Tubercle and Lung Disease

10-year assessment of treatment outcome among Cambodian refugees with sputum smear-positive tuberculosis in Khao-I-Dang, Thailand

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SUMMARY. Tuberculosis control among displaced persons is fraught with difficulties to ensure adherence of patients to treatment for a prolonged period of time. In the Khao-I-Dang camp for Cambodian refugees an approach with daily, directly observed treatment throughout the course of 6 months duration was chosen to address the problem. Of a total 929 patients with sputum smear-positive tuberculosis who were enrolled from 1981 to 1990, 5.0% died, 75.5% completed treatment and were bacteriologically cured with a day-to-day adherence of more than 98%, none failed bacteriologically, 19.2% were transferred to another camp where continuation of treatment was guaranteed, and only 0.4% absconded from treatment. These data suggest that the approach to tuberculosis control in this refugee camp was very effective in cutting the chain of transmission of tuberculosis in a highly mobile population and in reducing substantially unnecessary morbidity and mortality.

RÉSUMÉ. Dans le contrôle de la tuberculose chez des personnes déplacées, il est très difficile d'assurer l'observance des malades au traitement pendant une durée prolongée. Dans le camp Khao-I-Dang pour réfugiés cambodgiens, afin de résoudre ce problème un essai a été choisi comprenant un traitement quotidien et directement surveillé tout au long d'une durée de 6 mois. Sur un total de 929 malades atteints d'une tuberculose frottis positif enregistrés entre 1981 et 1990, 5,0% d'entre eux sont morts, 75,5% ont terminé leur traitement et ont été bactériologiquement guéris avec un taux quotidien d'observance de 98%, aucun échec bactériologique n'a été relevé, 19,2% ont été transférés dans un autre camp où la continuation du traitement a été assurée, et seulement 0,4% ont abandonné le traitement. Ces données suggèrent qu'une telle méthode de contrôle de la tuberculose dans ce camp de réfugiés a été très efficace pour interrompre la chaîne de transmission de la tuberculose au sein d'une population très mobile, et pour réduire considérablement une morbidité et une mortalité inutiles.

RESUMEN. El control de la tuberculosis en las personas desplazadas se enfrenta a la dificultad de asegurar el cumplimiento del tratamiento por parte del paciente durante un tiempo prolongado. Para resolver este problema, en el campo de refugiados cambodianos de Khao-I-Dang, se optó por un tratamiento diario, directamente supervisado durante un período de 6 meses. De un total de 992 pacientes tuberculosos con baciloscopia positiva que habían sido puestos en tratamiento entre 1981 y 1990, un 5 % falleció, un 75,5 % completó el tratamiento y curó bacteriológicamente, con un cumplimiento día a día de 98 %, no hubo fracasos bacteriológicos, el 19,2 % fue trasladado a otro campo donde se garantizó la prosecución del tratamiento y sólo un 0,4 % abandonó el tratamiento. Estos datos sugieren que el enfoque elegido para el control de la tuberculosis en este campo de refugiados fue muy eficaz para interrumpir la cadena de transmisión de la tuberculosis en una población de alta movilidad y para reducir sustancialmente una morbilidad y una mortalidad innecesarias.

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Tuberculosis control programs in many resource-poor countries are deficient. Largely because of their failure to achieve bacteriologic cure in a sufficiently large proportion of patients, the epidemiologic situation in such countries has improved very little.[1,2] Among displaced persons, tuberculosis control is additionally complicated, because of the often unforeseen mobility of such people.[3]

