Tuberculosis after hematopoietic cell transplantation: Retrospective study on behalf of the Infectious Diseases Working Party of the EBMT

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ABSTRACT

Tuberculosis (TB) is rare following hematopoietic cell transplantation (HCT). In this multinational retrospective study, we report the frequency, characteristics and outcome of TB following HCT performed during 2000-2019. Fifty-two patients (35 (67%) males, 15 (29%) children) from 24 centers developed TB following allogeneic (n=47) or autologous (n=5) HCT; with the relative frequency of 0.21% and 0.025%, respectively. Forty (77%) were bacteriologically, 12 (23%) clinically confirmed. The median time from HCT to TB was 135 (range, 16-3225) days. Eighteen (35%) patients with extrapulmonary TB (mainly involving lymph nodes and liver/spleen) were significantly younger, developed TB shorter after HCT, more often had inherited underlying disease, and received immunosuppressive therapy at TB diagnosis as compared to pulmonary TB. Five (22%) of 23 patients with drug-susceptibility testing performed, were resistant to at least one anti-TB drug. Treatment success was achieved in 38/50 (76%) of treated patients. One-year overall survival reached 75.7% and the 1-year cumulative incidence of TB-associated death was 18.1%.

Concluding, TB is a rare, albeit severe complication, which can develop any time after HCT, frequently involves extrapulmonary sites, and results in high mortality rates. High proportion of drug-resistant TB warrants routine susceptibility testing.

Key words: Tuberculosis, hematopoietic cell transplantation, extrapulmonary, anti-tuberculosis treatment, rifampicin, drug-resistant tuberculosis

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB), an acid-fast bacilli (AFB), spreading through AFB-containing aerosol droplets. Robert Koch was the first to identify the pathogen in the nineteenth century(1). TB can affect anybody, while it is especially prevalent in undernourished, alcohol-abusing, and immunocompromised patients. As such, TB may complicate the clinical course of patients with hematological malignancies, and the patients undergoing hematopoietic cell transplantation (HCT), both allogeneic (allo-HCT) and autologous (auto-HCT).

The frequency of TB is known to be influenced by environmental factors leading to the geographical-region frequency variation. Based on the published data, the frequency of TB in both patients with hematological malignancies and those after HCT spanned between 0.7% (range, 0.4%–2.3%) and 2.7% (range, 1.5%–16.0%), respectively, depending on whether the report covered a low or high TB-burden region (2). Additionally, TB frequency variations can be observed based on the period covered by the analysis (3). In general, there is a paucity of data on the frequency and outcome of TB in patients after auto- and allo-HCT(4-17), especially the ones coming from the more recent era. The outcome of TB after HCT is considered dismal (4, 5), but large studies confirming this finding are lacking.

Therefore, we launched a retrospective analysis of TB in centers aligned at the EBMT to elucidate the issue of its frequency in the modern era, including the frequency of drug-resistant TB, and its clinical presentation, as well as to analyze the outcome of patients developing TB after HCT.

METHODS

Data source

The study was performed on behalf of the Infectious Diseases Working Party (IDWP) of the EBMT. EBMT is a voluntary organization comprising more than 600 transplant centers from Europe and beyond. Accreditation as a member center requires submission of minimal pseudonymized essential data (MED-A form) from all consecutive patients to a central database, including demography, underlying disease, response to the pretransplant treatment, HCT characteristics, follow-up including response to hematologic treatment, relapse/progression, survival status, development of secondary malignancies, post-transplant treatment and cause of death.

All member centers were invited to provide additional study-specific data about eligible patients, specifically information about TB developing after HCT. Informed consent was obtained locally according to the regulations applicable at the time of transplantation.

Study Population and outcome

This was a retrospective analysis of all patients who developed TB after autologous or allogeneic HCT performed during 2000-2019. Patients with latent tuberculosis infection (LTBI) were not included.

