SHORT COURSE CHEMOTHERAPY FOR PULMONARY TUBERCULOSIS ON INDIVIDUAL BASIS – FINAL REPORT –

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(Received for publication November 1, 1985)

INTRODUCTION

The discovery of Rifampicin constituted a major breakthrough in the treatment of tuberculosis. A 9–month regimen of INH plus RMP plus SM or EMB has been proved to be 100% successful[1)2)]. Six months regimen of INH, SM, PZA and RMP for 2 months followed by INH plus RMP for 4 months was also proven to be 99% effective[3)]. Since too long duration of treatment has been regarded as the most important cause of "non–compliance", the question arises "Can the duration be cut even shorter ?"

Kreis has shown in his pilot study that daily INH , SM and RMP for 3 months had 15% of relapse after 2 years ' follow–up[4)]. This is to say, only 15% of his patients need treatment for longer than 3 months. If these 15% of patients could be detected before or during the first three months of treatment they alone could be given longer treatment, of 4, 5, or 6 months duration. Presumably there would be no relapses and the whole group of patients would then be treated successfully with the least expense.

With these thoughts in mind, three clinical trials were designed. The first trial with SHER followed by INH was started in 1974 with its chief aim being to clarify :

1). The extent to which it is possible to shorten further the duration of intensive chemotherapy of bacillary cases of pulmonary tuberculosis.
2). What are the criteria which could be used to terminate intensive chemotherapy before 6 months.
3). What other factors may be influencing the optimal duration of intensive chemotherapy.

It has been found[5)] that the sputum conversion was extremely rapid, complete and permanent ; 63%, 93%, 98%, and 100% at 1, 2, 3, and 4 months, respectively, and that at least 60% of cases can terminate the intensive chemotherapy in 3, and 100% of cases in 6 months, respectively without any relapse. Background factors influencing the duration of intensive treatment has been analysed. Furthermore, it was found that if sputum converted within 1 month, cavity closed, more than 50% of the lesions absorbed within 2 months after intensive chemotherapy, the intensive chemotherapy can be most likely terminated in 3 months[5)]. The successive two clinical trials were carried out in order to further clarify the followings :

4). What is the value of INH monotherapy following the intensive chemotherapy.
5). What are the differences between the effectiveness and side effects between daily SHER and SHZR.

MATERIAL AND METHODS

Consecutive patients with previously untreated pulmonary tuberculosis attending the out—patient departments of National Taiwan University Hospital and Taiwan Provincial Tuberculosis Control Bureau and fulfilling the enrollment criteria were admitted into this study

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The enrollment criteria were :

1). Presence of positive sputum smear and or

2). Presence of cavitary or far advanced disease with subsequent positive culture

3). Willingness to be hospitalized for up to 6 months

Patients with co-existing extrapulmonary tuberculosis or underlying diseases such as diabetes mellitus, pneumoconiosis etc. were excluded.

The number of patients enrolled into each trial was 61, 42 and 60. Their characteristics are shown in Table 1. Their age varied between 15 and 76 years. It will be noted that the average age was higher in the third trial. All cases (except one in the first trial) had moderately or far-advanced disease (NTA classification), most were cavitary cases. Mixed type lesions (by OKA classification) were found in larger percentage (43.3%) in the third group comparing with the other two groups (26.2% and 38.1%) suggesting that patients in that group had generally more old standing disease. Primary resistance to at least INH or SM were found in 22.9%, 11.9% and 15.0% respectively (Table 1).

