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Study of clinical characteristics, risk factors and outcomes for tuberculosis post allogeneic stem cell transplant: never count it out

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Jyotsna Kapoor, Sumeet Prakash Mirgh, Vishvdeep Khushoo, Pallavi Mehta, Rayaz Ahmed, Nitin Bansal, Dinesh Bhurani and Narendra Agrawal

Abstract

Background: Allogeneic stem cell transplant (AlloSCT) recipients remain at a higher risk of developing tuberculosis (TB), especially in endemic populations. We conducted a retrospective study to identify the incidence, clinical presentation, and risk factors for active TB among our alloSCT recipients.

Methods: Records of all patients transplanted between 1 January 2012 and 31 July 2020 were reviewed. Patients were followed up for outcome until 30 September 2020. None of the patients received prophylactic anti-tubercular drugs. Proven diagnosis of active TB was considered if *Mycobacterium tuberculosis* (MTB) was cultured from clinical samples or acid-fast bacilli (AFB) or MTB demonstrated on Ziehl-Neelsen (ZN) staining or histopathology or XPERT MTB, while probable diagnosis of TB was considered if histopathology findings were suggestive of caseation necrosis/epithelioid cell granulomas without any evidence of malignancy or lymphocyte rich exudative effusions (pleural/pericardial) without an alternative cause.

Results: Among 381 alloSCT recipients, 15 patients (3.9%) developed TB at median of 246 (74–279) days post AlloSCT, after being symptomatic for a median of 22 (7–60) days, amounting to a cumulative incidence of 4.9%. All patients were started on four-drug anti tubercular therapy, ATT [Rifampicin, Isoniazid, Ethambutol, Pyrazinamide (RHEZ)], of which five patients developed hepatotoxicity at a median of 12 days after start of ATT, leading to drug modification. At last follow up, TB was cured in 13 (86.67%) patients, one succumbed to disease relapse, while others are still on treatment. Age $\geqslant$ 30 years, immunosuppression for graft *versus* host disease (GvHD) $>$ 6 months, prior use of tyrosine kinase inhibitors (TKI) and chronic GvHD on univariate analysis and immunosuppression for GvHD $>$ 6 months on multivariate analysis were found to be associated with development of TB.

Conclusion: A high index of suspicion with timely workup and treatment of TB is the key in AlloSCT recipients, especially in endemic TB populations.

Keywords: allogeneic stem cell transplantation, chronic graft *versus* host disease, endemic population, immunosuppression, tuberculosis, tyrosine kinase inhibitors

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Correspondence to:
Narendra Agrawal
Department of Hematology and Bone Marrow Transplant Unit, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, Delhi 110085, India
narendra_ag1@rediffmail.com

Jyotsna Kapoor
Department of Hematology and Bone Marrow Transplant Unit, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, Delhi, India

Sumeet Prakash Mirgh
Adult Hematolymphoid and BMT Unit, Tata Memorial Hospital ACTREC, Navi Mumbai, India

Homi Bhabha National Institute, Mumbai, India

Vishvdeep Khushoo
Pallavi Mehta
Rayaz Ahmed
Department of Hematology and Bone Marrow Transplant Unit, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, Delhi, India

Nitin Bansal
Department of Infectious Diseases, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, Delhi, India

Dinesh Bhurani
Department of Hematology and Bone Marrow Transplant Unit, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, Delhi, India

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (MTB), remains an important cause of global health burden with an estimated global incidence of 10 million new cases and deaths of 1.5 million patients in 2018.[1] According to the World Health Organization (WHO), India is 1 of the 30 countries with a highest burden of TB, with an estimated 2.69 million new cases in 2018, thereby accounting for

more than one-fourth of the global incidence.[1] It has been estimated that 4 of 10 individuals living in India are infected with TB, of which the majority have latent tuberculosis infection (LTBI) rather than active TB disease.[1] LTBI may activate into active TB infection once the immunity of an individual declines.[2]

One of the high-risk groups for TB is allogeneic stem cell transplantation (AlloSCT) recipients, accounting for an incidence of TB, that is, 2–40% higher than the general population.[3,4] AlloSCTs performed for hematological malignancies, aplastic anemia, inherited genetic or metabolic disorders, and immunodeficiency disorders employ extreme iatrogenic immunosuppression, posing the threat of opportunistic infections not only during the peri-transplant, but also during receipt of immunosuppressive therapy for treatment of graft *versus* host disease (GvHD).[5]

Various studies have reported an incidence of active TB among alloSCT recipients ranging from 0.80% to 2.8% over the past decade.[5–9] Among the studies reported, clinical features of TB and the risk factors predicting TB infection have not been thoroughly described. We conducted a retrospective study to identify the incidence, clinical presentation, and risk factors for active TB amongst 381 patients post-alloSCT over a period of 8 years in an endemic population.

Methods

Patients

All consecutive patients who received AlloSCT from 1 January 2012 until 31 July 2020 were included in the study. Medical records were reviewed for demographic data, primary disease history, transplant details and TB infection details of all AlloSCT recipients. Patients were censored at second AlloSCT and were excluded from the study if there was co-infection with human immunodeficiency virus (HIV). The approval to conduct and publish the data was obtained from the institutional review board of our tertiary care cancer center.

Pre-transplant work up included radiological tests to rule out any active infection (including TB) or lung parenchymal/pleural disease. Considering the endemicity of our population, recipients were not screened for LTBI before proceeding with AlloSCT and not given any prophylactic treatment for TB infection.

HEPA-filtered rooms were used for treating AlloSCT recipients from the start of the conditioning regimen. GvHD prophylaxis for matched related donors comprised a calcineurin inhibitor with a short course of methotrexate (MTx), with the addition of anti-thymocyte globulin (ATG) for unrelated donors. All haploidentical AlloSCT recipients were given T-cell replete unmanipulated grafts, with post-transplant cyclophosphamide on day +3 and +4 (PTCy) followed by tacrolimus with or without mycophenolate mofetil (MMF) (from day+5) as GvHD prophylaxis. Patients were diagnosed with acute or chronic GvHD based on revised Seattle classification.[10,11] Suspected or confirmed cases of GvHD were started on systemic prednisolone and/or local/topical therapy for GvHD depending on the site involved; those refractory to steroids were initiated on second-line agents mostly MMF, etanercept, tyrosine kinase inhibitors (TKI) (imatinib and ruxolitinib) basiliximab, MTx, or rituximab.