The primary objective of the study was to analyze the outcome of TB, i.e., the attribute TB mortality and the overall survival (OS) of the patients with TB. The secondary objectives were to examine the frequency of TB, clinical presentation, resistance pattern, the efficacy of anti-TB treatment and factors associated with OS.

Definitions

A TB case was defined as either a bacteriologically confirmed or clinically diagnosed case.

A bacteriologically confirmed TB was defined as the growth of MTB in *Mycobacteria* culture media or the positivity for MTB in the nucleic acid amplification test (NAAT). A diagnosis of a clinically diagnosed TB was made when the patient did not fulfil the criteria for bacteriological confirmation but was diagnosed with active TB by a treating physician who decided to give the patient a full course of TB treatment. This could for instance include cases with positive AFB smears, radiological abnormalities or suggestive histopathology (18).

Pulmonary TB was defined as TB involving the lung parenchyma or the tracheobronchial tree either as the only clinical manifestation or as a part of a miliary TB or when lungs were involved together with other organs. Extrapulmonary TB was defined as TB involving solely organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges) (18).

Latent tuberculosis infection (LTBI) was defined as the presence of immunoreactivity to TB antigens, tested by interferon-γ release assay (IGRA) or tuberculin skin test (TST) in the absence of clinical and radiologic manifestations of TB (19).

Mono-resistant MTB was defined as MTB resistant to one first-line anti-TB drug only; poly-resistant MTB as MTB resistant to more than one first-line anti-TB drug, other than both isoniazid (INH) and rifampin (RIF) simultaneously; multidrug-resistant (MDR) MTB as MTB resistant to at least both INH and RIF; extensive drug-resistant (XDR) MTB as MTB resistant to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin or amikacin) in addition to multidrug resistance; and RIF-resistant (RR) MTB as MTB resistant to RIF with resistance detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs (20).

Immune reconstitution inflammatory syndrome (IRIS) was defined as a paradoxical worsening of symptoms, signs, or clinical manifestations of TB emerging in a patient receiving anti-TB treatment after reconstitution of immune responsiveness after HCT(21).

Hematological treatment after HCT and before the development of TB comprised any type of anti-neoplastic treatment active against the underlying hematological disorder or donor lymphocyte infusions (DLI).

For the purpose of the analysis, we used the below mentioned thresholds to define the burden of TB: low TB burden countries: <10 new and relapse cases per 100 000 population per year (22); lower-moderate TB burden countries: 10-49 cases per 100 000 population per year; upper-moderate TB burden countries: ≥50-99 cases per 100 000 population per year. Countries with the annual incidence of ≥100 cases per 100 000 population were considered high TB burden (2).

Management of tuberculosis

Performance of screening for LTBI depended on the center policy. Treatment of LTBI, also termed prophylaxis for active TB development, was performed with the usage of INH or RIF and was also at the discretion of the transplant center.

TB treatment was divided into the intensive phase and the continuation phase (19). The duration of both phases was dependent on the localization of the TB and drug susceptibility and was at the discretion of the treating physician.

Response to treatment

Response to treatment was assessed according to the criteria proposed by WHO and comprised categories: 1) cured, 2) treatment completed, 3) treatment failed, 4) lost to follow-up, 5) not

evaluated, and 6) died (18). Responses of either “cured” or “treatment completed” were summed up and categorized as “treatment success”.

Relapsed TB was defined in patients who had previously been treated for TB, had been declared cured or treatment completed at the end of their most recent course of treatment, and eventually were diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Statistical analysis

Continuous variables were presented as median values (and their min-max or 1Q-3Q values, being specified in the brackets), while absolute and percentage frequencies were used for categorical variables.

The relative frequency of TB was calculated based on the information on the number of cases and transplantations at centers which reported the TB cases. The Kaplan-Meier estimator was used for OS: death due to any cause was considered as an event. The cumulative incidence method was used to estimate the death due to TB: death due to TB was considered as event of interest, whilst death from other causes was considered as competing event. Time from TB diagnosis to death or latest follow-up was considered as interval time for both the estimates. The median follow-up was calculated using the reverse Kaplan–Meier estimator.