Table 1. Background Factors of Patients

Background		I N = 61	II N = 42	III N = 60
Sex	Male	35	20	34
	Female	26	22	26
Age	Average	26.8	28.4	33.6
	Range	16—66	15—76	15—76
Extent of disease				
Mod adv. cavity (−)		1	0	0
Mod adv. cavity (+)		26	6	20
Far adv. cavity (−)		1	6	4
Far adv. cavity (+)		33	30	36
Type of lesion				
Disseminated		3	2	4
Pneumonic		17 } 45 (73.8%)	8 } 26 (61.9%)	13 } 34 (56.7%)
Infiltrative		25	16	17
Mixed		16 (26.2%)	16 (38.1%)	26 (43.3%)
Bacteriology				
M (−) C (+)		25	18	20
M (+) C (+)		36	24	40
Primary resistance		14 (22.9%)	5 (11.9%)	9 (15.0%)

In the first trial, in which 12 months of INH was given after termination of intensive chemotherapy, EMB 800mg was added in patients with primary resistance to INH. In the second and third trials, placebo was used in the second phase. In all three trials intensive chemotherapy was given for at least 3 months and at most for 6 months. The decision whether to terminate it after 3, 4, or 5 months was made on individual basis according to whether the 3 preset target points were met—sputum conversion, cavity closure and 75% lesion absorption.

The preliminary results of the first trial, that of SHER for 3 to 6 months followed by INH monotherapy for one year, have already been published[5]. In this final report, comparisons were made on the findings of the first trial and two subsequent ones—in which no INH monotherapy was used following intensive chemotherapy. In the second trial, intensive phase was the same as in the first one (SHER for 3-6 months) while in the third Pyrazinamide was given in place of Ethambutol (SHZR for 3-6 months).

The drug dosages were as follows : INH 300mg daily, EMB 1,200mg in the first two months, then 800mg daily, SM 0.75gm daily intramuscularly, RMP 450mg daily for patients weighing under 50kgs and 600mg for those above 50kgs, PZA 1.5gm daily divided in 3 doses.

All patients were hospitalized during the intensive phase of treatment to ensure supervised administration of drugs. Sputum examination of both smear and culture were done for 3 days before treatment. During treatment chest X-ray and 3 daily sputum examinations were done every month during intensive phase and every three months subsequently. Follow up period after cessation of treatment was 3 years. Tomography was performed when there was doubt about cavity closure by P-A film. Routine blood studies, liver function test and, in the third trial, uric acid examination were done monthly. Adverse effects were also carefully observed and recorded in all three trials.

RESULTS

1). Sputum conversion

Table 2 shows that in the first and second trials with SHER, the sputum conversion rates were 64%, 92%, 98% and 100% at 1, 2, 3, & 4 months respectively. In the third trial,(SHZR) the rates were almost identical 60%, 92%, 97% and 100% respectively.

Table 2. Sputum Conversion Rate

Order of study	Months after intensive Chemotherapy			
	1	2	3	4
I + II N = 103	64.0	92.2	98.0	100
III N = 60 *	60.0	91.7	96.7	100

* one changed regimen because of severe side effect

2). Improvement of chest X-ray findings during intensive chemotherapy.

a. Cavity closure

Among the 94 cavitary cases in the first two trials, cavity closure was found in 63 (67%), 73 (78%), 80 (85%) and 82 (87%) at 3, 4, 5 and 6 months respectively. Twelve cases (13%) remained "open negative". Among the 56 cavitary cases in the third trial, cavity closure was found in 30 (54%), 39 (70%), 42 (75%) and 43 (77%) respectively at consecutive month.Thirteen cases (23%) remained open negative after six months of treatment.

b. Absorption of lesions

Among the 103 cases in the first two trials, 75% or more of lesions absorption was found in 69%, 79%, 86%, and 90% at 3, 4, 5, & 6 months respectively. In the third trial, the rates at consecutive month were 58%, 73% 78% and 92% respectively.