None of our patients were on anti-bacterial prophylaxis. For prevention of pneumocystis-carinii pneumonia, cotrimoxazole prophylaxis was started after engraftment until discontinuation of immunosuppression. Acyclovir (400 mg thrice a day for adults, 5 mg/kg twice a day for children) was used for herpes simplex virus prophylaxis from day +1 until discontinuation of immunosuppression. All patients received antifungal prophylaxis with voriconazole/posaconazole, from start of conditioning until engraftment, during treatment of acute GvHD, and during active moderate–severe chronic GvHD. During remaining period, subjects were administered fluconazole (including pediatric) as primary antifungal prophylaxis until discontinuation of immunosuppression. CMV-DNA (cytomegalovirus deoxyribonucleic acid) was monitored weekly from engraftment until day 100 and during treatment of GvHD with steroids. Pre-emptive treatment with intravenous ganciclovir (5 mg/kg iv BD) was given for > 500 copies CMV-DNA for matched related transplants and for any detectable CMV copies for unrelated or haplo-identical transplants.

Diagnosis of TB infection

Patients presenting with unexplained weight loss, persistent low-grade fever without any alternate cause, cough with/without expectoration, unexplained breathlessness or any palpable lymphadenopathy were evaluated for infection. The diagnosis of active TB was considered "proven" if MTB was cultured from clinical samples or acid fast bacilli (AFB)/MTB demonstrated on Ziehl-Neelsen (ZN) staining or histopathology or XPERT MTB. It was considered "probable" when histopathology findings were suggestive of caseation necrosis/epithelioid cell granulomas without any evidence of malignancy, patients with pleuro-pericardial effusion that were lymphocyte-rich exudative fluid with/without high ADA levels ⩾40 U/l for pleural fluid and ⩾30 U/l for ascitic fluid] without any evidence for malignancy and had shown clinical improvement with ATT.

ATT consisted of 2 months of rifampin, isoniazid, ethambutol, and pyrazinamide (RHEZ), followed by isoniazid and rifampicin (and ethambutol for the patients in whom drug susceptibility is not done/not grown/not available) for the rest of the treatment period to complete a total of 9 months therapy. Treatment outcomes were defined in accordance to WHO guidelines for TB.[1]

Statistical analysis

The primary objective of our study was to determine the incidence and risk factors for active TB in our alloSCT population. Secondary objectives included assessment of survival outcomes [overall survival (OS) and disease-free survival (DFS)] of whole cohort. Patients were followed up for clinical outcomes until 30 September 2020.

OS and DFS were plotted using the Kaplan–Meier method and univariate comparisons were done using the log rank method. The cumulative incidences of TB disease were computed using Gray's competing risk method, where death without TB disease was considered as a competing risk event of TB disease. The cumulative incidence of non-relapse mortality (NRM) was computed using Gray's competing risk method, where relapses were considered as competing risk event. Normality of the data was determined using the Kolmogorov–Smirnov test. Categorical and continuous variables were analysed using a Pearson's chi square (χ^2) or Fisher's exact and Student's *t* test to determine the potential factors for TB disease. Multivariate analysis for categorical variables was done using a stepwise backward logistic regression method. A *p* value of less than 0.05 was considered statistically significant. All statistical analysis was done using the statistical package for social science software (SPSS 21, IBM SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, NY, USA), Graph Pad Prism Version 7.05 (trial version; GraphPad, San Diego, CA, USA) and NCSS2020, v20.0.3 (trial version).

Results

Overall AlloSCT recipients characteristics

During the study period, 381 patients underwent AlloSCT, of which two underwent a second alloSCT and were censored at the time of their second transplant. Median age of the cohort was 31 (1–66) years with a male:female ratio of 2:1. Matched related donors and peripheral blood was used as common donor and graft source for our alloSCT recipients, respectively. More than half of the patients were conditioned with myeloablative intensity regimens. Notably, 15 had a history of ATT in past before AlloSCT. Patient characteristics are shown in Table 1.

Clinical characteristics of cohort of AlloSCT patients with TB

Pre-transplant disease characteristics and prior treatment history. During the study period, 15 patients (3.9%) developed active TB, amounting to a cumulative incidence of 4.9%. The median age of the patients was 38 (16–57) years, with male:female ratio of 2:1. Of the 15 patients, 3 had comorbid conditions (diabetes mellitus = 1, hypertension = 1, and hypoparathyroidism = 1), while one patient had a co-infection with hepatitis B virus. None of these had past history of TB. Indication of AlloSCT was acute leukemia in seven (acute myeloid leukemia = 4, acute lymphoblastic leukemia = 3), MDS in one, MDS/MPN in one, MPN (including CML) in three, benign disorders (severe aplastic anemia) in two and lymphoma in one (mantle cell lymphoma). Patients were treated with median one (range: 1–3) line of prior therapy before AlloSCT, of which seven (46.67%) and four (26.6%) patients were treated with tyrosine kinase inhibitors (TKI) and steroids (either oral or Intravenous) for a period greater than a month, respectively

Table 1. Characteristics of all recipients of AlloSCT, recipients who developed TB and those who did not post alloSCT and *p* values for associated risk factors using Fisher's exact test and independent *t* test.

