

## Original Article

# Tuberculosis in Patients with Lymphoproliferative Disorders: Is It As Common As Historically Stated?

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**ABSTRACT**

**Objective:** Retrospective studies suggest a 20 to 40 fold increase in the incidence of tuberculosis in patients with lymphoproliferative disorders as compared to the general population. This study was undertaken to determine the incidence of tuberculosis in patients with lymphoproliferative disorders undergoing systemic chemotherapy.

**Methods:** A prospective single-institution study in which 174 newly diagnosed patients with lymphoproliferative disorders requiring systemic chemotherapy were enrolled. The reactivity to the tuberculin skin test was determined at the beginning of the study. Patients were closely followed during the treatment period and for a minimum follow-up

period of two years for any evidence of reactivation of tuberculosis. None of the patients received isoniazid chemoprophylaxis.

**Results:** None of the 152 analyzable patients developed any evidence of tuberculosis reactivation during the study period.

**Conclusion:** Tuberculosis complicating lymphoproliferative disorders may occur at a lesser frequency than historically stated. The role of a tuberculin skin test as an indicator of prior exposure to tuberculosis as well as its value in initiating isoniazid chemoprophylaxis in patients with lymphoproliferative disorders should be reevaluated.

**KEYWORDS:** complications, lymphoma, lymphoproliferative disorders, *Mycobacterium tuberculosis*, tuberculosis

**INTRODUCTION**

The individual's susceptibility to tuberculosis (TB) is largely determined by the prevalence of the disease in the community as well as the individual's history of prior exposure to the disease, and the state of his cell-mediated immunity<sup>[1]</sup>. While the prevalence of TB in any community can often be determined by epidemiological studies, the other two determinants of the individual's susceptibility are harder to determine. This is true for patients with cancer, in general, and patients with lymphoproliferative disorders (LPD) in particular. Patients with LPD often have impaired cellular immunity, either by the disease itself or by its therapeutic immunosuppression<sup>[2-4]</sup>. Previous exposure of any individual to *Mycobacterium tuberculosis* is usually determined by the tuberculin skin test (TST), which is based on the presence of an intact cell-mediated immunity<sup>[5]</sup>.

Patients with impaired cellular immunity, such as patients with LPD, often give a negative result to tuberculin testing even if they have been previously exposed to the organism<sup>[3,4]</sup>. In addition, some patients with LPD who have a negative reaction to the TST could, in fact, represent a subgroup of patients at highest risk for TB as their advanced malignancy renders them anergic despite prior

exposure to *M. tuberculosis*. It is, therefore, crucial to determine the incidence of TB in patients with LPD undergoing immunosuppressive therapy. This may help in determining the need for isoniazid (INH) chemoprophylaxis in this group of patients.

Although the first report describing the occurrence of TB in 20% of patients with Hodgkin's Disease (HD) appeared in the literature in 1932<sup>[6]</sup>, accurate data on the incidence of TB in patients with LPD is lacking. Retrospective studies describing the frequency of LPD among other forms of cancers in patients diagnosed to have concurrent TB and malignancy suggest a higher frequency of TB in patients with LPD than in the general population<sup>[7,8]</sup>. According to these studies, TB was described to be 20 to 40 times more frequent in patients with LPD than in the general population<sup>[7,8,9]</sup>.

In this study, we prospectively followed a group of newly diagnosed patients with LPD in an attempt to assess their risk for TB reactivation. All the patients had been receiving cytotoxic therapy from the time the diagnosis of LPD was made, for a minimum of two years. Despite the limitations encountered because of the relatively small number of patients included in this study, it is to the best of our knowledge the first of its kind.

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## PATIENTS AND METHODS

This prospective study was conducted at King Khalid University Hospital, a 780-bed tertiary care referral center in Riyadh, the capital city of Saudi Arabia. Riyadh has a population in excess of three million. The study was initiated in May 1989 and closed in April 1996.

### PATIENTS

Patients included in the study were those who fulfilled the following inclusion criteria:

- 1) Age of 15 years and older
- 2) Unequivocal diagnosis of Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) requiring cytotoxic chemotherapy
- 3) Absence of clinical or radiological evidence of either active or previous TB
- 4) Absence of any associated condition which could lead to additional immunodeficiency, such as HIV infection.

### METHODS

#### Tuberculin Skin Test (TST):

All patients in the study were given a Tuberculin Skin Test (TST) using an intradermal injection of a fixed dose of 10 units of protein purified derivative of *M. tuberculosis* (Tuberculin Berna, Swiss Serum and Vaccine Institute Berna, Switzerland) in the middle third of the volar aspect of the forearm. Adequate technique was ensured by the appearance of a weal at the injection site. An initial reading of the reaction was made at 48 hours and, for those patients who gave a negative reaction, a repeat reading was made at 72 hours. A positive reaction was defined as an area of cutaneous induration at least 10 mm in diameter.