3). Duration of intensive chemotherapy (Table 3)

Table 3. Duration of Intensive Chemotherapy in Monthly Accumulative Number and Percentage

	Target points reached in (months)				Not reached in 6 months	
	3	4	5	6	Open negative	Lesion absorption less then 75%
I + II N = 103	62	76	82	91	12 (11.7)	1 (0.97)
(%)	(60.2)	(73.8)	(79.6)	(88.3)	12 (11.7)	
III N = 60*	23	34	38	46	13 (21.7)	5 (8.3)
(%)	(38.3)	(56.6)	(63.3)	(76.6)	14 (23.4)	

* one case change regimen

In the first two trials, the duration of chemotherapy required for reaching the target points was 3 months in 62 cases (60%), 4 months in 76 cases (74%), 5 months in 82 cases (80%) and 6 months in 91 cases (88%). The remaining 12 cases failed to reach the target points. In all this was due to persisting cavities, (in one there was also failure to have 75% lesions absorption.) In the third trial, acumulative proportion of cases reaching the target points at consecutive month were lower with 23 (38%), 34 (57%), 38 (63%) and 46 (77%) respectively. Fourteen cases (23%) failed to reach the target points by 6 months, 13 of them because of persisting cavity, one because of failure of lesion absorption and 4 because of both. However further improvement of chest X-ray findings, such as increasing absorption of lesions, disappearance of open negative cavities were often observed within the first 6 months after termination of chemotherapy.

4). Side effects (Table 4)

Table 4. Side Effects during Intensive Chemotherapy

Side Effects / Studies	I + II (N = 103)	III (N = 61)	Total	
			Number	%
Abnormal LFT				
Transient elevation of GOT, GPT	16	8	24	14.7
Hyperbilirubinemia	1	1+	2	0.1
Transient leukopenia	4	3	7	4.3
Dizziness or vertigo	9(2)	6(6)	15	9.2
Tinnitus	2	6(6)	8	4.9
Blurring of vision	5	— —	5	4.9
Skin rash or itching	3	6	9	5.5
Elevation of uric acid	—	39	39	63.9
with joint pain	—	6	6	9.8

+ caused by pyrazinamide, regimen was therefore changed.
( ) number of patients had to discontinue SM

Side effects including transient abnormal liver function, transient leukopenia, dizziness or vertigo, tinnitus, blurring of vision, skin rash and elevation of uric acid were observed as shown in Table 4 . One case in the third trial had to change regimen because of severe hyperbilirubinemia caused by PZA. Two cases in SHER group and 6 cases in SHZR group had to discontinue Streptomycin because of tinnitus or vertigo. Although elevation of uric acid was found in 64% of cases in the third trial, all were controlled by benemide, none had to discontinue PZA.

5). Relapse and overall results

Table 5 shows that there were 8 relapses. Relapse was defined as obvious radiological deterioration with at least one positive sputum (7 cases) or without positive sputum (one case). We have not observed any patients who developed positive sputum while their X-ray remained

Table 5. Overall Result and Time of Relapse

Trials	No. of patients assessed	Drug regimen	Second phase chemotherapy	Follow-up period (months)	Relapse No.	Relapse %	Time of relapse (months after cessation of chemotherapy) 0 — 6	7 — 24	24	Overall result
I	61	3-6 SHER	12H	36	0	0	0	0	0	100 %
II	41*	3-6 SHER	placebo	36	4	9.8	3	1	0	90.2%
III	60	3-6 SHZR	placebo	36	4	6.7	0	1	3	93.3%

* one default

stable. In the first trial, the result was 100% successful, although 7 cases (12%) did not reach the "target points" by 6 months. In the second trial, one defaulted. Among the remaining 41 cases assessed, 5 cases (12%) failed to close their cavities by six months. In this series, 4 cases (10%) relapsed with the successful outcome rate of 90%. In the third trial, two patients died of nontuberculosis causes in the follow up period, one at 22 month, another at 27 month. Both were included in the assessment. Among the 60 cases assessed, 14 cases failed to reach the target points by 6 months. Four cases (7%) relapsed with the overall result being 93% successful. The difference between the relapse rates of the first and second trial and the first and third trial were statistically significant ($P < 0.025$) but they were non-significant between the second and third trials ($P > 0.3$). It is noteworthy that relapse was noted in only one case among the 19 cases who failed to reach the target points by 6 months in the second and third trials. Of the 4 relapsed cases in the second trial, 3 occurred within 6 months after cessation of chemotherapy. While in the third trial, only one case relapsed within 6 months, the other 3 cases relapsed more than 2 years after cessation of chemotherapy. Review of relapsed cases revealed that all 8 cases were cavitary, 6 of them received 3 to 5 months of chemotherapy, only two received 6 months treatment. Six of them were sensitive to all drugs, while two had primary resistance to SM.