Characteristics	Overall population (*n* = 381)	AlloSCT recipients with TB (*n* = 15)	AlloSCT recipients without TB (*n* = 366)	*p* value
Age, median (range)	31 (1–66) years	38 (16–57) years	30 (1–66) years	0.039**
Age ⩾30 years (%)	203 (53.2)	12 (80)	191 (52.2)	0.037**
Male sex, *n* (%)	257 (67.4)	10 (66.67)	247 (67.4)	1.000
Comorbidity, *n* (%)	67 (17.6)	4 (26.67)	63 (17.2)	0.486
History of TB, *n* (%)	15 (3.9)	0	15 (4.1)	0.654
Number of previous lines of therapy, median (range)[a]	2 (1–7)	1 (1–3)	2 (1–7)	0.732
Indication for AlloSCT				0.282
• Acute leukemia (%)	• 200 (52.5)	• 7 (46.67)	• 193 (52.7)	
• MDS (%)	• 6 (1.5)	• 1 (6.67)	• 5 (1.3)	
• MDS/MPN/CMML (%)	• 10 (2.6)	• 1 (6.67)	• 9 (2.4)	
• CML (%)	• 33 (11.7)	• 3 (20)	• 30 (8.2)	
• Benign disorders (%)	• 101 (26.5)	• 2 (13.34)	• 99 (27)	
• Lymphoma (%)	• 27 (7)	• 1 (6.67)	• 26 (7.1)	
• Plasma cell dyscrasia (%)	• 4 (1)	• 0	• 4 (1.1)	
Acute myeloid leukemia as indication for AlloSCT (%)	119 (31.2)	4 (26.67)	115 (31.4)	0.785
Prior use of TKI, *n* (%)	91 (23.8)	7 (46.67)	84 (23)	0.057*
Duration of TKI use in months, median (range)	8.4 (2–131)	11.7 (2–50.7)	7.75 (2–131)	0.714
TKI used Prior to AlloSCT :				NA
• Imatinib (%)	• 9 (2.36)	• 0	• 9 (2.4)	
• Dasatinib (%)	• 50 (13.1)	• 4 (26.67)	• 46 (12.5)	
• Nilotinib (%)	• 9 (2.36)	• 2 (13.34)	• 7 (1.9)	
• Sorafenib (%)	• 4 (1)	• 0	• 4 (1.1)	
• Ruxolitinib (%)	• 4 (1)	• 0	• 4 (1.1)	
• Ibrutinib (%)	• 5 (1.3)	• 1 (6.67)	• 4 (1.1)	
• Ponatinib (%)	• 9 (2.36)	• 0	• 9 (2.4)	
• Midastaurin (%)	• 1 (0.26)	• 0	• 1 (0.27)	
Prior use of prednisolone >1 months (%)	103 (27)	4 (26.67)	99 (27)	1.000
Donor type, *n* (%)				0.789
• Matched family (%)	• 249 (65.3)	• 11 (73.33)	• 238 (65)	
• Matched/mismatched unrelated (%)	• 39 (10.2)	• 1 (6.67)	• 38 (10.3)	
• Haplo-identical (%)	• 93 (24.4)	• 3 (20)	• 90 (24.6)	

(Continued)

Table 1. (Continued)

Characteristics	Overall population (*n* = 381)	AlloSCT recipients with TB (*n* = 15)	AlloSCT recipients without TB (*n* = 366)	*p* value
Related donor, *n* (%)				0.724
• Yes (%)	• 342 (89.7)	• 14 (93.3)	• 328 (89.6)	
• No (%)	• 39 (10.2)	• 1 (6.6&)	• 38 (10.3)	
Matched donor, *n* (%)				1.000
• Mismatched (%)	• 101 (26.5)	• 4 (26.67)	• 97 (26.5)	
• Matched (%)	• 280 (77.5)	• 11 (73.3)	• 269 (73.4)	
Stem cell source, *n* (%)				0.248
• Bone marrow (%)	• 39 (10.3)	• 0	• 39 (10.6)	
• Peripheral blood (%)	• 342 (89.7)	• 15 (100)	• 327 (89.3)	
Conditioning regimen, *n* (%)				0.781
• Myeloablative (%)[b]	• 204 (53.5)	• 6 (40)	• 198 (54.1)	
• Reduced intensity (%)[c]	• 96 (25.2)	• 6 (40)	• 90 (24.6)	
• Non myeloablative (%)[d]	• 81 (21.3)	• 3 (20)	• 78 (21.3)	
Pre-transplant status, *n* (%)[e]	*n* = 280	*n* = 13	*n* = 267	1.000
• CR1/CP (%)	• 147 (52.5)	• 8 (61.5)	• 140 (52.4)	
• Beyond CR1/CP (%)	• 133 (47.5)	• 5 (38.4)	• 127 (47.5)	
Use of TBI > 4 Gy conditioning (%)	62 (16.3)	3 (20)	59 (16.1)	0.719
Use of ATG as Conditioning, *n* (%)	108 (28.3)	3 (20)	105 (28.6)	0.571
GvHD prophylaxis				0.291
• Post transplant Cyclophosphamide + Tacrolimus + MMF (%)	• 158 (41.47)	• 4 (26.67)	• 154 (42)	
• Cyclosporine + Methotrexate (%)	• 222 (58.3)	• 11 (73.3)	• 211 (57.6)	
Acute GvHD, *n* (%)	145 (37.5)	6 (40)	139 (37.9)	1.000
Acute GvHD (Grade III–IV), *n* (%)	61 (16)	2 (13.34)	59 (16.1)	0.705
Chronic GvHD, *n* (%)	112 (29.4)	8 (53.3)	104 (28.4)	0.046**
Chronic GvHD grading, *n* (%)[f]	*n* = 112	*n* = 8	*n* = 104	0.589
• Mild (%)	• 36 (32.1)	• 4 (50)	• 32 (30.7)	
• Moderate (%)	• 46 (41)	• 2 (25)	• 44 (42.3)	
• Severe (%)	• 30 (26.7)	• 2 (25)	• 28 (27)	
Site of chronic GVHD, *n* (%)[g]	*n* = 112	*n* = 8	*n* = 104	–
• Skin (%)	• 58 (51.7)	• 4 (50)	• 54 (52)	
• Oral mucosa (%)	• 53 (47.3)	• 6 (75)	• 47 (45.2)	

(Continued)

Table 1. (Continued)

