Characteristics, treatment and outcomes of nontuberculous mycobacterial pulmonary disease after allogeneic haematopoietic stem cell transplant

To the Editor:

Allogeneic haematopoietic stem cell transplant (alloHCT) recipients are at risk for a variety of opportunistic infections. While typical bacterial infections occur most frequently, nontuberculous mycobacteria (NTM) are becoming increasingly recognised as pathogens after alloHCT [1]. The prevalence of NTM pulmonary disease (NTM-PD) is increasing worldwide, with a rise in Ontario's period prevalence from 29.3 per 100 000 in 1998–2002 to 41.3 per 100 000 in 2006–2010 [2]. Likewise, the incidence of NTM-PD post alloHCT increased from 0.11–0.23% [3, 4] in early studies to 2.7–3.15% in recent investigations [5, 6]. Despite the incidence of NTM-PD after alloHCT being far higher than in the general population [6], there are few reports addressing management and treatment outcomes of NTM-PD after alloHCT. We reviewed the experience with NTM-PD among alloHCT recipients at our institution to better characterise clinical features and treatment outcomes.

Patients who underwent initial alloHCT at the Princess Margaret Cancer Centre in Toronto, ON, Canada, were retrospectively analysed, as approved by our institutional ethics board. The study protocol was reviewed by University Health Network research ethics board (research ethics board number 14-8116). In light of the retrospective design, the requirement of informed consent was waived. NTM-PD was diagnosed according to American Thoracic Society/Infectious Disease Society America criteria [7]. NTM isolates from respiratory specimens including sputum, intratracheal aspiration or bronchial alveolar lavage from alloHCT recipients were included. Radiological patterns were classified into nodular bronchiectasis (NB), fibrocavitary (FC) and unclassified based on chest computed tomography: NB required bronchiectasis and nodules, FC required cavitation without significant bronchiectasis or nodules, and unclassified was defined when radiological features did not meet NB or FC. In addition, the presence of cavitation, bronchiectasis [8], centrilobular nodules, consolidation/grand glass opacity, fibrosis (honeycombing plus traction bronchiectasis), emphysema, pulmonary arterial trunk enlargement (>29 mm at bifurcation) and mediastinal lymphadenopathy (>10 mm in short axis) was determined. Radiological improvement was defined by our global impression of change. Images were reviewed by an experienced respirologist. If the review differed from the radiologist's report, the scan was reviewed by a second experienced respirologist. Culture conversion was defined by two consecutively negative sputum cultures at least 4 weeks apart or the inability to produce sputum and an absence of ongoing positive cultures. Graft *versus* host disease (GvHD) and its severity were determined using National Institutes of Health criteria [9].

Between January 2000 and December 2013, 1097 consecutive patients underwent alloHCT at our centre. NTM were isolated from 45 patients, among whom 20 patients were treated with antimycobacterial drugs for a diagnosis of NTM-PD (table 1). Seven patients (35%) received T-cell-depleted grafts (Alemtuzumab), which we previously found not to be associated with NTM disease [6]. At the time of NTM-PD diagnosis, immune suppression included prednisone (75%), mycophenolate (60%) and calcineurin inhibitors (20%). Of 20 NTM-PD patients, 95% had been diagnosed with GvHD, half of whom had lung involvement (mean forced expiratory volume in 1 s 36.7% of predicted). Co-isolation of *Aspergillus* species in 50% and

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TABLE 1 Characteristics of nontuberculous mycobacteria pulmonary disease (NTM-PD) in allogeneic haematopoietic stem cell transplant (alloHCT) recipients enrolled in the study (n=20)