6). Correlation of background factors to the duration of intensive treatment

All patients in the three trials were divided for statistical analysis into two groups—the three months' group and the remainder with intensive treatment for 4 to 6 months.

It was found that longer duration of treatment (i. e. later achievement of target points) was associated significantly with increasing age, greater extent of disease, presence of mixed lesions, presence of larger and "older" cavities and presence of positive smears. Furthermore, it was found that most of the 3 months' group had converted their sputum in the first month, and showed cavity closure and 50% absorption of lesions in the first two months. Sex and drug susceptibility could not be statistically correlated with the duration of intensive treatment.

DISCUSSION

The first trial with SHER for 3 to 6 months followed by INH monotherapy for 12 months had no relapse at all. While the second trial with SHER without INH for maintenance phase gave a relapse rate of 10%, in other words, intensive chemotherapy for 3 to 6 months followed by 12 months of INH monotherapy is a very effective regimen. The same good results were seen in the Singapore and the Mexican controlled trials[6)~8)]. Recently, another individually adapted clinical trial in Switzerland has also shown the same result[9)].

Without INH monotherapy, in the continuation phase the SHER group had a disappointing relapse rate of 10% and the SHZR group of 7%. Their results are comparable to the British trials[10)] and the Singapore trials[3)]. The 4th British trials with 2SHRZ / HRZ and 2HSRZ / HR for 4 months had a combined relapse rate of 13%. In the Singapore trials, 2SHZR / HRZ or 2SHZR / HR for 4 months gave 10% of relapse, the same regimens for 6 months had 2 relapse in 155 patients. Since in our studies, most of the patients (78.5% in SHER and 56.6% in SHZR) received treatment for 3 and 4 months, our results falling between those of the 4-month and 6-month trials of the British and Singapore trials are reasonable.

Ethambutol, being a bacteriostatic drug, has been reported to be of little value in short course chemotherapy. In Hong Kong / BMRC study, a 2-month intensive phase with daily SHER followed by twice weekly administration of $S_2 H_2 E_2$ for 6 months was compared with a regimen which differed only in that PZA replaced EMB in both daily (SHZR) and intermittent phase ($S_2 H_2 Z_2$). Culture negativity at 2 months were 81% and 95% respectively. Relapse rates in one year were 21% and 7% respectively. If continued for 8 months, the relapse rates were 10% and 4% respectively[11)]. In a USPHS

Tuberculosis Rifampicin therapy trial, it has also been shown that the addition of EMB to an INH plus RMP regimen provided only a modest improvement[12]. But in our study, culture negativity at 2 months were 92% both in SHER and in SHZR. In fact there were no statistical difference between the culture negativity rates at any month between two regimens. The difference between relapse rates of 10% and of 7% were not statistically significant ($P > 0.1$). The only explanation for this failure of PZA to improve the results may be due to the more severe disease and somewhat older age seen in patients in the third trial than in the other two. One thing noteworthy to mention is that of the 4 relapsed case in SHER group, 3 relapsed within the first 6 months after cessation of chemotherapy, another relapsed at 20th month, while in the SHZR group, one case relapsed at 9 months of follow up, the other 3 of the 4 relapses occurred more than 2 years after cessation of chemotherapy (27, 29, & 31 month respectively). If we had had follow-up period for only 2 years, the relapse rate would have been 1.7% (one in 60 cases), not inferior to the six-month regimens of British trials[13)~15)] and Singapore study[3)]. It seems that PZA-containing regimen will prolong the occurrence of relapse, and follow up period should be extended for longer than 2 years.