Characteristics	Overall population ($n=381$)	AlloSCT recipients with TB ($n=15$)	AlloSCT recipients without TB ($n=366$)	p value
• Eyes (%)	• 29 (25.9)	• 1 (12.5)	• 28 (27)	
• Lung (%)	• 22 (19.6)	• 1 (12.5)	• 21 (20.2)	
• Liver (%)	• 36 (32)	• 1 (12.5)	• 35 (33.6)	
• Musculoskeletal (%)	• 2 (1.78)	• 0	• 2 (1.9)	
• Soft tissue (%)	• 1 (0.9)	• 0	• 1 (0.9)	
Pulmonary GvHD (%)	22 (5.7)	1 (6.67)	21 (5.7)	1.000
Treatment of chronic GvHD using	$n=112$	$n=8$	$n=104$	0.063
• Local therapy (%)	• 18 (16)	• 2 (25)	• 16 (15.3)	
• Systemic therapy (%)	• 37 (33)	• 5 (62.5)	• 32 (30.7)	
• Local + systemic therapy (%)	• 57 (50.9)	• 1 (12.5)	• 56 (53.8)	
Time duration between diagnosis of GvHD and diagnosis of TB, median	–	179.5 (33–575) days[h]	–	–
Use of steroids for acute and chronic GvHD, *n* (%)	191 (50.1)	9 (60)	182 (49.7)	0.600
Steroid refractory GvHD, *n* (%)	79 (20.7)	4 (26.67)	75 (20.5)	0.746
Duration of immunosuppression post AlloSCT				0.006**
⩽6 months (%)	• 235 (61.7)	• 4 (26.67)	• 231 (63.1)	
>6 months (%)	• 146 (38.3)	• 11 (73.34)	• 135 (36.8)	
CMV infection, *n* (%)	120 (31.5)	7 (46.67)	113 (30.8)	0.255

[a]Includes prior lines of therapies of acute leukemias, plasma cell dyscrasia, lymphoma, MDS, MDS/MPN, MPN including CML.
[b]Reduced intensity conditioning included fludarabine-busulfan2 ± antithymocyte globulin, fludarabine-melphalan ± antithymocyte globulin, fludarabine-total body irradiation⩽8 Gy and fludarabine-melphalan-total body irradiation ⩽8 Gy.
[c]Non myeloablative conditioning included fludarabine-cyclophosphamide-total body irradiation (2 Gy), fludarabine-cyclophosphamide ± antithymocyte globulin and fludarabine-bendamustine-rituximab.
[d]Myeloablative conditioning included fludarabine-busulfan4 ± antithymocyte globulin, fludarabine-thiotepa-treosulphan ± antithymocyte globulin, busulfan4-fludarabine-cyclophosphamide ± antithymocyte globulin, fludarabine-total body irradiation >8 Gy ± antithymocyte globulin, cyclophosphamide-total body irradiation >8 Gy ± ATG, busulfan-cyclophosphamide ± antithymocyte globulin and BEAM.
[e]Includes the disease status of acute leukemias, plasma cell dyscrasia, lymphoma, MDS, MDS/MPN, and MPN including CML.
[f]Includes the grading of all the patients with chronic GvHD.
[g]One patient may have multiple sites affected with chronic GvHD.
[h]Applicable for those patients only who had GvHD ($n=10$).
*$p \leqslant 0.1$; **$p \leqslant 0.05$.
Acute leukemia includes acute myeloid leukemia, acute lymphoblastic leukemia, acute undifferentiated leukemia and mixed phenotypic acute leukemia; MDS, MPN, benign disorders includes β thalassemia, severe aplastic anemia, hemophagocytic syndrome, and cyclical neutropenia.
AlloSCT, allogeneic stem cell transplant; CML, chronic myeloid leukemia; GvHD, graft versus host disease; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; TB, tuberculosis; TKI, tyrosine kinase inhibitors.

before alloSCT. Of the 13 patients (excluding the severe aplastic anemia), 8 were in complete remission 1 (CR1), while 5 of them received alloSCT with disease status beyond CR1 or chronic phase. An equal number of patients received MAC/RIC ($n=6$ each), followed by NMA ($n=3$). Baseline characteristics are shown in Table 1.

TB infection

TB was diagnosed at a median of 246 (74–279) days post AlloSCT, during which five patients developed TB within 180 days of AlloSCT. Nearly three-quarters ($n = 11$; 73.3%) had pulmonary tuberculosis, including one with disseminated disease, while the remaining patients had extrapulmonary tubercular infection with lymph nodes ($n = 2$), spine ($n = 1$) and esophagus ($n = 1$) involvement. Patients diagnosed with TB had unexplained fever ($n = 11$, 73.3%) and cough ($n = 7$, 46.67%) and were not responsive to conventional antibiotics. Eight (53.34%) patients had significant weight loss, while three (20%), two (13.34%), and one (6.67%) patient developed chest pain, breathlessness, and lymphadenopathy, respectively. One patient (6.67%) each had dysphagia and paraparesis, subsequently diagnosed with esophageal TB and spinal TB, respectively. Median duration of symptoms prior to diagnosis of TB was 22 (7–60) days. Since the likelihood of fungal infection is high post AlloSCT, computed tomography (CT) scans of chest and/or fungal cultures/microscopy, and galactomannan test were done in all patients. On radiographic imaging of lungs, 8 of 11 (72.7%) patients with pulmonary TB had consolidation or nodular opacity with or without mediastinal lymphadenopathy, while one patient had a miliary pattern. Two patients demonstrated pleural effusion and pleuro-pericardial effusion. Proven diagnosis of TB was established in 11 patients by demonstration of AFB in seven patients on lung biopsy ($n = 1$), lymph node biopsy ($n = 1$), sputum ZN stain ($n = 1$), fine needle aspirate (FNA) of lung lesions ($n = 3$), and bronchoalveolar lavage (BAL) ($n = 1$); MTB was demonstrated using PCR test in four patients on BAL ($n = 1$), vertebral biopsy ($n = 1$), lung biopsy ($n = 1$), and transbronchial needle aspirate from lymph node biopsy ($n = 1$). Probable diagnosis of TB was established in four patients by histopathology findings suggestive of granuloma in two patients [necrotizing granuloma on lymph node biopsy ($n = 1$) and granulomatous esophagitis on esophagus biopsy ($n = 1$)], and clinico-radiologic findings [pleural effusion ($n = 1$), pleural + pericardial effusion ($n = 1$)] in two patients in the absence of any other causes (Table 2).