#### Patients Monitoring:

In addition to a complete history and physical examination, a complete staging workup was carried out for all patients entered into the study as per standard practice for patients with lymphoma. All study patients had, in addition to the TST, complete blood counts, full biochemical profile, chest X-ray, and computerized axial tomographic scan (CT scan) of the chest and abdomen. Other diagnostic and staging tests and procedures were carried out according to the individual's needs. Bone marrow biopsy was done in virtually all patients for the purpose of lymphoma staging. The mere presence of a non-caseating granuloma in the bone marrow was not taken as evidence of prior tuberculosis infection. None of the patients underwent staging laparotomies or splenectomies. For the purpose of diagnosis, laparotomy was carried out in seven patients in whom the disease was solely abdominal.

Patients were followed up at the Hematology/Oncology Clinic at least every four weeks while receiving cytotoxic chemotherapy and every 8-12 weeks following the completion of therapy for a minimum total period of 24 months. The follow-up evaluation consisted of physical examination, complete blood counts, full biochemical profile, septic screen for all febrile patients, including sputum staining for acid-fast bacilli with Zeil-Nelsson stain, and mycobacterial cultures for patients with respiratory complaints or findings. Patients with unexplained pulmonary infiltrates were considered for fiberoptic bronchoscopy. All obtained diagnostic material underwent microbiological evaluation for TB. Prior to the completion of the planned cytotoxic therapy, all patients underwent a full evaluation

**Table 1**  
Cytotoxic chemotherapy regimens used in the study patients

Non-Hodgkin's Lymphoma	Number of Patients Total =90	Hodgkin's Disease	Number of Patients Total=62
CHOP Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (Every 4 weeks for 6 courses)	78	ABVD Adriamycin, Bleomycin, Vinblastin, and Decarbazine (On days 1 and 14 of every course for 6 courses)	28
CVP Cyclophosphamide Vincristine, Prednisone (Every 3 weeks for 6 - 8 courses)	5	MOPP Methchloroethamine Vincristine, Procarbazine Prednisone (Every 4 weeks for 6 courses)	13
CHOP-BLEO As CHOP above plus Bleomycin (Every 4 weeks for 6 courses)	7	HYBRID(MOPP / ABV) Combined MOPP and ABVD regimens but without Decarbazine (Every 4 weeks for 6 courses)	5
		MOPP/ABVD(alternating) As shown above but alternating (Every 4 weeks for 6 courses)	16

similar to the one conducted following the initial diagnosis. Microbiological evidence for TB was sought every time a diagnostic or therapeutic body fluid aspiration was carried out. None of the patients was put on isoniazid (INH) chemoprophylaxis, regardless of the result of the TST reaction.

### Cytotoxic Chemotherapy

Cytotoxic chemotherapy was initiated for the specific type of LPD according to the protocol in effect during the study period. Cytotoxic drug dose adjustments and delivery were carried out according to the standard practice. Table 1 shows the combination chemotherapy regimens used in the study patients. Nine patients with HD and three patients with NHL received additional radiotherapy.

### RESULTS

Of a total 174 patients enrolled in the study (106 patients with NHL and 68 patients with HD), 152 patients were analyzable (90 patients with NHL and 62 patients with HD). Of the remaining 22 patients, 17 (12 with NHL and 5 with HD) expired during the study period before adequate follow-up data became available, and five patients were lost to follow up (4 with NHL and 1 with HD). There were 104 males (68 with NHL and 36 with HD) and 48 females (22 with NHL and 26 with HD). Patients with HD had an age range of 17-70 years with a mean of  $35 \pm 14.5$  (mean  $\pm$  SD). Patients with NHL had an age range of 15-81 years with a mean of  $44 \pm 14.7$  (mean  $\pm$  SD). There were 1, 9, 46, and 34 NHL patients with stage I, II, III, and IV, respectively, and 0, 5, 32, and 25 HD patients with stage I, II, III, IV, respectively.

### Results of TST

Of the 152 analyzable patients, 50 patients (33%) tested positive to the tuberculin skin test and 102 patients (67%) tested negative. Of the 90 patients with NHL, 37 patients (41%) tested positive and 53 patients (59%) tested negative. Of the 62 patients with HD, 13 patients (21%) tested positive and 49 patients (79%) tested negative.

### Follow-up Data

Most patients (70%) completed their treatment within six months; 20% and 10% of the study patients completed their treatment within eight and ten months, respectively. A total of 39 patients (28 with NHL and 11 with HD) had to be given further therapy after the completion of their first-line regimen because of residual or recurrent diseases during the follow-up period. None of the 152 analyzable patients had any clinical or microbiological evidence of TB reactivation or re-

infection during the study period. In addition, none of the 17 patients who expired during the study period had evidence of TB during their follow-up period. The causes of death were progressive disease (11 patients), sepsis secondary to neutropenia (5 patients), and acute myocardial infarction (1 patient).