Of the factors that influence the duration of chemotherapy, the findings in this study were similar with other investigations : An analysis of relapse in three trials, one in Hong Kong (HK Chest Service / BMRC 1977), two in East Africa (E. African / BMRC 1978) concluded that bacterial population, extent of cavitation and speed of sputum conversion are factors affecting relapse[16]. A study in Japan also disclosed that type of lesions and nature of cavities should be determining factors in the duration of chemotherapy[17].

In this study, sputum conversion, cavity closure and 75% lesion absorption were used as criteria for termination of chemotherapy. All these three criteria are closely correlated to the bacterial content of the lesion and the bacterial response to chemotherapy. However, bacteriological conversion is most important. The fact that the 26 patients not meeting all three criteria by six months (25 of them failure to close their cavities) did show only one relapse suggests that radiological criteria for termination of intensive treatment may be relatively unimportant for the 6 months treatment group. The residual cavities either became closed in the majority of cases or remained as thin-wall bullous cavities in some cases by the follow-up studies. Two representative cases are illustrated in Fig. 1s and Fig. 2s. This finding was similar with that in East African Study[16]. For the shorter duration treatment group however, confirmation of cavity closure by tomography seems to be necessary as retrospectively among the 8 relapse cases, 4 (being treated for 3, 3, 4, & 5 months respectively) were considered due to early termination of chemotherapy by misinterpretation of cavity closure. D. A. Mitchison has suggested that specific sterilizing activity of RMP is mainly directed against semi-dormant organisms in cavity wall and residual cavities did not matter if the organisms within them (that would otherwise have caused relapse) had been killed. At the same time these criteria may be helpful in those situations when the shortest possible treatment is desirable and when 7-10% relapse rate is considered acceptable. In the 2nd and 3rd trial the termination of treatment at 3 months did not result in significantly increased relapse rate compared with that seen in those treated for longer periods. Continuation phase of treatment even with INH alone does render such regimens 100% successfully.

In summary, we believe, that with careful assessment of both bacteriological and radiological finding, the majority of newly diagnosed infectious cases can be treated with SHER or SHZR for 3 to 4 months with 90% success. INH monotherapy for some time after intensive treatment would increase the success to 100%. Tomography is necessary to confirm the cavity closure if intensive chemotherapy is to be terminated in less than 6 months. In patients treated for 6 months, the importance of residual cavities or lesions is negligible.

