

THE PREVALENCE OF TB INFECTION AND DISEASE AMONG CHILDREN WITH ACUTE LEUKEMIA

Ma. Ysabel Lesaca-Medina, MD* and Cecilia Maramba-Lazarte, MD*

ABSTRACT

Objective: Immunocompromised patients, such as those diagnosed with leukemia and are on chemotherapy, are at increased risk of developing tuberculosis (TB). This study aims to determine the prevalence of TB infection and disease among children with acute leukemia on maintenance phase of chemotherapy.

Methodology: The study was conducted at the Philippine General Hospital. Patients included were children aged one to 18 years, with Acute Leukemia (ALL or AML) while on maintenance chemotherapy or at least one year from the last dose of chemotherapy. Chart reviews, interviews and physical examinations were performed. Patients were then screened with tuberculin test, Candida and Tetanus antigen to determine TB infection rates and presence of anergy. Chest x-rays were performed when necessary. The prevalence of TB infection and TB disease was then determined.

Results: A total of 29 patients were included in the study. Forty five percent (13 patients) had TB infection. But none of the patients proved to have active TB disease. No demographic factors correlated with either result. Anergy was present in only one patient.

Conclusion: There was a high rate of TB infection but a low rate of TB disease in this population of patients. Tuberculin testing remains a useful test in this population, as indicated by the low rate of anergy in this study. Annual tuberculin skin testing is recommended for patients with continuous exposure to TB and isoniazid preventive _____

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*Philippine General Hospital

therapy should be considered for these patients who are recent converters. A follow-up study should be done for this population to determine their TB status thru time. Larger sample studies involving several institutions to determine prevalence of TB infection and disease should be performed. To explain the low rate of

TB disease in this population, investigations into possible antimycobacterial activities of chemotherapeutic drugs should be looked into.

INTRODUCTION

The Philippines is a developing country where tuberculosis (TB) remains a major health problem. In the Philippines, the prevalence of pulmonary TB was 42 to 58.2 / 1000 population. The tuberculosis mortality rate was 6.1 per 1000.^{1,2}

Immunocompromised patients, such as those diagnosed with malignancies and receiving chemotherapy, are at even higher risk of developing TB. Furthermore, patients on chemotherapy often spend prolonged periods of time together in health-care facilities; this increases the potential for TB transmission. To successfully limit the spread of TB, timely identification and treatment of high-risk populations is essential. If infection is proven by a positive tuberculin skin test, preventive therapy should be started. It has been documented that there was a 50% to 70% decrease in the risk of developing TB among patients who received prophylaxis with INH as compared to controls.^{3,4}

This study sought to determine the prevalence of TB infection and disease among children with acute leukemia.

OBJECTIVE

This study aims to determine the prevalence of TB infection and disease among children with acute leukemia on the maintenance phase of chemotherapy.

MATERIALS AND METHODS

Study Setting

The study was conducted at the outpatient clinic of the Pediatric Oncology Section of a tertiary care state university hospital over the period of January to June 2006.

Study Population

Inclusion criteria

To be included in the study, the patient must satisfy all of the criteria listed below:

1. One month to 18 years of age;
2. Diagnosed with either Acute Lymphoblastic Leukemia or Acute Myelocytic Leukemia; and
3. Still receiving monthly maintenance chemotherapy, or at least one year from their last dose of induction chemotherapy (rationale for one year lag: in the majority of patients, T cell function recovers after 12 months from last dose of chemotherapy).

Exclusion criteria

If the patient had any of the following criteria listed below he/she would be excluded:

1. Active viral infection (measles, mumps, chicken pox, HIV);
2. Severe bacterial infection;
3. Recent live virus vaccination (within six months);
4. Chronic renal failure;
5. Failure to keep chemotherapy appointments (>1 week delay on more than 1 occasion); and
6. prior history of TB disease.

Chart Review, History and Physical Examination

The patients' charts were reviewed for patient's age, sex, prior TB history, type of leukemia, number of months on maintenance chemotherapy, failure to keep chemotherapy appointments, and frequency of infections. A brief interview was carried out to obtain further information on living conditions, exposure to smokers/dust/gas, regular intake of multivitamins, TB history/exposure, BCG vaccination, recent live virus vaccine and presence of other known immunodeficiency states. Physical examination was carried out to assess nutritional status and detect any active viral infection (measles, mumps, chicken pox, HIV), severe bacterial infection, chronic renal failure, and signs of TB infection. Case reports were filled out by the investigator accordingly.