Age	Sex	Underlying haematological disorders	GvHD	GvHD severity	FEV_1, %	FEV1/FVC	Immunosuppression	T-cell depleted graft	Days from alloHCT to NTM-PD	Mycobacterium species	Clinical specimens for diagnosis for NTM-PD	AFB smear	Coinfection	Radiological pattern	Radiological characteristics in HRCT	Antimycobacterial drugs	Treatment duration days	Treatment outcome	Cause of death	Radiological improvement	Culture conversion	Days from NTM PD to death days
39	M	Myelofibrosis	Lung	Moderate	42.0	72.2	Pred, MMF	No	363	*M. avium*	Repeated sputum	–	*Klebsiella*, *Aspergillus*	UC	Bronchiectasis	CLR, CIP, EMB	308	Completed	Unknown	Yes	Yes	770
52	F	ALL	Lung, skin, eye	Moderate	42.0	61.3	Pred	No	2798	*M. avium*	Repeated sputum	+	Influenza	NB	Bronchiectasis, multiple nodules	AZM, LVX, RIF, EMB, AWK	317	Died	Unknown	No	Yes	317
41	F	Myelofibrosis	Lung, skin, mouth	Severe	31.9	41.0		No	2755	*M. avium*	Tissue and culture	+	CMV	UC	Multiple nodules, pleural effusion	AZM, MXF, EMB, CLO	1093	Completed	GvHD progression	Yes	No	1733
56	M	AML	Lung, liver, mouth	Severe	21.8	27.2	Pred, MMF	No	1147	*M. avium*	Repeated sputum	–	*Haemophilus*, *Aspergillus*, CMV	FC	Cavity	AZM, RFB, EMB	37	Died	Intracranial haemorrhage	Yes	NA	37
55	F	Mantle cell lymphoma	Skin, intestine	Moderate	64.4	72.2	Pred. MMF	Yes	143	*M. avium*	BAL	–	*Escherichia*, *Nocardia*, CMV	UC	Multiple nodules	AZM, MXF, RIF, EMB	51	Died	CMV viraemia	Yes	NA	51
50	M	CLL	Skin, liver	Mild	142.9	75.4	Pred. CSA	Yes	224	*M. avium*	BAL	–	*Klebsiella*, *Staphylococcus*, *Candida*	NB	Bronchiectasis, multiple nodules, consolidation/GGO, pleural effusion	AZM, MEM	15	Died	Sepsis, GvHD progression	No	NA	15
65	F	MDS	Liver, lung, eye	Severe	54.6	50.5	MMF	Yes	1873	*M. avium*	BAL	+	CMV	NB	Bronchiectasis, multiple nodules	AZM, RFB, EMB	288	Completed	GvHD progression	Yes	Yes	598
41	F	Aplastic anaemia	Liver	Moderate	53.4	56.2	CSA	Yes	170	*M. avium*	BAL	–	*Aspergillus*, CMV	UC	Multiple nodules	AZM, MXF, EWB	10	Not tolerated		No	Yes	Alive
54	F	AML	Skin, intestine	Moderate	43.7	51.9		Yes	543	*M. avium*	BAL	–	CMV	NB	Bronchiectasis, multiple nodules	AZM, MXF, EMB	1840	Died	Unknown	Yes	No	1840
63	M	CML	Skin, liver, mouth	Severe	74.4	60.7	Pred, MMF, TAC	No	343	*M. avium*	BAL	–	*Klebsiella*, *Aspergillus*, CMV	UC	Bronchiectasis, multiple nodules, pleural effusion	AZM, MXF, EMB	7	Died	Respiratory failure other than NTM-PD	Yes	NA	7
48	F	AML	Lung, liver, skin	Severe	46.0	48.7	Pred, MMF	No	742	*M. fortuitum*	BAL	–	*Stenotrophomonas*, *Aspergillus*, CMV	UC	Cavity, bronchiectasis	AZM, MXF, AMK, DOX	447	Died	Respiratory failure other than NTM-PD	Yes	Yes	447
64	M	AML	Lung, skin	Moderate	27.5	42.3	Pred, MMF	No	664	*M. fortuitum*	BAL	–	*Pseudomonas*, *Aspergillus*, CMV	UC	Bronchiectasis, consolidation/GGO	CLR, CIP, SXT	136	Completed	Sudden death	No	Yes	166
59	M	AML	Skin, liver	Moderate	76.5	67.0	Pred, AZA	Yes	272	*M. fortuitum*	Blood	+	*Staphylococcus*, CMV	UC	Multiple nodules, lymphadenopathy	AZM, MXF, SXT, MEM	98	Completed		Yes	Yes	Alive
49	M	AML	Skin, liver, lung	Moderate	18.0	29.4	Pred, MMF	No	429	*M. fortuitum*	BAL	–	*Pseudomonas*, *Aspergillus*, CMV	NB	Cavity, bronchiectasis, multiple nodules, pleural effusion	CLR, LVX	428	Completed		Yes	Yes	Alive
64	M	Non-Hodgkins lymphoma	Skin	Severe	51.4	66.8	Pred, MMF	No	649	*M. xenopi*	BAL	+	*Pseudomonas*, *Aspergillus*	UC	Multiple nodules,Consolidation/GGO, pleural effusion	AZM, MXF, RFB, EMB	511	Died	Unknown	Yes	No	511
60	M	AML			106.5	72.3	Pred, MMF	Yes	310	*M. xenopi*	Tissue and culture	+	*Enterobacter*, CMV	UC	Bronchiectasis, consolidation/GGO, fibrosis, pulmonary hypertension	AZM, RFB, EMB	33	Died	Respiratory failure other than NTM-PD	No	Yes	33
45	M	CLL	Skin	Moderate	66.3	65.3	Pred, CSA	No	133	*M. xenopi*	BAL	–	RSV, CMV	UC	Multiple nodules, pulmonary hypertension	AZM, RFB, EMB	146	Not tolerated	CLL relapse	Yes	Yes	699
36	F	MDS	Lung, liver	Severe	28.2	41.5	Pred, MMF	No	356	*M. abscessus*	BAL	+	*Stenotrophomonas*, *Aspergillus*	NB	Cavity, bronchiectasis, multiple nodules	AZM, MXF, AMK, FOX, LZD	311	Died	Respiratory failure other than NTM-PD	Yes	No	311
45	F	MDS	Skin, intestine, eye, mouth	Severe	28.8	36.0	Pred, MMF	No	730	*M. abscessus*	BAL	–	*Moraxella*, *Aspergillus*	NB	Bronchiectasis, multiple nodules, consolidation/GGO	AZM, AMK, IPM	183	Completed		Yes	Yes	Alive
51	M	Myelofibrosis	Skin, lung	Severe	60.6	84.8		No	519	*M. gordonae*	BAL	+	*Staphylococcus*, *Candida*	UC	Bronchiectasis, consolidation/GGO, fibrosis, pulmonary hypertension	AZM, MXF, RIF, EMB	397	Died	Respiratory failure other than NTM-PD	Yes	Yes	397