In 1979, a large number of people fled from Cambodia into Thailand where the Thai authorities together with national and international governmental and non-governmental agencies provided food, shelter and medical care for these refugees. In Prachinburi province, close to the Cambodian border, a large camp called Khao-I-Dang Holding Centre for Kampuchean Refugees, was opened toward the end of 1979, to provide assistance to initially more than 130 000 Cambodians. Although tuberculosis was soon recognized as a major health problem, an effective program was put into place only after basic needs had been met, the initial rapid movement of refugees had ceased, and it was recognized that the only way to address the problem was utilization of the shortest possible, effective and acceptable regimen.[4] It was clearly understood that the emphasis had to be placed on effective treatment of the major sources of infection, i.e. patients with sputum smear-positive tuberculosis. To achieve the objective, a regimen of 6 months duration was chosen.[5] All drugs were to be given daily, directly observed throughout the entire course. Subsequently, a similar approach was introduced in another camp [6,7] and then the program was expanded to finally encompass all major camps for Cambodians along the border.[8]

As the closure of the various camps is hopefully to occur in the near future as the changes in the political situation will allow the return of Cambodians to their country, it was felt that there was a need to communicate to the medical community the results of the approach to tuberculosis control that was chosen in what once was the largest refugee camp in Thailand.

PATIENTS AND METHODS

The treatment protocol for patients with sputum smear-positive (or sputum smear-negative pulmonary) tuberculosis required 6 months of daily, directly observed treatment with rifampin plus isoniazid, supplemented by pyrazinamide plus streptomycin during the first 2 months [5] with the dosages of drugs adjusted to body weight.[4] Patients with extrapulmonary tuberculosis other than intrathoracic lymphatic were given the benefit of the same regimen, but for a total duration of 9 months. Throughout the course, every single dose was given every morning to each patient who had to swallow the drugs in front of a nurse. Patients who failed to attend the outpatient clinic were actively sought in the afternoon of the same day.

Between 1 April 1981 and 31 December 1990, 2039 patients were enrolled into the program. Of these, 183

were transferred in from other camps for continuation of treatment. Of the remaining 1856, 929 (50.1%) had sputum smear-positive tuberculosis including 31 who additionally had disease manifestation at an extrapulmonary site other than intrathoracic lymphatic. All 929 patients with positive sputum smears were included in the analysis of treatment outcome. Assessment of progress and the indication to complete the treatment in these patients was bacteriologic. In all patients, 3 sputum smears were examined on 3 consecutive days at the end of every month as long as they were able to produce sputum. Results were graded as recommended by the American Thoracic Society and the Centers for Disease Control.[9]

The analysis of treatment outcome was done by cohort, i.e. the denominator included only patients who should have completed the prescribed course at the time of analysis.[10] Five possible outcomes were considered, namely death, bacteriologic cure, bacteriologic failure, transfer out, and absconding. For the purpose of management and this analysis, the following definitions for these outcomes were utilized. Deaths were defined as patients who died after diagnosis, whatever the cause. Patients who converted their sputum within 4 months and never had any positive smear thereafter were declared bacteriologically cured after 6 months (or after 9 months, if they additionally had extrapulmonary tuberculosis). Patients who converted their sputum within 4 months, but who had an occasional positive smear at some later examination, had their treatment prolonged to 9 months. They were declared bacteriologically cured after 9 months if they had had no positive smear during the last 3 months. Patients who failed to convert their sputum or had a 'fall-and-rise' phenomenon [11] were to be considered as treatment failures and were to be placed on a specified retreatment regimen. Transfers out were defined as those patients who left Khao-I-Dang during treatment to another camp in an orderly fashion allowing transfer of patient and documents for continuation of therapy. Absconders were defined as patients who left the treatment prematurely without notice to another camp or back to Cambodia.

RESULTS

The basic demographic characteristics (age and sex) of the 929 patients with sputum smear-positive tuberculosis show that more than two-thirds were in the age brackets of 15–44 years and that almost half of the patients were female (Table 1).

Day-to-day compliance was excellent. More than 98% of the prescribed doses were administered to every patient who was not an absconder as defined.

Of the 929 patients, 5.0% died, 71.7% were declared bacteriologically cured after 6 months and an additional 3.8% were declared bacteriologically cured after 9 months, no patient failed bacteriologically, 19.2% were transferred out, and 0.4% absconded (Table 2).