Six patients (40%) had CMV reactivation before the diagnosis of TB post AlloSCT, which was managed with intravenous gancyclovir. Two-thirds ($n = 10$; 66.7%) of patients developed GvHD (acute GvHD only = 2, acute GvHD followed by chronic GvHD = 4, chronic GvHD = 4) prior to the development of TB. Acute GvHD with median grade II (I–IV) developed in six patients (40%), involving gastrointestinal tract ($n = 3$), skin ($n = 2$), and both gastrointestinal tract and skin ($n = 1$), with a median onset of 75 (41–172) days post AlloSCT. Chronic GvHD developed in eight (53.34%) patients (mild = 4, moderate = 2 and severe = 2) involving one organ ($n = 3$) (skin = 1, lung = 1, mucosa = 1), two organs ($n = 4$) (skin and mucosa = 2, liver and mucosa = 1, eye and mucosa = 1), or three organs ($n = 1$) (liver, skin and mucosa = 1), at a median onset of 241 (168–263) days post AlloSCT. Half of patients (50%) who developed chronic GvHD ($n = 4$), were on second-line therapy for GvHD at the time of diagnosis of TB.

All patients were started on four-drug ATT, with 13 patients completing their treatment with complete resolution of infection at a median of 6 (6–20) months, one patient with AML relapsed and succumbed while on ATT treatment, and treatment of other the patient is ongoing. Median time to symptomatic improvement after initiation of treatment was 69.5 (14–186) days. During ATT therapy, five patients developed hepatotoxicity [raised alanine aminotransferase grade 3 ($n = 1$), raised aspartate aminotransferase grade 3 ($n = 2$), raised serum total bilirubin grade 3 ($n = 2$)] at a median of 12 (5–127) days from the start of therapy, which led to drug modification of ATT in all patients. Importantly, none of our patients had rifampin or isoniazid resistance. At last follow up, two patients diagnosed with TB had died after resolution of TB infection because of unrelated causes, [myocardial infarction ($n = 1$) and H1N1 infection ($n = 1$)] at a median of 4.78 (3.8–5.5) years from AlloSCT.

Risk factors for TB occurrence and cumulative incidence of TB

On univariate analysis, patients with age ⩾30 years ($p = 0.047$), chronic GvHD ($p = 0.046$) and use of immunosuppression for greater than 6 months ($p = 0.009$) and prior use of TKI ($p = 0.043$) were identified as independent risk factors for occurrence of TB. Mode of treatment of chronic GvHD that is, systemic therapy alone [Systemic therapy alone *versus* (Systemic Therapy + Local Therapy and Local Therapy alone)] ($p = 0.052$) showed a trend for development of TB. Meanwhile, prior

Table 2. Clinical characteristics of patients who developed TB after AlloSCT.

Patient no	Age/ sex	History of TB	Dx	Prior use of TKI	Dis status	Type of transplant	Conditioning regime	Acute GvHD (grade, site)	Chronic GvHD (grade, site)	Therapeutic approach of chronic GvHD	Steroid refractory GvHD	Category of TB	Time to Dx of TB after AlloSCT, days	TB (pulmonary/ extrapulmonary)	ISA ongoing at time of diagnosis	Treatment	Days to symptomatic improvement	Treatment duration, months	Treatment outcome
1	54/F	No	AML	No	CR1	MUD	RIC	II, Gut	Moderate, Lung	Sys	No	Proven	211	Pulmonary	Yes	RHEZ	186	5	Cure
2	46/M	No	CMML2	No	CR1	MFD	RIC	IV, Skin + Gut	Severe, Liver + Skin + Mucosa	Sys + Local	Yes	Proven	246	Pulmonary	Yes	RHEZ	184	20	Cure
3	45/M	No	CML	Yes	AP1	MFD	MA	–	Severe, Skin + Mucosa	Sys + Local	Yes	Proven	574	Pulmonary	Yes	RHEZ	75	12	Cure
4	39/F	No	Ph+ ALL	Yes	CR1	MFD	MA	II, Gut	Moderate, Skin + Mucosa	Sys + Local	Yes	Proven	157	Pulmonary	Yes	RHEZ	125	9	Cure
5	38/M	No	AML	No	CR1	MFD	MA	–	Mild, Liver + Mucosa	Sys + Local	No	Probable	648	Extrapulmonary	No	RHEZ	69	6	Cure
6	33/M	No	Ph+ ALL	Yes	CR3	MFD	MA	–	–	–	–	Proven	80	Pulmonary	Yes	RHEZ	29	6	Cure
7	27/F	No	Ph+ ALL	Yes	CR1	Haplo	NMA	II, Skin	–	–	Yes	Probable	260	Extrapulmonary	Yes	RHEZ	30	6	Cure
8	52/M	No	CML	Yes	AP1	MFD	RIC	IV, Gut	Mild, Skin	Local	No	Probable	236	Pulmonary	Yes	RHEZ	120	17	Cure
9	25/M	No	SAA	No	NA	MFD	NMA	–	–	–	–	Proven	584	Pulmonary	Yes	RHEZ	70	9	Cure
10	16/M	No	SAA	No	NA	MFD	NMA	–	–	–	–	Proven	879	Pulmonary	No	RHEZ	62	6	Cure
11	37/M	No	CML	Yes	BP-CR1	MFD	RIC	–	–	–	–	Proven	160	Extrapulmonary	Yes	RHEZ	35	10	Cure
12	54/M	No	MCL	Yes	PR1	MFD	MA	–	Mild, Eye + Mucosa	Sys + Local	No	Proven	716	Extrapulmonary	Yes	RHEZ	129	6	Cure
13	57/F	No	AML	No	CR1	Haplo	RIC	I, Skin	–	–	No	Proven	74	Pulmonary	Yes	RHEZ	35	6	Cure
14	36/F	No	MDS-EB2	No	CR1	MFD	MA	–	Mild, Mucosa	Local	No	Probable	838	Pulmonary	No	RHEZ	14	6	Cure
15	32/M	No	AML	No	CR2	Haplo	RIC	–	–	–	–	Proven	78	Pulmonary	Yes	RHEZ	Ongoing	Ongoing	Ongoing

AlloSCT, allogeneic stem cell transplant; AML, acute myeloid leukemia; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CMML2, chronic myelomonocytic leukemia -2; CR, complete remission; Haplo, haploidentical donor; MA, myeloablative; MCL, mantle cell lymphoma; MDS-EB2, myelodysplastic syndrome with excess blasts-2; MFD, matched family donor; MUD, matched unrelated donor; NMA, non myeloablative conditioning; Philadelphia chromosome positive acute lymphoblastic leukemia; RHEZ, rifampin, isoniazid, ethambutol, pyrazinamide; RIC, reduced intensity conditioning; TB, tuberculosis.