GvHD: graft *versus* host disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; AFB: acid-fast bacilli; HRCT: high-resolution computed tomography; M: male; F: female; ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; MDS: myelodysplastic syndrome; CML: chronic myeloid leukaemia; Pred: prednisone; MMF: mycophenolate; CSA: cyclosporin; TAC: tacrolimus; AZA: azathioprine; BAL: bronchoalveolar lavage; CMV: cytomegalovirus; UC: unclassified; NB: nodular bronchiectasis; FC: fibrocavitary; GGO: ground glass opacities; CLR: clarithromycin; CIP: ciprofloxacin; EMB: ethambutol; AZM: azithromycin; LVX: levofloxacin; RIF: rifampin; AMK: amikacin; MXF: moxifloxacin; CLO: clofazimine; RFB: rifabutin; MEM: meropenem; DOX: doxycycline; SXT: sulfamethoxazole/trimethoprim; FOX: cefoxitin; LZD: linezolid; IPM: imipenem; NA: not available. All data were at the time of diagnosis for NTM-PD.

Gram negative bacteria in 50% was identified. Microbiological diagnosis was *via* bronchoscopy in 17 patients (85%). Radiologically, seven (35%) had NB, one (5%) had FC, and remaining 12 (60%) were unclassified. Cavitary lesions were noted in four (20%) patients, bronchiectasis in 12 (60%) patients, and multiple nodules in 14 (70%) patients. Fibrosis, emphysema, pleural effusion, pulmonary artery enlargement and lymphadenopathy were absent. The causative NTM species comprised *M. avium* (10/20, 50%), *M. fortuitum* (4/20, 20%), *M. xenopi* (3/20, 15%), *M. abscessus* (3/20, 15%), and *M. gordonae* (1/20, 5%). Among 20 patients, 90% received ⩾3 medications for NTM treatment; macrolides were used in 20/20 (100%), ethambutol in 13/20 (65%), and rifamycins in 8/20 (40%). Of 10 patients with *M. avium*, 90% were treated with at least macrolide plus ethambutol. All three *M. xenopi* patients were treated with azithromycin, ethambutol and rifabutin. *M. abscessus* was treated with at least a macrolide and two intravenous antibiotics. Overall, 15 patients (75%) showed radiological improvement (mean 2.4 months), and 12/16 patients (75%) who could be microbiologically assessed, achieved culture conversion (mean 3.9 months). Follow-up was until October 2017. The median survival from initiation of NTM-PD treatment was 357 days (range 7–1840 days), with four patients alive at the end of follow-up. No autopsies were performed on study subjects.