The Cox proportional hazards regression model was used in univariate analysis for comparisons of groups. Multivariate analysis was not performed because of the small patients’ group analyzed.

P-values <0.05 were considered significant. All estimates are reported with accompanying 95% confidence intervals in brackets. All analyses were performed using the statistical software SAS v.9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

Twenty-four centers from 16 countries (Czech Republic, France, Germany, Hungary, Italy, The Netherlands, Poland, Romania, Russia, Saudi Arabia, Spain, Sweden, Switzerland, Tunisia, Turkey, United Kingdom) reported the cases. Fifty-two patients developed TB after HCT, of which the

majority 35 (67%) were males. twenty-seven cases were from low TB burden countries, 19 cases were from lower-moderate TB burden countries and 6 cases were from an upper-moderate TB burden country. Forty-seven (90%) patients had TB after allo-HCT and the remaining 5 (10%) after auto-HCT. The total number of allo-HCTs performed at that time in the participating centers was 21,946, while the total number of auto-HCTs was 19,975, translating into the relative frequency of reported TB of 0.21% and 0.025% respectively for the whole study period. The median age of the patients at HCT was 30.8 years (range, 0.5-66.8), and the most frequent underlying disease was acute leukemia (20, 38%). Patients' characteristics are reported in Table 1.

History of tuberculosis and screening for tuberculosis before HCT

There were no patients with a history of active TB before HCT. The screening for TB was performed in 12 (23%) patients, but only for 9/12 (75%) the result of the screening was available, with 2/12 (17%) having positive results. Despite positive screening results these two patients did not receive prophylaxis for LTBI, while all 3/12 (25%) patients, for whom the results of screening were unavailable, received prophylaxis (2 patients INH-RIF, 1 patient INH) and still developed overt TB after 2, 2, and 4 months after HCT. Due to the retrospective nature of the study, the reason for these decisions were unknown.

Tuberculosis after HCT (Table 2)

The screening for LTBI after HCT was performed in 10/52 (19%) patients, its results were available in 9/10 patients, and in 2/9 (22%) they were positive; these two patients, however, did not receive prophylaxis. In the remaining patients, screening results were negative in six cases and indeterminate in one. Among patients without screening test performed, 4/42 (10%) patients did receive prophylaxis for LTBI. Again, the reason for the decision cannot be elucidated because of the retrospective nature of the study.

The median age at TB diagnosis was 32.0 years (range, 0.7-68.5), with patients developing extrapulmonary TB being significantly younger than patients with pulmonary TB, i.e., 9.3 (range, 0.7-57.8) vs 36.7 (range, 6.1-68.5) years respectively, p=0.002. The median time from HCT to TB was 135 days (range, 16-3225), significantly longer for patients with pulmonary TB (184 vs 97 days, p=0.02).

Fifteen (29%) patients had a concomitant infection at TB diagnosis, with 5 (10%) of them having more than one pathogen, including one patient with chronic hepatitis C virus and invasive fungal disease.

The median time from the first symptoms to TB diagnosis in 47 patients was 14 (range, -5-347) days, with one patient developing symptoms only after the diagnosis of TB. The time to TB diagnosis was significantly shorter in children than in adults (median 9 vs 28 days). Four out of 51 (8%) patients were asymptomatic (missing data for 1 patient). While fever was the most frequent symptom of TB (occurring in in 34/51 (67%) patients), still approximately a third of the patients was afebrile. The frequency of subsequent symptoms occurrence is presented in Table 2.