Table 3. Predictors of TB post AlloSCT using logistic regression.

Predictors	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Use of systemic therapy for chronic GvHD	8.750	0.979–78.224	*0.052*			
Age ⩾30 years	0.273	0.076–0.983	0.047	0.283	0.075–1.071	0.063*
>6 months of immunosuppression post AlloSCT	0.213	0.066–0.681	0.009	0.190	0.058–0.618	0.006**
Chronic GvHD	0.347	0.123–0.982	0.046	1.220	0.315–4.721	0.774
Prior use of TKI	0.340	0.120–0.966	0.043	0.372	0.125–1.106	0.075*

AlloSCT, allogeneic stem cell transplant; CI, confidence interval; GvHD, graft *versus* host disease; TB, tuberculosis; TKI, tyrosine kinase inhibitor.
*$p \leqslant 0.1$; **$p \leqslant 0.05$.

history of TB, previous number of lines of therapy, prior use of systemic steroids >4 weeks, donor type, conditioning regimen, stem cell source, acute GvHD, use of steroids for treatment of GvHD, steroid refractory GvHD and CMV infection were not significantly associated with development of TB. On multivariate analysis, greater than 6 months of immunosuppression ($p = 0.006$) was found to independently predict the occurrence of TB, while use of TKI prior to AlloSCT ($p = 0.075$), and age ⩾30 years ($p = 0.063$) was found to have a trend for development of TB. (Table 3)

Statistically, we could not find which TKI is predictive of TB, but, on comparing the proportions, we found patients with prior use of nilotinib (22%) are most likely to develop TB followed by prior use of ibrutinib (20%), and dasatinib (8%).

A significant difference was found in cumulative incidence of TB among patients aged ⩾30 years *versus* (vs) those <30 years, prior use of TKI before AlloSCT *versus* those without, and those who received immunosuppression for more than 6 months post alloSCT *versus* those who did not; 6.6% *versus* 2.3% ($p = 0.04$); 9.2% *versus* 3.3% ($p = 0.025$), and 8.3% *versus* 2.1% ($p = 0.014$), respectively (Figure 1). Meanwhile, prior history of TB, previous number of lines of therapy, prior use of prednisolone for more than a month, donor type, conditioning regimen, use of ATG/total body irradiation (TBI) in conditioning, stem cell source, acute GvHD, pulmonary GvHD, use of steroids for treatment of GvHD, steroid refractory acute GvHD, and CMV re-activation were not significantly associated with cumulative incidence of TB.

AlloSCT outcomes

The median follow-up duration of the study population was 3.6 (95% C.I. 3–4.1) years. At median follow up, OS and DFS of the whole cohort were 3.1 and 2 years, respectively. No statistically significant difference was found in OS of the whole cohort *versus* patients who developed TB (Median OS 3.06 *versus* 7.38 years; $p = 0.126$) while a significant difference in the DFS of whole cohort *versus* patients who developed TB (Median DFS 2 *versus* not reached years; $p = 0.011$) (Figure 2). During the study period, 182 (47%) patients succumbed, of whom two-thirds were due to NRM ($n = 114$) and rest to progressive disease ($n = 68$). None of our patients diagnosed with TB had mortality due to TB infection. At last follow up, cumulative incidence of NRM of the whole population was 31.3%. At last follow up, cumulative incidence of NRM of patients who developed TB *versus* those who did not was 30.1% *versus* 31.1%; $p = 0.12$ respectively.

Discussion

Tuberculosis, an opportunistic infection caused by MTB, a facultative intracellular organism, remains a global health burden for the general population, with a higher incidence in immunocompromised populations. A TB-naïve host develops primary TB infection upon first encounter with MTB, which remains well controlled because of cell-mediated immunity. It may further

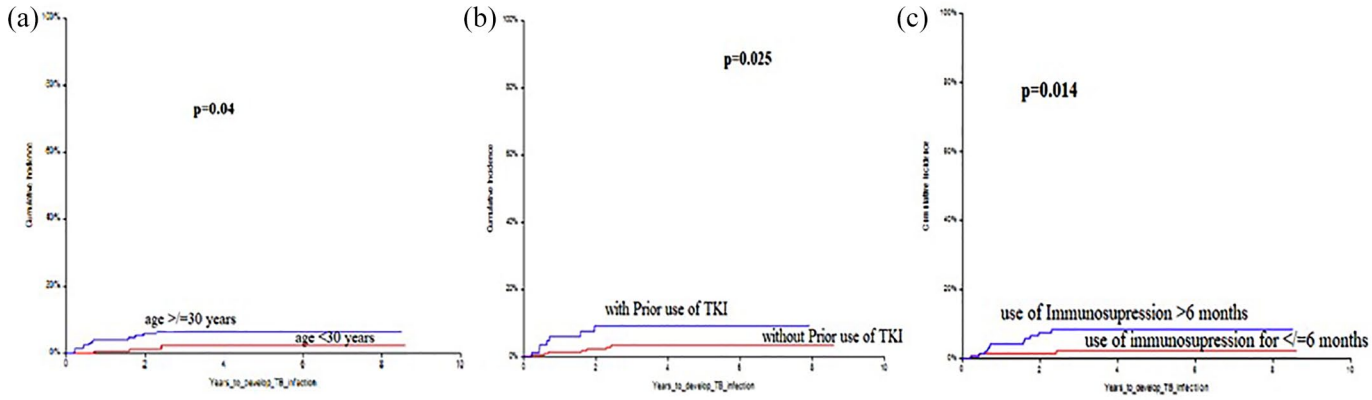

Figure 1. Independent risk factors of TB Incidence. (a) Curve comparing the cumulative incidence of TB among alloSCT recipients older than or equal to 30 years *versus* less than 30 years ($p = 0.04$). (b) Curve comparing the cumulative incidence of TB in patients with use of TKI prior to AlloSCT *versus* those without use of TKI prior to AlloSCT ($p = 0.025$). (c) Curve comparing the cumulative incidence of TB in patients with use of immunosuppression for >6 months *versus* those with the use of immunosuppression ⩽6 months ($p = 0.014$).
AlloSCT, allogeneic stem cell transplant; TB, tuberculosis; TKI, tyrosine kinase inhibitors.