Tuberculin and Anergy Testing

Tuberculin and anergy testing were performed on each subject simultaneously. The

senior allergy fellow-in-training of the hospital performed the skin tests, and read and interpreted the results. Patients were tested with tuberculin using the Mantoux technique with 0.1 mL (5 tuberculin units) of purified protein derivative (PPD) injected intradermally into the volar surface of the forearm. Areas of skin with scars, lesions or visible veins that might interfere with test interpretation were avoided by a minimum of 30 mm. Tuberculin positivity was defined as an induration of ≥ 5 mm, since the patient belonged to a high risk population.

Anergy testing was performed using 0.1 mL each of (1) *Candida albicans* antigen (2,000 units/mL); and (2) tetanus toxoid (550,000 units/mL). Antigens were injected through a similar technique separated by 30 mm of skin. Implantation by intradermal injection using a standard 26 gauge one-mL beveled needle and plastic syringe was considered correctly done only if a six-to-ten mm wheal was observed at the injection site. All injections were recorded on the patient's data sheet. Anergy is defined as ≤ 2 mm induration to *Candida* and/or tetanus antigen. A response of > 2 mm to any antigen was considered an intact cutaneous delayed-type hypersensitivity response; and the patient was considered to be non-nergic.

Skin tests (tuberculin and anergy panel) were interpreted after 48 hours by measuring the maximum diameter of induration using the ballpoint pen method. Skin tests were read by both the senior allergy fellow-in-training and by a junior allergy fellow-in-training.

Further investigations to determine disease status

Patients with a positive tuberculin test and/or with signs and symptoms of tuberculous disease underwent chest x-ray. The clinical history—including history of exposure to TB, signs and symptoms of TB, tuberculin test and chest x-ray results, were then assessed to determine presence of active TB disease. No sputum examination could be done as none of the subjects had a productive cough. Subjects with active TB disease were started on appropriate Anti-TB regimen. Patients with a positive tuberculin skin test, but without TB disease, were started on prophylactic INH therapy as recommended: 10-20 mg/kg once daily

(maximum 300 mg) or 20-40 mg/kg twice weekly (max 900 mg), x six-to-nine months.⁸ Those with signs and symptoms of TB, but without TB disease documented on chest x-ray, were followed-up closely.

Chi-square test was performed to determine the association between PPD positivity and risk factors of patients.

RESULTS

At the time of the study, there were 47 patients at the Pediatric Oncology Outpatient clinic. The following patients were excluded: four patients had a previous history of active TB; two patients had relapse of their disease; and 10 patients failed to keep chemotherapy appointments. Of the 31 patients interviewed and eligible for the study, two were later excluded for failure to return for the skin test; 29 patients, thus, went on to participate in the research study.

Population Profile

The patients' ages ranged from three to 18 years old: eight were less than six years old; 12 were in the six to ten years old group; and nine were ten to 18 years of age. 26 had Acute Lymphoblastic leukemia (ALL) and three had Acute Myelocytic Leukemia (AML). There was a preponderance of male patients.

With regard to duration of maintenance chemotherapy received: four patients had received treatment for one to two months; another four were on their 3rd to 6th month of treatment; six had completed 7 to 12 months of treatment; and seven had received more than 12 months of chemotherapy. Six more patients were already in remission, which meant that they had completed the two-and-a-half to three years of required maintenance chemotherapy.

All patients received BCG vaccine during infancy. Only six had significant exposure to a patient diagnosed with TB. Four had symptoms suspicious for TB. All had good appetite and received daily multivitamins.

Table 1. Demographic profile of Children with Acute Leukemia

Demographic Characteristics	Number	Percent
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Age (in years)		
≤ 5	8	27.6
6 – 9 years	12	41.4
≥ 10 years	9	31.0
Sex		
Male	18	62.1
Female	11	37.9

Incidence of Tuberculosis Infection

Overall, 13 patients (45%) had positive tuberculin skin tests. Among the 16 patients who had negative tuberculin skin tests, however, only one was anergic; whether said patient was not infected with TB could not be determined as of the time of this writing.