Extrapulmonary TB developed solely after allo-HCT. The pulmonary and extrapulmonary TB groups differed in terms of age and time to TB, as described above, as well as TBI usage in conditioning, immunosuppression administration at the time of TB diagnosis and underlying disorder. Patients developing extrapulmonary TB were more frequently on immunosuppression (89% vs 55%, p=0.02). TBI was used solely for patients with pulmonary TB (34% vs 0%, p=0.008). Among patients with extrapulmonary TB, a significant proportion (7/18, 39%) suffered from inherited disorders (5 bacteriologically confirmed, 2 clinically diagnosed), while none of the pulmonary TB patients had inherited disorders as an indication for HCT (p=0.0002). On the other hand, significantly fewer extrapulmonary TB patients were diagnosed with acute leukemias as compared to the pulmonary TB patients (2/18, 11% vs 18/34, 53%; p=0.003) (Table 1).

When children and adults developing TB were compared significant differences were found. Inherited disorders were an indication for HCT solely in a pediatric population (47% vs. 0%, p<0.0001); with children receiving T-cell depletion more frequently than adults (77% vs. 44%, p=0.04). Also, fewer children required treatment after HCT and before TB (0% vs. 27%, p=0.046). The clinical presentation was also distinct, with more frequent lymph node enlargement and the presence of skin lesions.

In patients with extrapulmonary TB, the most frequently involved sites were the lymph nodes (9/18, 50%) and the liver/spleen (5/18, 28%); and the most common presentations were lymphadenopathy (8/18, 44%) and skin abscesses (5/18, 28%) (Table 2).

Diagnostic procedures for tuberculosis and antimicrobial susceptibility

Forty (77%) patients had a diagnosis of bacteriologically confirmed TB and 12 (23%) had clinically diagnosed TB (Table 2). Among patients with clinically diagnosed TB, 5 cases were diagnosed solely clinically, 7 based on either AFB or histopathology. Concerning the localization of TB, among 18 extrapulmonary cases 14 were bacteriologically confirmed and 4 were clinically diagnosed TBs; of the 34 pulmonary cases, 26 were bacteriological and 8 were clinical.

Data on antimicrobial susceptibility were available from 23/52 (44%) isolates, and 5/23 (22%) of them were resistant to at least one antimicrobial by at least one test (Table 3), including 2/23 (9%) mono-resistant isolates (one to INH and one to Pyrazinamide (PZA)), one poly-resistant isolate (to INH and Ethambutol (EMB)), one MDR isolate (INH and RIF resistant) and one RR isolate (RIF and Fluoroquinolone resistant).

Treatment of tuberculosis

Fifty (96%) patients received anti-TB treatment. The anti-TB therapy consisted of 2 drugs in 3 (6%), 3 drugs in 11 (22%), 4 drugs in 28 (56%) and 5 or more drugs in 8 (16%) treated patients. The most used combination was INH-RIF/Rifabutin-PZA-EMB, which was administered to 20 (40%) patients (Supplementary Table S1).

The intensive phase lasted a median of 3 months (IQR, 2.0-6.0), while the whole treatment i.e., the intensive and continuation phase, was 8 months (IQR, 6.0-12.0). For patients with pulmonary TB, the median duration of the intensive phase was 2 months (IQR, 1.0-6.0), while of the whole therapy it was 6 months (IQR, 4.0-9.0). In patients with extrapulmonary TB, the intensive phase was 6 months (IQR, 3.0-7.5), and the whole treatment was a median of 12 months (IQR, 6.3-12.0) (Table 2). The only drug administered >18 months was levofloxacin in a single patient. For 2 (4%) patients there was missing data on the duration of therapy.

In 13/50 (26%) patients at least one drug was interrupted, most frequently RIF (7, 14%), INH and PZA (5, 10% each). The reasons for discontinuation were side effects, including mainly drug-induced hepatitis (4, 8%), gastrointestinal reactions (4, 8%) and neurotoxicity (2, 4%).

Two patients did not receive treatment and succumbed early after TB diagnosis; one due to hemorrhage complicating splenectomy performed for splenic TB, the other due to multiorgan failure in the course of multiple infections (including invasive aspergillosis).

IRIS complicated the anti-TB treatment in 3 (6%) patients who were diagnosed with TB 0, 2 and 3 months after HCT, and were treated with INH-RIF-Clarithromycin, INH-RIF-EMB, and INH-RIF respectively. All patients were alive at the last follow up.

