Edited by

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CHEMOTHERAPY

Volume 3

Special Problems in Chemotherapy

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Volume 1 **Clinical Aspects of Infections**
Prophylaxis; life-threatening infections; infection in leukaemia; surgical infection; anaerobic infection; respiratory and urinary tract infections; amikacin.

Volume 2 **Laboratory Aspects of Infections**
Sensitivity testing; assay methods; animal models of infection; sisomycin; tobramycin.

Volume 3 **Special Problems in Chemotherapy**
Tuberculosis; genital tract infections; antibiotic resistance and mode of action; topical chemotherapy and antisepsis.

Volume 4 **Pharmacology of Antibiotics**
Tissue concentrations; pharmacokinetics; untoward effects of antibiotics.

Volume 5 **Penicillins and Cephalosporins**
Penicillins and cephalosporins; betalactamases; new agents.

Volume 6 **Parasites, Fungi, and Viruses**
Parasitic infections; fungal infections; chemotherapy of viruses; co-trimoxazole.

Volume 7 **Cancer Chemotherapy I**
Symposia – new drugs and approaches; cell and pharmacokinetics; potentiators of radiotherapy; in vitro screening systems; immunological aspects.

Volume 8 **Cancer Chemotherapy II**
Free papers – new drugs and approaches; cell and pharmacokinetics; mechanisms of action; new analogues; cancer chemotherapy of specific organs.

CHEMOTHERAPY

Proceedings of the
9th International Congress of Chemotherapy
held in London, July, 1975

Preface

The International Society of Chemotherapy meets every two years to review progress in chemotherapy of infections and of malignant disease. Each meeting gets larger to encompass the extension of chemotherapy into new areas. In some instances, expansion has been rapid, for example in cephalosporins, penicillins and combination chemotherapy of cancer - in others slow, as in the field of parasitology. New problems of resistance and untoward effects arise; reduction of host toxicity without loss of antitumour activity by new substances occupies wide attention. The improved results with cancer chemotherapy, especially in leukaemias, are leading to a greater prevalence of severe infection in patients so treated, pharmacokinetics of drugs in normal and diseased subjects is receiving increasing attention along with related problems of bioavailability and interactions between drugs. Meanwhile the attack on some of the major bacterial infections, such as gonorrhoea and tuberculosis, which were among the first infections to feel the impact of chemotherapy, still continue to be major world problems and are now under attack with new agents and new methods.

From this wide field and the 1,000 papers read at the Congress we have produced Proceedings which reflect the variety and vigour of research in this important field of medicine. It was not possible to include all of the papers presented at the Congress but we have attempted to include most aspects of current progress in chemotherapy.

We thank the authors of these communications for their cooperation in enabling the Proceedings to be available at the earliest possible date. The method of preparation does not allow for uniformity of typefaces and presentation of the material and we hope that the blemishes of language and typographical errors do not detract from the understanding of the reader and the importance of the Proceedings.

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Contents

SINGAPORE STUDY OF INTERMITTENT RIFAMPICIN PLUS ISONIAZID FOR PULMONARY TUBERCULOSIS

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SUMMARY

In Singapore, 481 adult patients with newly diagnosed pulmonary tuberculosis were allocated at random to four regimens of intermittent rifampicin plus isoniazid. All patients received an initial two weeks of daily chemotherapy with streptomycin plus isoniazid plus rifampicin in standard daily dosages, followed by isoniazid 15 mg/kg body weight plus rifampicin 900 mg, both drugs twice a week (HR2 regimen) or once a week (HR1 regimen), or by isoniazid 15 mg/kg plus rifampicin 600 mg, both drugs twice a week (LR2 regimen) or once a week (LR1 regimen). All patients in addition received a supplementary daily capsule containing at random either rifampicin 25 mg or a matched placebo, to see if the daily supplement would reduce the incidence of adverse reactions to rifampicin.

The first 334 patients with fully drug-sensitive strains pretreatment were currently available for assessment at 12 months. Every single patient on the 2 twice-weekly regimens had a favourable bacteriological status at 12 months, as had 96% of the HR1 and 92% of the LR1 patients. Adverse reactions to intermittent rifampicin occurred in 26% of the HR1 patients, but on the other three regimens their incidence was low. In contrast, the incidence of rifampicin-dependent antibodies ranged from 21% (LR2) to 54% (HR1). The

incidence of adverse reactions and antibodies was unaffected by the rifampicin supplement.