Using a strict application of diagnostic guidelines, we identified 20 patients treated for NTM-PD post alloHCT, and observed radiological and microbiological improvement in the majority. The widespread environmental distribution of NTM and the difficulty differentiating contamination or colonisation from disease makes diagnosing NTM-PD especially challenging in alloHCT patients, who often have other potential causes for pulmonary symptoms. It was difficult to interpret clinical manifestations because of frequent simultaneous co-isolation of other potential pathogens and low lung function due to GvHD. Radiological abnormalities of GvHD may also further impede defining NTM-PD. Accordingly, the diagnosis of NTM-PD after alloHCT may necessarily rely more on microbiology. It may therefore be useful to consider Centers for Disease Control criteria for NTM-PD after alloHCT [3, 5, 10], wherein the diagnostic probability is primarily assessed microbiologically.

Treating NTM-PD in alloHCT recipients is complicated by drug interactions between antibiotics and immunosuppressants. All patients in our study received a macrolide, and 13 (65%) used ethambutol. For *M. avium*, although macrolide-based three-drug regimens (including ethambutol and rifamycins) are recommended as standard, the role of ethambutol is often considered superior to rifamycins. In fact, one small prospective trial found no benefit of the three-drug regimen over macrolide/ethambutol in immune-competent patients [11]. Rifampin or rifabutin are recommended first-line agents for *M. avium* and *M. xenopi*, but were often avoided because of concerns regarding drug interactions with calcineurin inhibitors, corticosteroids, anti-fungals and other drugs, likely explaining the high rate of fluoroquinolone use (70%).

A literature review revealed four studies describing treatment details in alloHCT recipients with NTM-PD (unpublished data, available on request from the authors) [3, 5, 12, 13]. A total of 22 patients were treated with antimycobacterial drugs; *M. avium* complex accounted for 11/22 (50%) cases, followed by *M. abscessus* (4/22, 18%), *M. fortuitum* (2/22, 9%) and *M. chelonae* (2/22, 9%). Antibiotic information was available in 16 cases, among whom macrolides were used in 88% (14/16) regardless of species, rifamycins in 50% (8/16), ethambutol in 44% (7/16) and fluoroquinolones in 31% (5/16). Similar to our study, macrolides were used in almost all patients, yet the use of fluoroquinolones differed. Our experience avoided rifamycins (used in 4/10 *M. avium* cases and 0/6 with rapid-growing mycobacteria), generally substituting fluoroquinolones. In the previous reports however, rifamycins were used more frequently in *M. avium* complex cases (5/8; 63%) compared to rapid-growing mycobacteria cases (2/7; 29%), and fluoroquinolones were used less (2/8 *M. avium* complex cases and 4/7 rapid-growing mycobacteria cases).

Despite immunosuppression and comorbidity, radiological improvement and culture conversion were achieved in most of our patients, suggesting NTM-PD is manageable if alloHCT recipients can tolerate multidrug antimicrobial therapy. Yet, survival was poor; 8/20 patients (40%) died within 1 year of diagnosis. In previous reports, among 21 patients (one patient was lost to follow-up) [3, 5, 12, 13], 11 patients (50%) completed antimycobacterial therapy, while 11 patients (50%) died before completing therapy (5/11 died from NTM-PD progression); mortality comparable to our study [6]. Based on our experience, we think that NTM-PD was unlikely the sole cause of death in all these patients, but more likely that mortality was also due to complications of GvHD, including poor lung function and superimposed polymicrobial infection. As previously identified, NTM-PD occurs most commonly in patients with severe GvHD and cytomegalovirus viremia [6].

In conclusion, we reviewed NTM-PD among alloHCT recipients who required antimycobacterial therapy and summarised NTM species distribution, radiographic appearance and outcomes. The strategy for NTM-PD diagnosis in alloHCT patients appeared similar to immunocompetent individuals, although a

greater emphasis on microbiology is probably required. Radiological and microbiological improvement was usually achievable, but survival was poor. For these reasons, alloHCT patients with suspected NTM-PD should be assessed by physicians with expertise in NTM in addition to those with expertise in alloHCT pulmonary complications.

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