Treatment success was achieved in 38/50 (76%) patients. The response to treatment was classified as treatment failure in 3 (6%) patients, 1 (2%) patient was lost to follow-up and 5 (10%) were not evaluated at last follow-up. Apart from the 2 patients who died without receiving anti-TB treatment, 3 (6%) patients died during the anti-TB treatment (Figure 1A).

Survival of patients with tuberculosis

With median follow-up time of 35.9 months (95% CI 23.2-65.1), the estimated 6-month and 1-year OS were: 84.4% (71.2-91.9%) and 75.7% (61.1-85.5%), respectively.

Nine patients (17%) succumbed to TB during the observation time, resulting in the cumulative incidence of TB-associated death of 15.9% (7.4-27.4%) and 18.1% (8.8-30.0%) after 6 months and 1 year respectively (Figure 1B). One patient (2%) out of 52 for whom the information was available had a recurrence of TB in the lungs after the initial successful treatment.

The 6-month and 1-year OS for allo-HCT was 82.8% (68.5-91.0) and 73.5% (58.0-84.9), respectively. For the 5 auto-HCTs we can only report that no deaths occurred.

No prognostic factors for the overall survival or for TB-associated mortality were identified in the univariable analysis. There was however a trend for shorter OS for patients on corticosteroids at the time of TB diagnosis (HR=3.21, 95% CI 0.97-10.7; p=0.06) and patients transplanted more recently (≥2016 vs <2016; HR=4.28, 95% CI 0.93-19.57; p=0.06). On contrary, patients treated with other protocols than INH-RIF-PZA-EMB combination did have a trend for better OS (HR=0.30, 95% CI 0.09-1.09: p=0.07) (Supplementary Table S2).

DISCUSSION

In this retrospective multinational study, we provide data on the rates, clinical manifestations, resistance pattern, and treatment outcomes of TB in HCT patients at centers aligned at the EBMT. To the best of our knowledge, this is the biggest cohort of HCT patients with TB reported ever and the most updated European study during the last 20 years. The existing data are from the endemic, non-European countries and the European reports are old (Table 4). Our main findings include: (a) high

rate of extrapulmonary TB (35%), with these patients diagnosed much earlier after HCT (97 vs. 184 days) and at much younger age (9.3 vs. 32.0 years) as compared to pulmonary TB; (b) high rate of resistance to at least one drug (22%) with overall low rate of drug susceptibility testing (DST) (44%); and (c) high rate of inability to obtain treatment success (24%), and 18.1% cumulative incidence of TB-associated death after 1 year.

Tuberculosis is an infrequent infectious complication after HCT, with frequency dependent both on the geographical region, as depicted in Table 4, and the time analyzed (3). In the current study, the TB relative frequency was established at 0.025% and 0.21% for auto- and allo-HCT, respectively, being much lower than the frequency of TB in high TB-burden countries (Table 4) (22), but also lower (0.13% and 1.06%, respectively) than the frequency reported in the pivotal EBMT study by Cordonnier et al covering the period 1994-1998 (4). We admit that this rate can be biased by underreporting, especially concerning the earliest years of analysis, and potentially also after auto-HCT, where post-HCT surveillance can be performed by non-transplant centers. However, looking at the TB frequency it can be seen that the number of TB cases is not approaching zero. Therefore, despite the likely decreasing incidence of TB, it is a still a non-negligible threat among post-HCT infectious complications.

Active TB treated before transplantation and inactive at the time of transplantation is considered a significant risk factor for TB development after HCT with HR of 8.494; 95% CI 3.31-21.79 (7). Interestingly, both EBMT studies performed 20 years apart, report on the rare history of pre-HCT TB (none in the current EBMT analysis and 1/20 in the previous EBMT report(4)). This is different from reports from intermediate/ high TB-burden countries; for example, in a Korean study, 10 out of 21 patients (47.6%) who developed TB after allo-HCT had a history of active TB prior to transplantation (6).