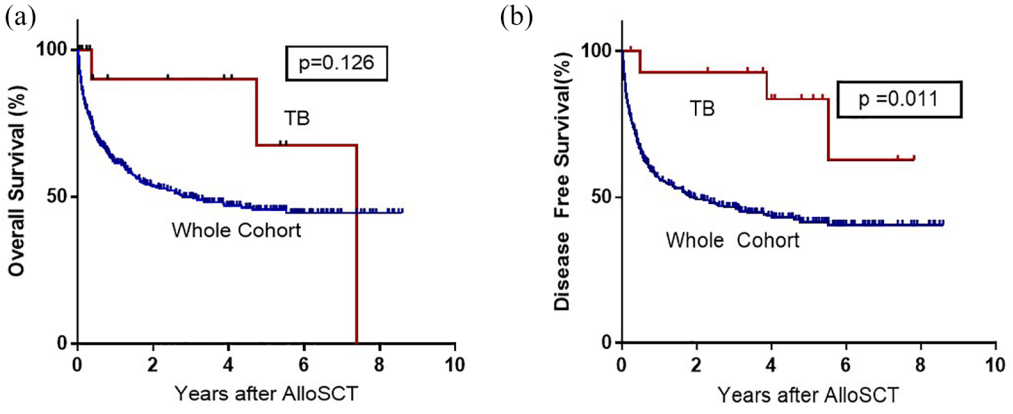

Figure 2. Kaplan–Meier curves. (a) Curves comparing the OS of whole cohort *versus* those who developed TB. (b) Curves comparing the DFS of whole cohort *versus* those who developed TB.
DFS, disease-free survival; OS, overall survival; TB, tuberculosis.

become an active infection from latent phase upon exogeneous re-infection or reactivation of latent bacilli in a host in an immune-compromised state.[12] It has been established that cell-mediated immunity plays a defensive mechanism against the development of active tubercular infection from either latent tuberculosis or acquired infection. A central role in the pathogenesis of MTB is played by macrophages, which not only recognize the organisms in the alveoli after inhalation of bacteria but also play a bactericidal role.[13]

Different immune cell subsets are distorted during and post AlloSCT, mainly because of conditioning (chemotherapy and radiation) therapy. Reconstitution of immune cells varies from 14 days to 2 years post alloSCT. Neutrophils reconstitute from the aplastic phase within 28 days of alloSCT using peripheral blood stem cells or bone marrow stem cell graft. Restoration of normal functioning of natural killer cells and T cells takes about 30–100 days and 100 days, respectively, from the day of alloSCT. CD+8 T cells and CD+19 B cells function is restored after 60–240 days and 1–2 years, respectively, post AlloSCT.[14] Poor immune response and delayed immune reconstitution make recipients of AlloSCT more susceptible to secondary TB infection upon

exogeneous exposure or reactivation of latent TB infection. Although infection with TB remains uncommon among alloSCT recipients, it remains prevalent in AlloSCT recipients in countries with high rates of endemicity, causing significant morbidity and mortality.[15]

According to a WHO report, India shares 27% of the global burden of TB infection, with an estimated TB incidence of 2.69 million new cases in 2018.[1] The incidence of TB among AlloSCT recipients is reported to be 2–40% higher than that of the general population.[3,4] Studies conducted over the past two decades reported an incidence of TB among AlloSCT recipients of 0.17–8%.[5–9, 16–18] Similar to the literature, we found the frequency of active TB to be 3.9% amongst alloSCT recipients despite the endemicity of TB in our country. In comparison with the general population of India, the incidence of TB is 37 times higher in the AlloSCT population.[1] Therefore, TB is not rare among AlloSCT recipients in India. Despite TB endemicity, inclusion of recipients with a past history of TB and absence of any prophylaxis before/during alloSCT, the incidence of TB in our cohort was relatively low. The incidence of TB in our current study is 1.4 times higher than the incidence reported in our previous analysis. This might be due to a larger sample size and longer duration of follow up in our current study.[8] Studies conducted in Turkey, China, Korea, India, Australia, and Taiwan have reported a variable incidence of 0.17–2.8% for TB post alloSCT,[8,9,18–22] relatively lower than our cohort. A study from Saudi Arabia ($n=477$) reported a similar incidence of 3.7% in their cohort.[2] On the contrary, literature from Hong Kong and Pakistan suggests an incidence of 5.5% and 8%, respectively, i.e., much higher than our study.[16,17] It should be borne in mind that the study from Pakistan included only 50 patients, while the study from Hong Kong was done in late 1990s analyzing a cohort of only 10 patients with TB *versus* 27 patients without.

In India, 16% of total new TB cases are reported as extrapulmonary TB cases in the general population.[23] Incidence of extrapulmonary TB rates among alloSCT recipients is usually higher than that of general population, owing to the fact that reduced cell mediated immune responses cannot contain the TB infection. Similarly, we observed that more than one-fourth (26.67%) cases among our alloSCT recipients were extrapulmonary, occurring at a median of 454 (160–716) days post AlloSCT (during the immune reconstitution phase). Three-quarters of extrapulmonary TB cases were receiving immunosuppression for GvHD at the time of diagnosis of TB.

Median time to diagnosis of TB post alloSCT was 246 (74–879) days; that is, within a year of AlloSCT. Similar results were obtained by studies conducted in Spain [257.2 (21–1410) days post alloSCT] and China [193.5 (43–909) days post AlloSCT].[9,24] Of 15 patients (20%), 3 developed TB within the first 3 months [median 78 (74–80) days]; 40% (6/15) of AlloSCT recipients developed TB beyond 1 year of AlloSCT – three of these patients were not on immunosuppressive drugs, indicating the possibility of an exogeneous infection or persistent effect of immunosuppression leading to TB reactivation.