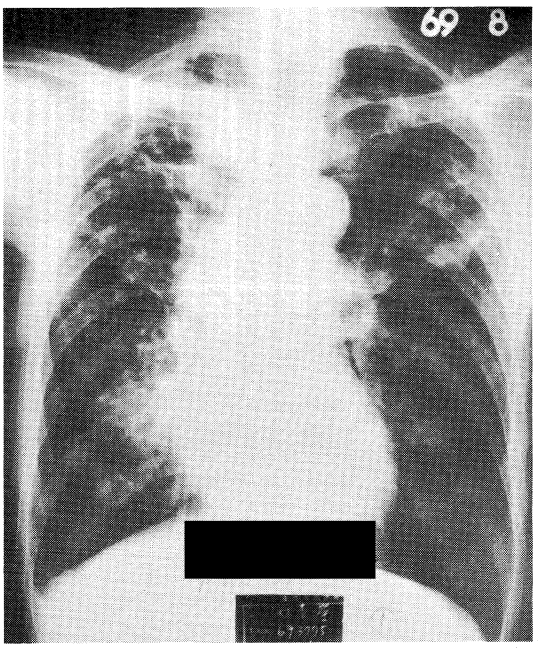

Fig. 1a

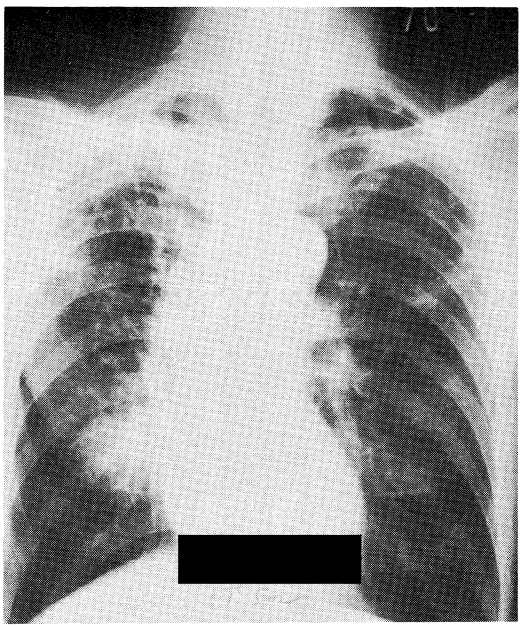

Fig. 1b

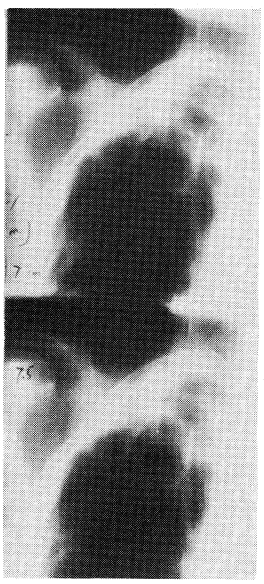

Fig. 1b'

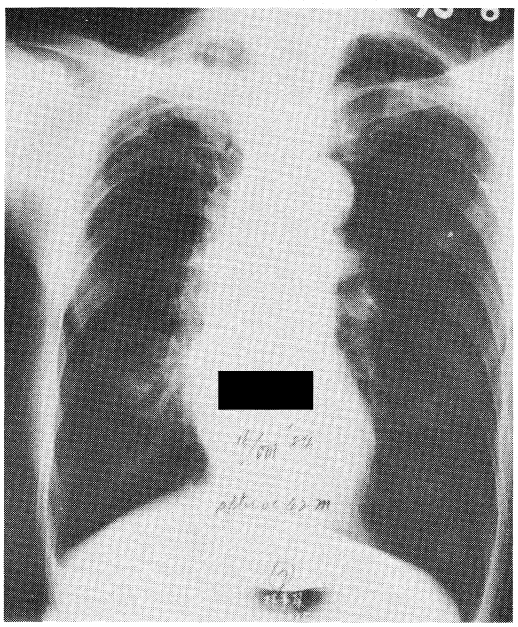

Fig. 1c

Fig. 1c'

Fig. 1a LSJ. age 58, male. Bilateral far advanced cavitary tuberculosis. Before intensive chemotherapy.
Fig. 1b Chest x-ray after SHZR for 6 months. Cavity in the right upper remained open.
Fig. 1c Forty-two months after cessation of chemotherapy, further absorption of lesions and closure of cavity were observed.
Fig. 1c' Tomogram confirmed the cavity closure.