INTRODUCTION

At the time this study was planned, animal and in vitro experimental evidence suggested that in man both isoniazid and rifampicin should be suitable for intermittent chemotherapy (Dickinson et al. 1968; Grumbach et al. 1969; Verbist 1969; Dickinson and Mitchison 1970). In clinical practice, however, rifampicin in dosages of 900 to 1800 mg once a week and twice a week although effective, induced a high incidence of adverse reactions (Girling and Fox 1971; Poole et al. 1971; Aquinas et al. 1972; Hong Kong Tuberculosis Treatment Services/Brompton Hospital/British Medical Research Council 1974; Hong Kong Tuberculosis Treatment Services/British Medical Research Council 1974). The commonest of these was the 'flu' syndrome, a febrile reaction which came on one to two hours after a dose, lasted for several hours and was often associated with circulating rifampicin-dependent antibodies. It occurred more frequently during once weekly rifampicin treatment then during twice weekly treatment with the same dose size and it could sometimes be stopped simply by reducing the intermittent dose size. It did not occur during daily chemotherapy and was thought to be immunological in origin. Therefore, it was envisaged that a small daily dose of rifampicin given as a supplement to an intermittent regimen might prevent or reduce the incidence of adverse reactions and the development of rifampicin-dependent antibodies.

The present study was, therefore, designed to find out, first, whether intermittent rifampicin in lower dosages would be both therapeutically effective and of low toxicity when given with high dosage isoniazid, and secondly, whether adverse reactions and the development of antibodies could be reduced or avoided by giving a very small dose of rifampicin i.e. 25 mg daily in addition to the intermittent doses.

CRITERIA OF ELIGIBILITY

Patients were admitted to the study if they had pulmonary tuberculosis, were aged 15 years or more, had received no previous antituberculosis chemotherapy and had sputum positive for tubercle bacilli on direct smear examination.

REGIMENS STUDIED

All patients received an initial two weeks of daily chemotherapy with streptomycin plus isoniazid plus rifampicin in standard daily dosages. They were allocated at random to one of four intermittent continuation regimens as follows:

1. Rifampicin 900 mg twice weekly (HR2 regimen)
2. Rifampicin 900 mg once weekly (HR1 regimen)
3. Rifampicin 600 mg twice weekly (LR2 regimen)
4. Rifampicin 600 mg once weekly (LR1 regimen)

All patients on all four regimens received the same dose size of isoniazid, i.e. 15 mg per kg body weight per dose. In addition, all patients received a supplementary capsule every morning containing at random either rifampicin 25 mg or a matched placebo, so that this part of the study was conducted double blind.

Of the 481 patients admitted, the first 371 have been under observation in the study for 12 months or longer. Of these, 13 patients were excluded for pretreatment reasons which were bacteriological in all except two. Another 24 were excluded for reasons encountered during treatment, the majority because of alteration to chemotherapy for drug toxicity (9 patients) or intercurrent disease (7 patients), leaving 334 patients with fully drug-sensitive strains pretreatment in the main bacteriological comparison. These patients have all completed a year under study and the findings at one year are presented.

PRETREATMENT COMPARISONS

The four regimens were similar in the pretreatment distribution of a number of factors including the following:

race (81% Chinese), age (average 43 years), sex (74% male), body weight (average 45 kg), radiological extent of disease (69% had moderate to gross disease), cavitation (55% had cavitation on a postero-anterior chest radiograph) and isoniazid inactivation rate (72% were rapid acetylators).

THERAPEUTIC RESPONSE

Patients with Fully Sensitive Strains Pretreatment

The single monthly culture results based on patients with fully drug sensitive strains pretreatment showed that the LR1 regimen lagged behind the other three regimens in the rate at which it produced sputum negativity in the early months of chemotherapy. At 12 months, all the HR2 patients had negative cultures, as did 90% of the HR1, 97% of the LR2 and 91% of the LR1 patients.

The bacteriological status at 12 months based on a total of 8 cultures at 10, 11 and 12 months is shown in Table 1. A favourable status was defined as all cultures negative or no more than 1 culture with a growth of 5 or more colonies. All patients on the two twice weekly regimens had a favourable status as did 96% of the HR1 and 92% of the LR1 patients. The therapeutic response on the twice-weekly regimens was significantly better than that on the once-weekly regimens ($P = 0.005$), but the dose size had no significant effect.

Table 1

BACTERIOLOGICAL STATUS AT 12 MONTHS

(based on 8 cultures at 10, 11 and 12 months)

	HR2		HR1		LR2		LR1	
	No.	%	No.	%	No.	%	No.	%
Patients assessed	85		78		87		84	
Favourable status	85	100	75	96	87	100	77	97

Ten patients (3 HR1, 7 LR1) had an unfavourable status. All 10 were excreting drug-resistant strains. Three of them developed isoniazid resistance followed by rifampicin resistance, 1 rifampicin resistance and then isoniazid resistance and another developed resistance to the two drugs at the same time. The remaining 5 developed resistance to isoniazid alone. All 10 were rapid acetylators of isoniazid.