Side effects of short course tuberculosis chemotherapy

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Summary

A retrospective study of 300 tuberculosis patients on short course chemotherapy registered in 1985 at the Chest Clinic, General Hospital Alor Setar, Kedah was carried out with the purpose of identifying patient characteristics, determining incidence of side-effects and modifying treatment regimens in order to minimise these side-effects. One hundred and sixteen (38.7%) patients developed side effects. Twenty seven (9%) had side effects severe enough to warrant a change in treatment regimen. Treatment modifications and ways to minimise or control side effects are discussed.

Key words: Tuberculosis, chemotherapy, side-effects, management, short course.

Introduction

Following a pilot trial of short course chemotherapy in 1979 in the states of Perlis, Kelantan and Malacca, and observing the benefits, it was decided to hold a National Conference on Short Course Chemotherapy at the National Tuberculosis Centre in March 1984.[1] Following this Conference, individual states were requested to implement short course chemotherapy depending on drug availability and cost consideration.

In Kedah the programme was fully implemented from September 1984. The treatment consisted of four drugs: Streptomycin, Isoniazid, Rifampicin and Pyrazinamide (SHRZ) for two months in the initial intensive phase and this was followed by an intermittent twice weekly regimen consisting of Streptomycin, Isoniazid and Rifampicin (SHR) for another four months.

A study was conducted with the following objectives:–

a) To determine characteristics of patients who were treated with the recommended short course chemotherapy of $2SHRZ/4S_2H_2R_2$ regimen.
b) To determine the side effects acquired by some of the above patients and to note whether they occur in the initial phase or in the twice weekly phase, or in both phases.

Materials and Method

A total of 411 cases were newly registered between 1st January and 31st December 1985 in the Chest Clinic of the Alor Setar General Hospital for various forms of tuberculosis. Of these cases, 300 patients who completed six months or more of treatment were available for analysis. These patients were initially started on the $2SHRZ/4S_2H_2R_2$ regimen. The rest were excluded because some were transferred out to other chest clinics or had been transferred in from other chest clinics while already on treatment. Some had abandoned treatment, or died while on treatment. Paediatric patients (below 12 years of age) whose treatment did not include Streptomycin and those patients who were not originally started on treatment with the SHRZ–SHR regimen, were also excluded. The age, sex, weight and racial distributions of the 300 patients, including those who developed side effects due to the above chemotherapy were studied.

The side-effects studied were adapted from the guidelines originally used for monitoring side-effects in the first trial of six-month short course chemotherapy in 1979. The major side-effects looked for were rash, vomitting, giddiness, abdominal discomfort, liver dysfunction, arthralgia, flu syndrome and others (e.g. exfoliative dermatitis, drug induced psychosis).[1]

Results

Of the 300 patients studied, 190 (63.3 percent) were males and 110 (36.7 percent) females, with a male:female ratio of 1.7 to 1. One or 0.3 percent of the patients was in the below 15-year age-group, 41.8% were in the 45–64 year age-group, 28.1% in the 25–44 year age-group and 16.7% were 60 years and above (Table 1). The age range was from 14 to 85 years.

Table 1
Distribution of Tuberculosis Cases in Kedah, 1985 by Age and Sex

	Male		Female		Total	
Age (Years)	No.	(%)	No.	(%)	No.	(%)
5 – 14	0	(0)	1	(0.9)	1	(0.3)
15 – 24	21	(11.1)	19	(17.3)	40	(13.3)
25 – 44	44	(23.2)	40	(36.4)	84	(28.1)
45 – 64	83	(43.7)	42	(38.2)	125	(41.8)
>= 65	42	(22.1)	8	(7.2)	50	(16.7)
Total	190	(63.3)	110	(36.7)	300	(100)

Most of the patients were Malays (79.3%), followed by Chinese (13.3%), Siamese (4.7%) and Indians (2.7%). Ninety eight (41.2%) of the Malay patients and 15 (37.5%) of the Chinese were between 45–64 years old (Table 2). The percentage of male patients was higher than that of female patients for all races (Table 3).

