Original Article

Role of Isoniazid Prophylaxis for Prevention of Tuberculosis in Haemopoietic Stem Cell Transplant Recipients

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Abstract

Objective: To evaluate the role of isoniazid prophylaxis in prevention of tuberculosis among allogeneic stem cell transplant recipients.

Methods: This study was conducted at Armed Forces Bone Marrow Transplant Center Rawalpindi, Pakistan from July 2001 to October 2003. Patients suffering from various haematological disorders undergoing allogeneic stem cell transplantation were included in the study. The demographic information, primary diagnoses and relevant investigations were recorded. Patients had negative tuberculin skin tests and chest X-Ray at pre-transplant assessment. First 25 patients (group I) did not receive isoniazid prophylaxis while the next 25 (group II) were given isoniazid in a dose of 5-10 mg/kg (maximum 300 mg/day). Isoniazid prophylaxis was started on day-1 and continued for 6 months post transplant. The patients developing tuberculosis were treated with rifampicin, ethambutol, isoniazid, and pyrazinamide during first 3 months followed by 2 drugs for a total duration of 12 months. Minimum follow up in group I and II was 783 and 403 days respectively.

Results: There was significant difference ($p<0.001$) in frequency of tuberculosis between two groups. In group I, four patients developed Tuberculosis (frequency 16%) whereas none of the patients in group II had the disease. Out of these four cases 3 had extrapulmonary disease. One patient died two weeks after the start of anti tuberculosis treatment while others successfully completed the treatment.

Conclusion: Tuberculosis in stem cell transplant recipients is an important opportunistic infection especially in areas of high disease prevalence like Pakistan. Isoniazid prophylaxis for 6 months is effective in preventing tuberculosis among this class of patients (JPMA 55:378;2005).

Introduction

Every year over eight million people in the world develop active tuberculosis[1] of whom 2 million die, most being in developing countries. Pakistan is ranked 8th in first 22 high burden countries in terms of estimated number of cases by WHO.[2]

Allogeneic stem cell transplantation (SCT) is associated with severe immunosuppression during which the recipient is susceptible to various opportunistic infections including tuberculosis (TB). Although TB in allogeneic SCT recipients is not a major challenge in developed countries but the situation is different in developing countries due to high prevalence of disease in general population. Some transplant centers in areas of high TB prevalence are using TB chemoprophylaxis. Four of the first 25 SCT recipients at our center developed TB following which we decided to start TB chemoprophylaxis in SCT recipients. This study evaluates the role of isoniazid (INH) prophylaxis in prevention of TB among allogeneic SCT recipients.

Patients and Methods

A non-randomized, Quasi Experimental study was carried out at Armed Forces Bone Marrow Transplant Center Rawalpindi, Pakistan from July 2001 to October 2003.

Patients suffering from various haematological disorders undergoing allogeneic SCT at our center were included in the study. The demographic information, primary diagnoses and relevant investigations were recorded. The patients had negative tuberculin skin tests (Mantoux) and chest X-Ray at pre-transplant assessment. Standard isolation facilities in the form of HEPA filters, positive air pressure and barrier nursing were applied during peri

transplant period. Prophylactic regimens for bacteria, fungi and viruses included oral ciprofloxacin, fluconazole, and acyclovir. Ciprofloxacin was stopped after neutrophil recovery of >1.0 x 10^9/l while other drugs were continued for a variable period of time. Pneumocystis carinii prophylaxis with cotrimoxazole was started after neutrophil recovery of >1.0 x 10^9/l and was continued till cessation of immunosuppressive therapy. First 25 patients (group I) did not receive INH prophylaxis while the next 25 (group II) were given INH in a dose of 5-10 mg/kg (maximum 300 mg/day). INH prophylaxis was started on day-1 and continued for 6 months post transplant.

The conditioning regimens used during SCT include anti thymocyte globulin (ATG) plus cyclosphosphamide (Cy) for aplastic anaemia, busulphan (Bu) plus cyclosphosphamide for beta thalassaemia, and standard or mini Bu/Cy for haematological malignancies. The patients received cyclosporin plus prednisolone with or without methotrexate as graft versus host disease (GVHD) prophylaxis for 6-12 months. Cyclosporin was given to maintain trough levels between 200-300 ng/ml. Prednisolone was started on day +7 in a dose of 0.5 mg/kg and finally tapered off by day +90. After discharge from hospital the patients were followed up in OPD till the time of death or for at least 225 days post transplant.

Patients with clinical manifestations suggesting TB were thoroughly investigated, and diagnosis of TB was based on one or more of the following criteria: (a) Demonstration of acid fast bacilli (AFB) in the clinical material taken from the involved site and/or growth of mycobacterium TB in culture specimens. (b) Demonstration of Mycobacterial tuberculosis antigens by PCR in clinical materials (Roche Molecular System Branchburg, N.J.). (c) Demonstration of granulomatous inflammation on histopathological examination of biopsy specimens. (d) Therapeutic response plus fluid examination showing high protein and lymphocytosis, or radiological findings consistent with tuberculosis on chest X-ray, MRI and CT scan.