Table 2. Characteristics of Children with Acute Leukemia

Medical History	Number	Percent
Type of Leukemia		
Acute Lymphoblastic	26	89.7
Acute Myeloblastic	3	10.3
Maintenance chemo received (in months)		
1-2	4	13.8
3-6	4	13.8
7-12	8	27.6
>12	7	24.1
In remission (<1 year)	6	20.7
House / Living Area		
Crowded	5	17.9
Not Crowded	23	82.1
Chronic exposure to dust/gas/fumes		
Yes	11	39.3
No	17	60.7
Frequent infections (other than TB)		
With	26	92.9
Without	2	7.1
TB exposure		
Yes	6	21.4
No	22	78.6
Symptoms of TB at time of evaluation		
Negative	24	85.7
Positive	4	14.3
Regular intake of multivitamins		
Yes	27	96.4
No	1	3.6
Wasting		
Normal	28	93.1
Mild	1	3.4
Moderate	0	3.4
Stunting		
Normal	27	93.1

Mild	1	3.4
Moderate	1	3.4
Result of TB skin test (PPD)		
Negative	16	55.2
Positive	13	44.8

Tuberculin Test and relation with patient variables

Sex and Age

There was a slight predominance of males in the positive PPD group. Half of the male patients tested positive, while only 31% of the female subjects were PPD positive. Tuberculin-positive patients were equally distributed among all age groups. More or less, one third of the PPD-positive reactors belonged to each age group. Analyzing each age group, one half of each age group was positive reactors. An exception was the six-to-nine year old group, in which there were more non-reactors (63%) than reactors.

Type of Leukemia and Number of Months on Maintenance Chemotherapy

Forty-eight percent of patients with ALL tested positive for TB infection. Only one of the three subjects with AML tested positive. None of the patients who had received two months or less of maintenance chemotherapy was tuberculin test positive. But for patients who had received seven months or more of maintenance chemotherapy, a directly-proportional relation was noted between months of chemotherapy received and percentage of patients who tested positive for the TB skin test. The largest percentage of patients who were tuberculin reactors (67%) was noted in the group, which had already completed three years of chemotherapy.

Using the chi-square test, no significant relation was noted between positive PPD reaction and among the following factors: frequent infections, crowded living conditions, exposure to dust/smoke, MVI intake, TB exposure, BCG vaccine, wasting and stunting.

Active Tuberculous Disease

Further evaluation with a chest x-ray was recommended for the 13 patients who yielded positive tuberculin skin tests; two patients had symptoms of tuberculosis and one patient was anergic. However, only the 13 patients with positive TST had complied, as of the time of

this writing. All 13 had no significant chest findings on radiograph. We therefore have no proven case of TB disease.

Table 3. Tuberculin (PPD) skin test positivity of Children with Acute Leukemia

No. of patients N=29	No. of patients	Percent
(+) PPD N = 13	13	45%
(-) PPD N = 16	16	55%

Status of Anergy in Children with Leukemia

Only one patient proved to be anergic; testing negative to all three antigens (see Table 4). Among all subjects, reactivity to either Candida or Tetanus was noted in 28 (96.5%) patients; only two were not reactive to tetanus, while seven did not react to Candida.

Table 4. Status of Anergy and PPD Positivity among Children with Acute Leukemia

PPD positivity	No. of patients N=29	Anergy	No anergy
(+) PPD	13	0 (0)	13(45)
(-) PPD	16	1 (3)	15(52)

Table 5. Demographic and other patient factors correlated with PPD (*anergic patient excluded*)

Variable		PPD (+) N=13 (%)	PPD (-) N=15 (%)	Total
Age	≤ 5	4 (50)	4 (50)	8
	6-10	4 (36)	7 (64)	11
	>1	5 (56)	4 (44)	9
Sex	Male	9 (53)	8 (47)	17
	Female	4 (36)	7 (64)	11
Type of leukemia	ALL	12 (48)	13 (52)	25
	AML	1 (33)	2 (67)	3
No. of months of maintenance chemotherapy received	1-2 months	0	4 (100)	4
	3-6 months	3 (75)	1 (25)	4
	7-12 months	2 (33)	4 (67)	6
	> 12	3 (42)	4 (57)	7

	<i>months</i>			
	<i>In remission (<1 year)</i>	5 (71)	2 (29)	7
Frequent infections	<i>Yes</i>	1 (50)	1 (50)	2
	<i>No</i>	12 (46)	14 (54)	26
Crowded living conditions	<i>Yes</i>	2 (40)	3 (60)	5
	<i>No</i>	11 (48)	12 (52)	23
Chronic exposure to dust/ gas/ fumes	<i>Yes</i>	3 (27)	8 (73)	11
	<i>No</i>	10 (59)	7 (41)	17
Regular MVI intake	<i>Yes</i>	13 (46)	15 (54)	28
	<i>No</i>	0	0	0
TB exposure	<i>Yes</i>	1 (17)	5 (83)	6
	<i>No</i>	12 (55)	10 (45)	22
BCG vaccine given	<i>Yes</i>	13 (46)	15 (54)	28
	<i>No</i>	0	0	0
Wasting	<i>None</i>	12 (44)	15 (56)	27
	<i>Mild</i>	1 (100)	0	1