One hundred and sixteen or 38.7% of the patients studied had side effects due to the TB treatment. Patients 45 years of age and above had significantly more side-effects than those below

Table 2
Distribution of Tuberculosis Cases in Kedah, 1985 by Age and Race

Age (Years)	Malay No.	(%)	Chinese No.	(%)	Indian No.	(%)	Siamese No.	(%)	Total No.	(%)
5 – 14	1	(0.4)	0	(0)	0	(0)	0	(0)	1	(0.3)
15 – 24	33	(13.9)	4	(10.0)	2	(25.0)	1	(7.1)	40	(13.3)
25 – 44	70	(29.4)	9	(22.5)	1	(12.5)	4	(28.6)	84	(28.0)
45 – 64	98	(41.2)	15	(37.5)	4	(50.0)	8	(57.1)	125	(41.7)
>= 65	36	(15.1)	12	(30.0)	1	(12.5)	1	(7.1)	50	(16.7)
Total	238	(79.3)	40	(13.3)	8	(2.7)	14	(4.7)	300	(100)

Table 3
Distribution of Tuberculosis Cases in Kedah, 1985 by Race and Sex

Race	Male No.	(%)	Female No.	(%)	Total No.	(%)
Malay	144	(60.5)	94	(39.5)	288	(100.0)
Chinese	29	(72.5)	11	(27.5)	40	(100.0)
Indian	6	(75.0)	2	(25.0)	8	(100.0)
Siamese	11	(78.6)	3	(21.4)	14	(100.0)
Total	190	(63.3)	110	(36.7)	300	(100.0)

45 years ($P < 0.05$) (Table 4). Differences in the prevalence of side-effects by ethnic group and sex were not significant (Table 5 & 6).

Most of the patients experienced the side effects in the initial phase (77.6%) of their treatment, 9.6% in the twice weekly phase and 12.1% in both the phases (Table 7). This pattern is seen across all age and sex groups.

Amongst the side effects experienced by the patients, giddiness was the most prevalent (34.8%), followed by rashes (29.9%), vomitting (14.6%), abdominal discomfort (9.1%), liver dysfunction (5.5%), and arthralgia (3.0%) (Table 8). In all the four age groups, the most frequent complaints were rashes and giddiness.

Similarly, the most frequently occurring side effects among Malay and Chinese were rashes (28.4% and 42.9%) and giddiness (35.8% and 28.6%). The type of side effects recorded most in the initial and twice weekly phase were again rashes and giddiness.

Table 4
Distribution of Tuberculosis Cases in Kedah, 1985 by Age and Presence of Side Effects

	With side effects		Without any side effects		Total	
Age (Years)	No.	(%)	No.	(%)	No.	(%)
5 – 44	38	(30.4)	87	(69.6)	125	(100.0)
> 45	78	(44.6)	97	(55.4)	175	(100.0)
Total	116	(38.7)	184	(61.3)	300	(100.0)

Table 5
Distribution of Tuberculosis Cases in Kedah, 1985 by Race and Presence of Side Effects

	With side effects		Without any side effects		Total	
Race	No.	(%)	No.	(%)	No.	(%)
Malay	95	(39.9)	143	(60.1)	238	(100.0)
Chinese	14	(35.0)	26	(65.0)	40	(100.0)
Others	7	(32.0)	15	(68.2)	22	(100.0)
Total	116	(38.7)	184	(61.3)	300	(100.0)

Table 6
Distribution of Tuberculosis Cases in Kedah, 1985 by Sex and Presence of Side Effects

	With side effects		Without any side effects		Total	
Sex	No.	(%)	No.	(%)	No.	(%)
Male	67	(35.3)	123	(64.7)	190	(100.0)
Female	49	(44.6)	61	(56.4)	110	(100.0)
Total	116	(38.7)	184	(61.3)	300	(100.0)

Of the 300 patients who were initially treated with the $2SHRZ/4S_2H_2R_2$ regiment, 27 (9.0%) had side-effects severe enough to warrant a modification in their therapy. The majority of the patients complained of giddiness and/or pruritic rashes probably due to Streptomycin.

Of the 27 cases, 11 patients required modification of therapy during the intensive phase. Ten of these had therapy modified before the first 28 doses, while one required treatment modification

Table 7
Distribution of phase of treatment in which side effects occurred

Phase in which side effects occured	No.	(%)
Initial phase	90	(78.3)
Twice weekly phase	11	(9.6)
Both phases	14	(12.1)
Total	115	(100.0)

No. (%) of unknowns = 1 (0.9)

Table 8
Distribution of Tuberculosis Cases in Kedah, 1985 by Age and Type of Side Effects

Type of side effects	Rash	Vomitting	Giddiness	Abdominal Discomfort	Liver Dysfu.	Anthralgia	Others	Total
Age (years)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
5 – 14	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
15 – 24	5 (41.7)	2 (16.7)	4 (33.3)	1 (8.3)	0 (0)	0 (0)	0 (0)	12 (100.0)
25 – 44	14 (35.9)	5 (12.8)	11 (28.2)	4 (10.3)	1 (2.6)	1 (2.6)	3 (7.7)	39 (100.0)
45 – 64	18 (25.4)	11 (15.5)	23 (32.4)	7 (9.9)	6 (8.6)	4 (5.6)	2 (2.8)	71 (100.0)
>= 65	12 (28.6)	6 (14.3)	91 (45.2)	3 (7.1)	2 (4.8)	0 (0)	0 (0)	42 (100.0)
Total	49 (29.9)	24 (14.6)	57 (34.8)	15 (9.1)	9 (5.5)	5 (3.0)	5 (3.0)	164 (100.0)

after 40 doses. Alternative regimens included four patients with REHZ* and RHZ each, and one patient each with EHZ, EH and REZ.

