprosy patients are currently undetected. Before RMP-resistance becomes so frequent that it threatens leprosy control, more solid information about its magnitude should be collected in different parts of the world.

Although it is no longer feasible to undertake a relatively large-scale survey of RMP-resistant leprosy by means of the mouse footpad technique, PCR-based DNA-sequence analysis of the *rpoB* gene of *M. leprae* represents a cost-effective alternative technique [34–36]. At this stage, surveys of RMP-resistance should focus on MB patients who have relapsed after completion of MDT, and surveillance for the emergence of RMP-resistance among relapsed MB patients should be carried out by special centers. For this purpose, a proportion of MB patients should be systematically examined clinically and bacteriologically after completion of MDT, and skin-biopsy specimens should be obtained from those patients suspected of relapse for DNA sequence analysis of the *rpoB* gene of *M. leprae* [34–36].

MDT was developed mainly because of the widespread emergence of dapsone resistance, and the MDT regimens were designed on the principle that they would be effective against all the strains of *M. leprae*, regardless of their susceptibility to dapsone [1, 2]. Hence, in the MDT era, whether the global prevalence of dapsone-resistance is increasing or declining is virtually irrelevant to the therapeutic effect of MDT, and there is no need to monitor trends of resistance to dapsone.

Recommendations.

- To guarantee the quality of leprosy services, training in leprosy should be strengthened among general health workers.
- The skin-smear remains an important tool for diagnosing MB relapse; wherever possible, it should be reintroduced, particularly in areas in which there are a significant number of MB patients who have completed MDT, or the prevalence is greater than 1 per 10,000 population.
- Currently, almost all MB patients are being treated by 12-months MDT; however, no information is available regarding the 5-year relapse rate among MB patients treated by this regimen. Therefore, field programs with adequate facilities should monitor the relapse rates. Surveillance among relapsed MB patients for the emergence of rifampicin resistance should be carried out by special centers.
- A flexible, patient-friendly system for delivery of MDT must be implemented. At the same time, the principle that monthly RMP is to be administered under supervision should not be compromised. Only in exceptional cases, in which the patients cannot be seen monthly, should more than a one-month supply of MDT blister-packs be provided.
- Health workers should actively trace absentees and encourage them to complete their treatment, instead of passively awaiting their return and removing them as defaulters from the register after an absence of 12 or more consecutive months.

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