The patients who developed TB were treated with rifampicin, ethambutol, INH, and pyrazinamide during first 3 months followed by 2 drugs for a total duration of 12 months. Assessment of possible nosocomial transmission was made by reviewing hospital records for admission and discharge dates and room assignment in the hospital. Cases of open tuberculosis were isolated to avoid nosocomial transmission. The visitors and health care workers used surgical masks while attending these patients.

Response to anti tuberculosis treatment was defined as disappearance of all the presenting features along with resolution of radiological and laboratory evidence of the disease.

Statistical Package for Social Sciences (SPSS) computer software was used to enter and analyze data. The chi-square test was applied to find out significant difference among the groups with and without INH prophylaxis.

Results

During the study period, 50 patients (25 in each group) suffering from different haematological disorders received allogeneic SCT. Table 1 shows the demographic information, primary diagnoses, immunosuppressive drugs used for conditioning and GVHD prophylaxis in both groups. Frequency of TB was 16% (4/25) in group I while none of the patients in group II developed the disease. There was significant difference ($p<0.001$) in frequency of TB between the two groups.

Table 1. Characteristics of Allogeneic SCT Recipients with and without INH Prophylaxis (n=50).

Features	Group I (n=25)	Group II (n=25)
Age in years:		
Median	7	13
Range	2-37	1.3-40
Sex:		
Male	19	17
Female	6	8
Disease:		
thalassaemia	10	8
Aplastic Anaemia	8	14
Chronic myeloid leukemia	5	3
Miscellaneous	2	-
Conditioning:		
$Bu_{14}Cy$	10	7
Cy/ATG	8	14
Big Bu/Cy	3	1
Mini Bu/Cy	1	1
Others	3	2
GVHD Prophylaxis:		
CSA + Pred	16	18
CSA + Pred + Mtx	9	7
Acute GVHD:	**11**	**7**
Stage I	3	4
Stage II	5	2
Stage III	2	1
Stage IV	1	-
Chronic GVHD:	**7**	**3**
Local	5	2
Extensive	2	1
Number of TB cases	4	Nil
Follow up (days)		
Median	868	558
Minimum	783	403
Maximum	1213	758

Group 1= No INH prophylaxis; Group 2= INH prophylaxis

Bu:Busulphan; ATG:Anti thymocyte globulin; Cy:Cyclophosphamide; CSA:Cyclosporin A; Pred: Prednisolone; GVHD:Graft versus host disease; Bu14/Cy:Bu 14 mg/kg, Cy 200 mg/Kg; Cy/ATG:Cy 200 mg/Kg, ATG 45 mg/Kg; Big Bu/Cy:Bu 16 mg/Kg, Cy 200 mg/Kg; Mini Bu/Cy:Bu 16 mg/Kg, Cy 120 mg/Kg

The characteristics of the patients who developed TB are given in table 2. Patients 1 and 2 received cyclosphosphamide (200 mg/kg), anti thymocyte globulin (45 mg/kg), cyclosporin and prednisolone with methotrexate for conditioning and GVHD prophylaxis respectively.

Patient 1 developed grade II GVHD that was controlled by increasing the dose of prednisolone to 1 mg/kg for 2 weeks. This patient also developed chronic GVHD of oral mucosa and cyclosporin was continued till 15 months post transplant in this case. Patient 3 was given mini Bu/Cy (Busulphan 16 mg/kg, cyclophosphamide 120 mg/kg) while patient 4 received busulphan 14 mg/kg and cyclophosphamide 200 mg/kg during conditioning. Both of these were given cyclosporin with prednisolone for GVHD prophylaxis. Patients 3 and 4 developed mild acute GVHD (grade I) that settled without any therapeutic intervention. Patient 1 developed TB when he was off all immunosuppressive therapy while other patients were on GVHD prophylaxis at the time of diagnosis.

Table 2. Demographic and Clinical Features of Allogeneic SCT Recipients with Tuberculosis.

Features	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Male	Female	Male
Age (years)	35	19	37	5.5
Disease	Aplastic anaemia	Aplastic anaemia	Chronic myeloid leukemia	Beta thalassaemia
Acute GVHD (Grade)	Yes (II)	No	Yes (I)	Yes (I)
Chronic GVHD (Grade)	Yes (Local)	No	No	No
Post BMT day of diagnosis	525	49	42	112

GVHD= Graft versus host disease; BMT:Bone marrow transplant.

Site of involvement by TB, methods used to establish diagnosis, treatment and response are given in table 3. Patient 1 developed pulmonary TB while other 3 had extrapulmonary disease. All the patients were given four anti TB drugs for initial three months followed by two drugs for a total duration of one year. Patient 4 died two weeks after the start of anti tuberculosis treatment while others successfully completed the therapy.

Table 3. Mode of Diagnosis, Therapy and Outcome of Patients with Tuberculosis.