All 27 patients required treatment modification from the usual $4S_2H_2R_2$ in the twice weekly phase. Of these, 15 had R_2H_2, one had E_2H_2, two had EH, one had P & I, one had RE, one had R_2H_2 and Rifinah, four had RH while two had $R_2E_2H_2$. (Patients who had Rifampicin omitted, in several cases, had their treatment extended to beyond the six month usual regimen).

* E = Ethambutol, R = Rifampicin, H = Isoniazid, Z = Pyrazinamide, S = Streptomycin.
Rifinah = combination tablet of Rifampicin & INH

Discussion

It can be seen from the above results that the majority of the patients in our study were Malay males. More than a third of the patients developed side-effects and it is pertinent to note that these were significantly higher in the older age groups and tended to occur in the initial phase.

Giddiness and rashes were the commonest side-effects which are ascribed mainly to Streptomycin.[2] Thus patients who are intolerant to Streptomycin may need to have this treatment altered to ensure completion. In fact treatment for 27 patients had to be modified. An example is the substitution of Ethambutol for Streptomycin in the initial phase. Similarly, in the continuation phase, omission of Streptomycin alone, or, in selected cases, omission of both Streptomycin and Rifampicin and substituting with Ethambutol may be necessary.

Side-effects due to other drugs were less prevalent; noteworthy among those were abdominal discomfort, vomitting and liver dysfunction presumably due to Rifampicin. These occurred in a small percentage of patients. Arthralgia, most likely due to Pyrazinamide, is again a rare event.[2]

In our study the incidence of jaundice is comparable to that obtained in other similar studies.[3] However, jaundice can also be caused by PZA and INH. We also noted that in the majority of patients, jaudice occurred in the initial phase. The maximum absorption of Rifampicin occurs when the drug is taken on an empty stomach. It is then excreted predominantly in the bile competing with bilirubin, but also to some extent in the urine. In dose sizes of 300 mg or more the concentration of rifampicin in the serum tends to rise due to saturation of the excretory capacity of the liver.[3] In this study over two thirds of our patients weighed less than 50 kg. Although the usual recommended dose of Rifampicin is 8–10 mg/kg, in the context of a patient with compromised liver function this dose may be too high. Thus even a dose of 450 mg (which the National Tuberculosis Control Programme recommends) may not be tolerated by some patients. Rifampicin can undoubtedly disturb liver function especially in those with a previous history of liver disease but in our study the significant cause of jaundice was the relatively high dose used in the large proportion of our patients. Other causes of jaundice notably gallstones, cirrhosis and hepatitis were investigated and excluded. In Kedah the recommended policy for doctors whenever faced with a patient with jaundice is to omit antituberculous drugs until the liver function tests are back to normal, and then reintroduce them at a lower dosage i.e. Rifampicin (5.0–7.5 mg/kg), Isoniazid (5 mg/kg) and Pyrazinamide (17–21 mg/kg). For example, in a 60 kg patient, we would recommend Rifampicin at 300–450 mg, Isoniazid at 300 mg and Pyrazinamide at 1000–1250 mg.

The side-effects of chemotherapy could be a significant factor contributing to defaultation of treatment. Judging from the above results, selected patients in the older age group especially those above 45 years of age may need an initial period of hospitalisation, both for education about the illness as well as to monitor and treat side-effects of chemotherapy. This is especially so due to the fact that most of the side-effects occur in the intensive phase. In our experience, we note that there is an improvement in compliance with greater cooperation and understanding when patients are hospitalised for a variable period of time in the intensive phase. Hence while we agree with the policy of ambulatory chemotherapy[4] there is a role for initial hospitalisation in some cases to improve case-holding.

In conclusion we have attempted to study the incidence of side-effects due to the antituberculous drugs namely Streptomycin, Rifampicin, Isoniazid and Pyrazinamide used in the short course chemotherapy. Although these drugs used may be effective against the tubercle bacillus, the

efficacy of the treatment regimen may be affected due to side-effects and resulting non-compliance. We have attempted to overcome the problems by necessary modification of therapy with the hope of ensuring eventual completion of treatment.

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