Several risk factors, including myeloid malignancy as an underlying disease, therapies impairing T cell function like fludarabine, alemtuzumab, ATG, total body irradiation or steroids, conditioning with busulfan or cyclophosphamide, development of GvHD, donor/host histocompatibility, unrelated donor stem cells, etc., have been reported as predisposing factor for development of TB post alloSCT.[3,9,17,24] We observed that patients older than 30 years, those who develop chronic GvHD, immunosuppression >6 months post alloSCT, and prior use of TKI, were predisposing factors of TB on univariate analysis. Surprisingly, we found no significant difference in the development of TB on the basis of severity of chronic GvHD (mild *versus* moderate *versus* severe). In contrast to Lee *et al.*, we did not find TBI as a risk factor for development of TB post alloSCT.[25] This might be because only 16% of our patients received TBI, in contrast to 45% of patients in the cohort of Lee *et al.*[25] Similarly, in contrast to Chinese data, there was no difference amongst the two calcineurin inhibitors with respect to development of TB in our cohort.[9]

Unrelated donor transplants were not found to be significantly associated with TB. This could be viewed as being because only 10.2% of AlloSCTs done at our center used unrelated donor. A total of 28.3% and 16.3% of patients were only conditioned with ATG and TBI > 4 Gy for alloSCT, which might have resulted in non-significant

association of TB with ATG and TBI > 4 Gy in our cohort of patients.

While multiple studies have shown GVHD as a risk factor for development of TB post alloSCT,[4,5,8] our study is the first to show that duration of immunosuppression >6 months increases its risk significantly.

TKIs have well-characterized immunomodulatory effects on T and natural killer cells. A study conducted on CML patients revealed that relative and absolute B cell numbers dropped significantly in patients with TKI therapy.[26] As TKIs affect predominantly cell-mediated immunity, patients with a prior history of TKI use may have a predisposition towards the occurrence of TB post alloSCT. We observed a statistically significant increased cumulative incidence of TB amongst patients with prior TKI use (cumulative incidence of TB with prior use of TKI = 9.27% *versus* cumulative incidence of TB without prior use of TKI = 3.36%; $p = 0.025$). In 2009, Daniels *et al.* proposed that TKIs might impair the signal transduction through T-cell receptors in CD8+ T-cells, and thereby impair immune responses necessary for intracellular mycobacterial killing.[27] Similar findings have also been reported recently from India (albeit in non AlloSCT setting).[28]

It has been observed that infection with TB among alloSCT recipients plays a pivotal role in NRM. A study conducted by Yang *et al.* has shown that 3-year NRM of patients with TB was 4.35 times higher than those who did not develop TB.[9] In contrast, we did not find any difference in NRM in either cohort (30.1% with TB *versus* 31.1% without TB; $p = 0.12$). This could be explained partly by an effective strategy of timely diagnosis and treatment of TB infection, and partly by high early NRM in remaining patients. All the patients with TB who completed ATT responded to first line ATT (RHEZ) except one who died early because of progressive disease.

We observed that patients with TB had better OS than the whole cohort (median OS 7.38 *versus* 3.06 years; $p = 0.126$). This observation could plausibly relate to early diagnosis of TB at a median of 22 days from development of symptoms to diagnosis and the fact that there were no TB-related mortalities in our study. We observed that patients with TB had better DFS with respect to the whole cohort. This could be explained as patients who develop chronic GvHD having a better DFS due to lower relapse rates. However, the same also necessitates immunosuppression, which can lead to TB. Time to development of TB post AlloSCT is 9 months. Since this is a very late complication, it might indirectly reflect that the better the survival, the higher the chance of such infections, and vice versa.

It is known that chronic GvHD is an important complication that not only impairs quality of life and requires prolonged immunosuppression but is also associated with fewer relapses.[29] We observed that more than half of our patients with TB had chronic GvHD, while nearly one-third of patients without TB developed chronic GVHD. The significantly higher DFS observed in patients with TB than in the whole cohort (median DFS 2 *versus* not reached years; $p = 0.011$) might be justified on the basis of incidence of chronic GvHD in our cohort of patients. The higher incidence of chronic GvHD in our cohort might be due to increased use of peripheral blood stem cell (PBSC) grafts (90%) in our cohort.

According to the Center for International Blood and Marrow Transplant Research (CIBMTR), endemicity of population and past history of TB infection of recipient and family members remain important predisposing factors for development of TB post alloSCT.[15] It has been recommended to diagnose latent TB infection in recipients during pre-transplant work up using interferon gamma release assay (IGRA) assessments to prevent active TB. Recipients in endemic countries are also advised to receive isoniazid (INH) prophylaxis.[15] However, being an endemic country, with a very high prevalence of latent TB, INH prophylaxis could not be prescribed to all patients because of its hepatotoxicity, drug interaction with immunosuppressants, problems of INH resistance, and absence of its recommendation in our national guidelines.[8,30] Importantly, a retrospective analysis from Korea did not find any statistical difference with INH prophylaxis ($n = 48$) or not ($n = 35$) amongst patients with positive IGRA results ($n = 83$) ($p = 0.54$).

Being retrospective in nature, the presence of high early NRM, and absence of immune reconstitution data in our cohort are the major limitations of our study. However, a larger sample size of alloSCT recipients and long follow-up period constitute the major strengths of our study.

The importance of early diagnosis plays a major role in the management and control of TB, especially in patients with reduced immune response. Diagnosing TB remains challenging in post alloSCT patients because of nonspecific clinical features.

Conclusions

In conclusion, most patients including those with extrapulmonary and disseminated TB were salvaged with appropriate use of ATT. Transplant physicians should be cognizant of this entity, especially in patients who have received >6 months immunosuppression post alloSCT.

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Authorship contribution

JK collected the data, performed the statistical analysis and wrote the manuscript.

SPM designed the study, wrote the portions of manuscript and revised the manuscript critically.

VK revised the manuscript critically and approved the final versions of manuscript.

PM revised the manuscript critically and approved the final versions of manuscript.

RA revised the manuscript critically and approved the final versions of manuscript.

NB revised the manuscript critically and approved the final versions of manuscript.

DB revised the manuscript critically and approved the final versions of manuscript.

NA designed, performed the study, revised the manuscript critically and approved the final versions of manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical approval

The study has been approved by our Institutional Review Board of Rajiv Gandhi Cancer Institute and Research Centre (IRB approval ID – RGCIRC/IRB-BHR/120/2020). We received a waiver from the consenting process from the Institutional Review Board.

ORCID iD

Sumeet Prakash Mirgh https://orcid.org/0000-0003-0642-2207

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