Table 6. Demographic and other patient factors correlated with PPD (*Anergic patient excluded*)

No. of patients N = 28	With active TB	Without active TB
(+) PPD N=13	0	13
(-) PPD N=16	0	16

DISCUSSION

TB infection / disease prevalence among patients with leukemia

At present, there is no study on the prevalence of TB infection or disease in this population. There was, however, a study done on TB infection in another population of immunocompromised individuals – chronic renal patients. They concluded that there was a high prevalence of TB in this population of patients—19% were diagnosed to have TB infection.⁵ There was also a high anergy rate in their subjects (40%). Another study was done on HIV seropositive patients in which a higher rate of anergy was found at 63%; but none tested positive for TB on skin test, which is probably because of anergy.⁶ A similar study to determine the prevalence of TB infection among children with Type 1 Diabetes mellitus was done in an institution; this revealed a very high prevalence rate of 56% (14 of 25 subjects). The control group in this study, consisting of non-

diabetic siblings of these patients, showed a 43% prevalence of TB infection.

Similarly, immunocompromised populations of patients (e.g. chronic renal patients) were recommended to undergo annual tuberculin and anergy testing. But for leukemic patients, no recommendation for TB testing or Isoniazid prophylaxis was given. To successfully battle the spread of TB, timely identification and treatment of high risk populations are important. Should this study prove a high prevalence of TB infection and/or disease, then routine annual tuberculin testing and prophylaxis will be recommended.

In literature, there were opposing views on whether leukemia was a risk factor for the development of TB. Miller stated that leukemia was a predisposing factor for mycobacterial infections.⁹ According to other experts, mycobacterial infections were uncommon in children with cancer. There had only been sporadic reports of mycobacterial infection in non-HIV immunocompromised children.^{9,10} Pizzo agreed that mycobacterial infections were uncommon in children with cancer.¹²

Therefore, there seems to be some basis for saying that TB will be more prevalent in children with leukemia: the clinical expression of tuberculosis is intimately related to the immune status of the host.

Cellular immune deficiency can lead to infections with intracellular pathogens (CMV, Herpes Simplex, HIV, Candida, Aspergillus, Pneumocystis jirovecii and Mycobacterium). T cells elaborate an array of cytokines capable of activating macrophage bacterial activities. It is this cell-mediated response to infection with Mycobacterium tuberculosis that controls the spread of primary infection. Factors that compromised this cell-mediated immunity such as AIDS, therapy with steroids or chemotherapeutic drugs, and malignancy (such as leukemia) may permit the infection to spread and cause symptomatic disease. Because of this, TB in immunocompromised patients is most of the times already in advanced stages before they are recognized by the physician.¹³

We, therefore, hypothesized that we would find a high prevalence of TB infection and disease in this patient population. True enough,

this study documented a high TB infection rate at 45%. If the patient who was anergic from the total number studied was excluded, the calculated tuberculin positivity rate was 46.4%. And if the four patients excluded from the study for a positive TB history were added to our results, the prevalence of TB infection increased to 53.1%, 17 of 32 non-anergic leukemia patients. This was 2.8 times more than the 19% prevalence of TB infection found in chronic renal patients.⁵ But this rate was very similar to the 56% prevalence seen in Filipino Type 1 DM children.⁷ We noted, however, that this was significantly lower than the TB infection rate among children living in households of Filipino patients with TB. A 69.2% prevalence of latent TB infection was reported in this study by Salazar-Vergara et al.¹⁴

Though TB infection rate was high, surprisingly, the prevalence of TB disease was quite low in this population. All patients in the study population had no evidence of TB disease. There were still three, however, who failed to return for further workup. If we were to include in our analysis the four patients excluded because of a history of tuberculous disease, the prevalence rate would have been 12%. This was still higher than the prevalence rate in the general population estimated at 6%. However, these four patients contracted TB even before they were diagnosed to have leukemia. It is thus not the leukemia or the chemotherapy that predisposed them to TB.

Our study therefore supports the view of Pizzo and others that mycobacterial disease is uncommon in children with leukemia. At present there are no theories to explain this phenomenon. We can only propose a few:

a. *Chemotherapy given to these patients is also an effective drug against the mycobacterium.*

Our patients on maintenance receive weekly doses of Methotrexate (20 mg/m²); monthly doses of Prednisone (40 mg/m²/day x 5 days) and Vincristine (1.5 mg/m²); and daily doses of 6-mercaptopurine (75 mg/m²/day).