Features	Patient 1	Patient 2	Patient 3	Patient 4
Site of involvement	Lung	Pericardium	Pleura	Lymph node
Diagnostic methods:				
CXR	Nodulo-striate lesions	Pericardial effusion	Pleural effusion	Mediastinal widening
Biopsy	-	-	-	Granulomatous lymphadenitis
Fluid cytology	-	Positive	Positive	-
AFB culture	-	-	-	M tuberculosis
TB-PCR on fluid	-	Positive	Positive	-
Drugs given (Duration)	RHMZ (3 months) RH (9 months)	RHMZ (3 months) RH (9 months)	RHMZ (3 months) RH (9 months)	RHMZ (2 weeks) -
Outcome	Remission	Remission	Remission	Died within two weeks

CXR:Chest X-ray; AFB:Acid fast bacillus; PCR: polymerase chain reaction; R: Rifampicin; H: Isoniazid; M: Ethambutol; Z:Pyrazinamide.

Note: Positive fluid cytology means increased proteins and lymphocytosis.

Discussion

The incidence of TB has increased dramatically over the past few years after decades of decline and now every third person in the world is believed to be infected with TB.[3] The prevalence of tuberculosis in Pakistan is more than 1% with 0.26 million new cases occurring every year.[4] One of the reasons for recent upsurge in TB cases is due to increase in number and prolonged survival of immunocompromised patients like HIV cases and SCT recipients. After being infected with Mycobacteria the immunocompetent patients have 10% chance of developing overt TB whereas in immunocompromised this risk increases to as high as 50%.[5]

The first case of TB in SCT recipient was reported in 1984 from MD Anderson Cancer Center[6] and since then 52 cases of TB have been added to the series.[7] In this study 16% (4/25) SCT recipients developed TB as compared to the incidence of around 1% in general population[4] indicating quite high frequency of the disease among this category of patients. Diverse figures on frequency of TB in SCT recipients have been reported from various countries mainly reflecting the prevalence of the disease in general population in that area. In USA the incidence of tuberculosis in BMT recipients is less than 1%.[7] Another study has described 10 cases of TB in 5000 SCT recipients[8] with a frequency of 0.2% while Martino et al have reported 2 cases of TB among 355 SCT recipients (frequency of 0.56%).[9] Yuen and Woo[10] have described a frequency of 0.4% among 13881 BMT recipients. The maximum cases in their series were from Spain and Hong Kong, the areas where TB is more prevalent in general population. Recent reports from SCT centers in developing countries have shown a high frequency of TB. Budak-Alpdogan et al[11] have reported that the incidence of TB may be as high as 40 times in allogeneic BMT than in general population. Similarly Ip et al[10] have reported 10 cases of TB in 183 bone marrow transplant recipients in Hong Kong. Although our figure is higher than reported in most of the studies but still is in agreement with high incidence of the disease in developing countries. Contrary to the published data from developing countries, a relatively low frequency (3 out of 217) of TB among BMT recipients has been reported from India.[12]

Chronic GVHD is reported to be a risk factor for the development of TB among SCT recipients.[8] In our study although the incidence of chronic GVHD was more in group I as compared with group II but the difference was not statistically significant (p=0.158). Moreover only one patient out of four TB cases received additional immunosuppressive treatment for GVHD.

Three out of 4 cases in our study developed extrapulmonary TB and this is in agreement with other studies in

in immunocompromised patients.[13,14] Keeping in mind the limitations of diagnostic methods[15-18], and the aggressive nature of disease in immunocompromised patients[3], some centers are following TB chemoprophylaxis. Our study has confirmed its importance since 4/25 cases in group I developed TB whereas none of SCT recipients developed TB in the group receiving INH prophylaxis. Statistical analysis revealed a highly significant difference of TB incidence between two groups ($p<0.001$).

There is no agreement on the number of drugs and optimum duration of treatment especially among the transplant recipients.[19] The overall response to treatment with the standard four-drug regimen for a longer duration has been satisfactory. We used rifampicin, ethambutol, INH, and pyrazinamide during first 3 months followed by 2 drugs for a total period of 12 months. One of the patients died soon after start of anti TB treatment while other 3 cases showed a satisfactory response.

INH has been the accepted drug for TB prophylaxis in immunocompetent as well as in HIV positive cases.[20] Multiple drug prophylaxis for TB is not more effective than prophylaxis with INH alone.[21] Moreover it is costly with increased chances of noncompliance and adverse reactions. INH prophylaxis given for duration of 6 months to one year is effective in preventing TB in immunocompromised patients.[22,23] Regimens of INH plus rifampicin for 3 months and rifampicin plus pyrazinamide for 2 months have been reported to be as effective as 12 months INH.[23]

It is concluded that TB is not a rare opportunistic infection in BMT recipients in Pakistan where the background prevalence of TB in the community is quite high. INH prophylaxis for 6 months is effective in preventing TB among this population of patients.

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