Table 1.   Age and sex of 929 patients with sputum smear-positive tuberculosis, enrolled between 1 April 1981 and 31 December 1990

Age group	Male	Female	Total
0–14	12	12	24
15–24	74	70	144
25–44	244	238	482
45–64	128	83	211
65+	46	22	68
Total	504	425	929

DISCUSSION

Introduction of mass chemotherapy in low-income countries has dramatically reduced case-fatality from sputum smear-positive tuberculosis (and other forms), but has often had little impact on the reduction of transmission, because among survivors, the number of cases who were bacteriologically positive after 2 years remained essentially the same as in the pre-chemotherapy era.[12] The major reason for this failure to exert impact on the epidemiologic situation lies with the difficulty of ensuring patient's adherence to a 12-month course with often unpleasant drug combinations such as thioacetazone and isoniazid that are effective only when taken very regularly over the entire course, and initial isoniazid resistance is infrequent.

Regimens based on isoniazid, rifampin, and pyrazinamide allow the cure of a large proportion of patients, even if they choose to abscond after 2 or 3 months.[13] Because refugees do often stay for only short periods of time in temporary settlements, short-course chemotherapy was introduced early in Thailand's camps for Cambodian refugees, first in Khao-I-Dang,[4] then in Nong Samet (now Site 2 South)[6,7] and subsequently in most other camps along the Thai/Cambodian border.[8] Because of the poverty of the patients, it was apparent that treatment had to be given directly observed throughout the course, if the sale of valuable drugs on the thriving black markets was to be prevented.

Taking a firmer stance on tuberculosis control, the World Health Organization has now advocated a new strategy to achieve an objective of an 85% cure ratio in low-income countries.[14] Three-quarters of patients with

Table 2.   Treatment outcome in 929 patients with sputum smear-positive tuberculosis, enrolled between 1 April 1981 and 31 December 1990

Outcome	Number (%) of patients	
Died after diagnosis	46	(5.0)
Declared cured after 6 months	666	(71.7)
Declared cured after 9 months	35	(3.8)
Transferred out	178	(19.2)
Failed bacteriologically	0	(0)
Absconded from treatment	4	(0.4)

sputum smear-positive tuberculosis in Khao-I-Dang had documented bacteriologic cure, and the 20% who were transferred out had the continuation of their treatment guaranteed. All taken into account, these data suggest that transmission has been definitively arrested in perhaps more than 90% of cases.

The regimen that was chosen ranks among the most efficacious known today. It is also the most expensive per patient treated, but not necessarily per patient cured. The International Union Against Tuberculosis and Lung Disease has developed principles for national tuberculosis programs in low-income, high-prevalence countries [10] which have proved highly effective [1] and have provided the scientific basis upon which the World Health Organization is building its new strategy.[14] These principles include the provision of directly observed treatment with the most powerful available drugs for the first 2 months of treatment for patients with sputum smear-positive tuberculosis. If smears are negative at the end of the second month the patient is discharged with 1-month supplies of isoniazid and thioacetazone (or ethambutol, if thioacetazone is not being tolerated and resources for its replacement are available) for an additional 6 months of self-administered treatment. This approach has been shown to be cost-effective, at least in all those resource-poor countries that were evaluated.[15] A 6 month regimen, based on rifampin throughout, as is being used in the refugee camps along the Thai/Cambodian border, is to be encouraged when supervision of the treatment can be guaranteed throughout the course, the mobility of the population is high, and resources for drug procurement are made available.[3] The data from the Khao-I-Dang Holding Centre tuberculosis program suggest that the funds provided for tuberculosis control over the past 10 years have been a good investment because the program accomplished reduction of unnecessary mortality and morbidity, effective cutting of the chain of transmission and avoidance of the creation of chronic excretors with drug resistant strains which may become a serious problem in other places in Southeast Asia where complacency towards drug control is rampant.[16]

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