On literature search in 2001, a new class of potent antimycobacterial agents had been developed: 9-sulfonylated/ sulfenylated – 6 mercaptopurines, prepared by reaction of 6-

mercaptopurine with sulfonyl/sulfenyl halides. They possessed an MIC value against *Mycobacterium tuberculosis* in the range of 0.39-3.39 ug/ml, as well as, appreciable activity against *Mycobacterium avium*. Furthermore, a compound of this small series exhibited good activity (MIC under 1 ug/ml) against several drug-resistant strains of *M. tuberculosis*.¹⁵ It could be that the daily dose of 6-mercaptopurine taken by our patients caused a protective effect against TB.

In addition, there was a case report of a 26-year old man with endobronchial TB. He initially deteriorated on standard antituberculosis drugs, but rapidly improved with the addition of corticosteroids. It was thought that steroids helped because the pathogenesis of this disease was a hypersensitivity reaction to tuberculoprotein.¹⁶

Methotrexate, on the other hand, was thought to predispose to TB. There was a report of late reactivation of spinal tuberculosis by low dose methotrexate therapy in a patient with rheumatoid arthritis.¹⁷ Genesteir, et al, reported that methotrexate's immunosuppressive properties were secondary to apoptosis and clonal deletion of activated peripheral T cells.¹⁸ Evidently, however, the low dose that our patients received did not cause an increased risk for TB disease.

We encountered no report on vincristine or prednisone in relation to risk of acquiring TB.

b. *Despite active disease, manifestations are not immediately apparent because of a possible lack of cellular-mediated response.*

In HIV patients for instance, the clinical presentation of TB may be altered and radiographic features may be changed or absent in approximate proportion to the individual's degree of immunosuppression.¹⁹

However, as proven in this study, cellular-mediated immune response was intact in most of our patients. Thus, though probably true for HIV patients, this theory may not be valid in this study population.

Relationship of patient variables with TB infection/disease

There was no significant relationship between demographic factors, BCG vaccine, TB

exposure, living conditions or symptoms and either tuberculin reactivity or TB disease. At the five percent level of significance, the chi-square tests of association between PPD and the selected risk factors yielded insignificant results.

However, an increasing rate of infection can be noted as the number of months on chemotherapy also increased. This may be due to the increased risk of infection because of prolonged exposure to other patients in the facility.

Status of Anergy

Another significant finding in this study was the low rate of anergy in this patient population (one out of 29 patients). This proved false the popular belief that the majority of patients on chemotherapy are anergic. This would make TB skin testing a valid diagnostic tool in the evaluation of similar patients suspected to have TB infection or disease.

CONCLUSIONS

This study demonstrated both a high rate of TB infection (45%) and a low rate of TB disease (0%) among children with leukemia on maintenance chemotherapy. There was also a low rate of anergy among the subjects (one out of 29), which made the tuberculin skin test a valid diagnostic tool for TB in this population.

We would be cautious to extrapolate these findings to patients in other countries, as the Philippines is still endemic for TB. Other clinics should perform tuberculin testing and should work-up their patients to ascertain TB infection and disease rates specific to their populations.

The finding that TB disease was not prevalent in this population may make us complacent. However, we recommend that further studies be performed to validate this initial finding. Multi-institution studies enlisting a larger number of subjects should be done. Patients in this study should be followed up through time to document possible development of TB skin test conversion and/or TB disease. Studies to ascertain the activity of certain chemotherapy drugs against *Mycobacterium tuberculosis* should be proposed.

RECOMMENDATIONS

Physicians should still be vigilant to successfully combat the spread of TB in this

population. The high rate of TB infection in these subjects, coupled with the efficacy of INH prophylaxis, make the timely identification and treatment of latent tuberculosis essential.

Our recommendations are:

- a. Every patient with newly-diagnosed leukemia should be assessed for the presence of active TB disease. A physical examination that includes assessment of extrapulmonary sites of disease, such as lymph nodes and chest radiography, should be performed; and features of current or past TB sought. Patients with suspected active TB should have sputum or other appropriate specimens submitted for acid-fast bacilli (AFB) smear and culture.
- b. Except in those with a history of active TB or a well-documented, previous positive tuberculin skin test (TST), every leukemic patient should be given a TST with intermediate strength (five-TU) purified protein derivative by the Mantoux method Annual. Yearly tuberculin testing should be performed to detect recent converters in these patients especially if they have exposure.
- c. Unless specifically contraindicated, patients who: 1) have a positive TST (\geq 5mm of induration), 2) have not already been treated for TB infection, and 3) have test results excluding active TB, should be strongly encouraged to take preventive therapy. This preventive therapy is indicated even if the date of TST conversion cannot be determined.

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