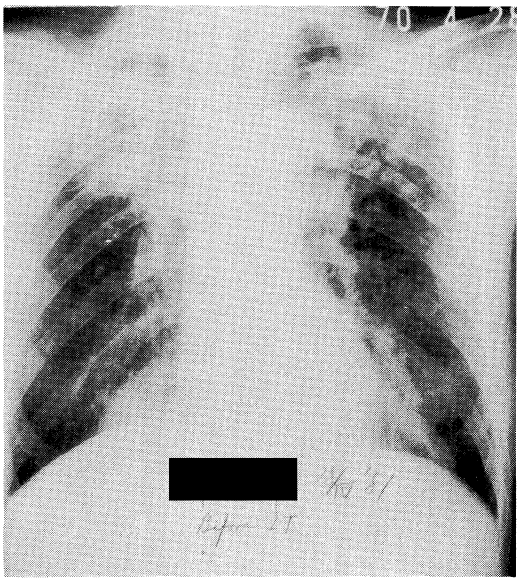

Fig.2a

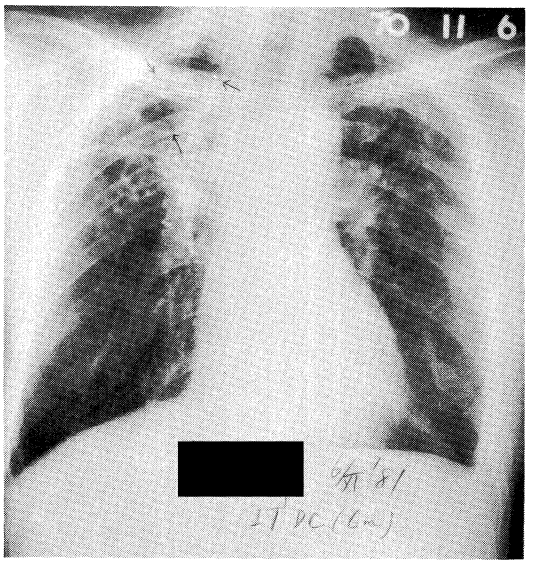

Fig.2b

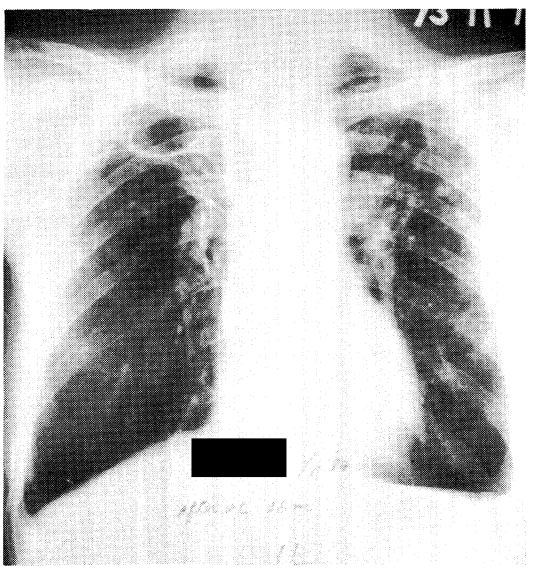

Fig.2c

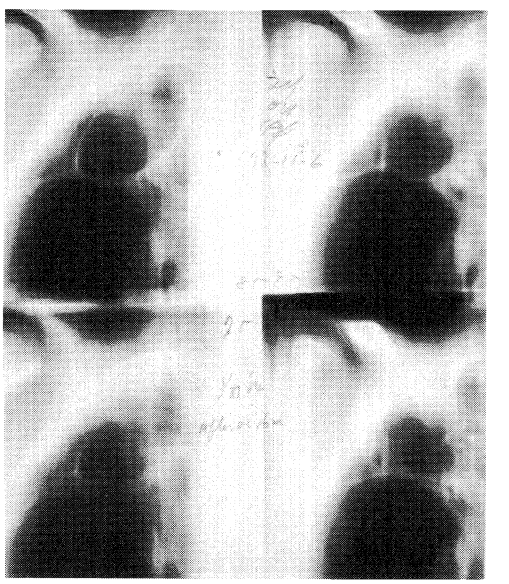

Fig. 2c'

Fig. 2a LMJ, male, age 53. Bilateral far-advanced cavitary tuberculosis, before treatment.
Fig. 2b Chest x-ray after SHZR for 6 months. Cavity in the right upper remained open.
Fig. 2c Thirty-six months after cessation of chemotherapy, further absorption of lesions with residual thin wall cavity.
Fig. 2c' Tomogram confirmed the residual thin wall cavity.

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