### DISCUSSION

The true incidence of TB complicating LPD is unknown. Available literature suggests a higher prevalence of the disease in patients with LPD than in the general population. Most studies, however, originate from retrospective estimations of the frequency of LPD among other cancers in patients diagnosed to have both cancer and TB at some stage during their illness. Kaplan and associates published the largest of these studies in 1974<sup>[7]</sup>. In their extensive review, they identified 201 cases of TB occurring in cancer patients treated at the Sloan-Kettering Cancer Center during the period 1950-1971. TB was found to be most prevalent in patients with HD (96/100,000 cancer cases), followed by patients with lung cancer (92/100,000 cancer cases), while patients with NHL come third in frequency (83/100,000 cancer cases). A more recent retrospective report from the M.D. Anderson Cancer Center suggested a TB frequency of 209 per 100,000 LPD patients compared to a prevalence rate of 10 per 100,000 in the general populations during the study period (1989-1994)<sup>[8]</sup>.

The incidence of TB complicating LPD is expected to be higher in the third world countries as opposed to the industrialized world since TB is a common health problem in these countries. Saudi Arabia is by no means an exception. The incidence of TB in Saudi Arabia has been estimated to be 30 per 100,000 per year in the general population<sup>[10]</sup>. A radiologically active disease was reported to have a prevalence rate of 2.3% in the capital city, Riyadh<sup>[11]</sup>. In addition, Tuberculin positivity rate of 48.5-68.0% has been found in Saudi citizens between the ages of 45 and 64 years<sup>[12]</sup>. With these figures in mind, it was felt that Saudi Arabia would make an ideal place to evaluate the incidence of TB occurring in LPD patients receiving cytotoxic chemotherapy. If the incidence of TB in patients with LPD was 20-40 times that in the general populations, as has been suggested<sup>[7,8,9,13]</sup>, an annual incidence of 600-1200 per 100,000 (0.6-1.2%) patients would be expected in our series. Furthermore, during the two-year study period, an incidence of 1200-2400 per 100,000 (1.2-2.4%) LPD patients would be expected. None of the 152 patients in the current study showed clinical or radiological evidence of TB reactivation over the two-year follow-up period, despite the lack of INH chemoprophylaxis. While this finding does not

define the actual incidence of TB in LPD patients, it does suggest that the annual incidence of TB in LPD patients could be less than 20 times its incidence in the general population. Furthermore, the actual incidence is possibly less than 300 per 100,000 (0.3%) LPD patients (i.e., less than 10 times the incidence in the general population).

Unless the difference in the incidence of TB in our patients and the estimated incidence in the retrospective studies occurred as a result of chance alone, two possible explanations exist. First, the frequency of TB in LPD could be historically overestimated by the nature of reported studies. Second, the incidence of TB complicating LPD is actually falling. The first explanation seems, however, the more likely.

The results of the current study do not permit any conclusion on the predictive value of the TST reaction for the risk of TB reactivation as none of our patients, whether tuberculin-positive or tuberculin-negative, developed any evidence of TB. Despite the lack of supporting data, Kaplan and coworkers recommended early TST in all LPD patients, and isoniazid chemoprophylaxis for all patients with positive responses who have radiological evidence of previous TB, especially if they are to be treated with immunosuppressive chemotherapy<sup>[7]</sup>. Most recent guidelines for initiating isoniazid chemoprophylaxis for patients at increased risk are essentially based on the presence of a positive TST<sup>[5]</sup>. Patients with LPD are classified as moderate-risk patients who should receive chemoprophylaxis if they develop at least a 10 mm positive TST reaction<sup>[5]</sup>. Although these recommendations are practical, they may not be applicable to a substantial number of LPD patients who may react negatively to the TST despite prior exposure to TB. This is particularly true for patients with advanced diseases in whom gross impairment of the cell-mediated immunity has taken place<sup>[2,4]</sup>. Corticosteroids and cytotoxic immunosuppressive agents, which are the cornerstones of LPD therapy, are additional risk factors for TB reactivation<sup>[13]</sup>. It is, therefore, necessary to establish specific guidelines for TB chemoprophylaxis for patients in whom a false-negative TST is possible due to impaired cellular immunity.

None of our patients was put on isoniazid chemoprophylaxis regardless of the TST reaction. Based on our estimated annual incidence of TB (less than 0.3% LPD patients), isoniazid can not be routinely recommended for patients lacking objective evidence of prior TB other than a positive TST. This recommendation is further supported by the fact that most of our patients were older than 35 years of age; the age limit beyond which significant isoniazid-induced hepatotoxicity may occur<sup>[14-16]</sup>.

The value of high clinical suspicion, early diagnosis, and treatment can not, however, be overemphasized if chemoprophylaxis is withheld.

In summary, although the exact incidence of TB in patients with LPD is still not determined, the results of this study suggest a lesser frequency than historically stated. Larger multi-center studies, with an adequate number of patients, are required to better define the actual incidence of the disease in patients with lymphoproliferative disorders. Guidelines for chemoprophylaxis based on criteria other than the tuberculin skin test are required for this group of patients.

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