The profile of the TB-affected patients in our study indicates a high degree of immune deficiency. First, similar to the other studies (3-5, 10), the incidence of TB in our study was substantially higher in patients undergoing allo-HCT in comparison to auto-HCT. Approximately two thirds of patients were still receiving immunosuppression at the time of TB diagnosis and 50% of patients underwent T-cell depletion. As reported elsewhere, TB development may be dependent on a complex dysfunction of immunity, including T- and NK-cells (23), monocytes, as well as disturbed extracellular matrix (24), and not simply on neutropenia. To advocate for disturbed immunity,

385 approximately one-third of patients suffered from a concomitant infection at the time of TB diagnosis.
386 Unlike in previous reports in which most concomitant infections were bacterial (4), in the current
387 analysis, patients with invasive fungal or viral infections prevailed, while patients with bacterial
388 infections constituted only a small proportion of all cases.
389 Tuberculosis developed at a wide range of times from HCT, though most cases were
390 diagnosed within the first months after HCT, with the median time to TB of 135 days. It is worth noting,
391 that patients with extrapulmonary disease developed TB much earlier than patients with pulmonary
392 disease (median 97 vs. 187 days, p=0.03). This timing of TB in general is similar to the timing reported
393 by the previous EBMT report (4), however significantly shorter than the timing reported by others (5, 6,
394 25), where TB was diagnosed after approximately a median one year after HCT. It must however be
395 kept in mind that at some centers the surveillance over the transplanted patients after HCT may be
396 short, which precludes reporting cases that occur late after HCT.
397 The clinical presentation of TB is similar as reported earlier. Alike in the previous EBMT study,
398 the lung was the most frequently involved organ, though the respiratory tract symptoms were present
399 in a smaller proportion of patients e.g. cough (38% vs. 48%) and dyspnea (21% vs. 32%). The
400 prevailing symptom was fever, regardless of the site of TB, present in 67% of patients. Even though
401 pulmonary TB prevailed in the analyzed group, extrapulmonary TB was diagnosed in 35% of patients.
402 In other reports the proportion of extrapulmonary TB spanned between 10% and nearly 50% (4-7),
403 and its clinical features are poorly described. The current ratio of 35% for extrapulmonary TB is within
404 the upper limit of the range. It supports the finding that patients developing TB after HCT are severely
405 immunocompromised, and children and adolescents prevailed in this cohort (median age 9.3 years)
406 with unique profile of indications for allo-HCT (inherited disorders: 39% vs 0% in cases of pulmonary
407 TB). Importantly, patients with bacteriologically confirmed TB prevailed in this cohort which precludes
408 the diagnosis of BCG-itis. It is also worth emphasizing that patients with extrapulmonary TB were
409 receiving immunosuppression more frequently (89% vs 55%, p=0.02) than patients with pulmonary
410 TB. The most frequently involved extrapulmonary sites in our study were the lymph nodes, the
411 liver/spleen and skin/soft tissues.
412 The worrying finding in our study is a relatively high (22%) rate of resistance to at least one
413 drug, and the presence of poly-resistant, MDR and RIF-resistant bacteria, compared to the previous
414 report, where no strain was resistant to any of the anti-TB drugs tested (4), although a similar

proportion of isolates were tested for susceptibility (44% in our study, and 47% in the previous report). Globally, the estimated annual number of people who developed MDR/RR-TB was relatively stable between 2020 and 2022, after a slow downward trend between 2015 and 2019 as reported by WHO in their Global Tuberculosis Report 2023 (22). There is however a concern that the rate of drug-resistant TB may increase as a result of COVID-19 pandemic e.g. (26). Current European Conference on Infections in Leukemia (ECIL) guidelines (27) recommend performing DST for all MTB isolates, to enable delivering curative treatment and prevent from developing resistance (20). Unfortunately, the rate of DST remains low in the EBMT centers, although it is higher than the 15% rate of DST in the Chinese study (7). This increasing resistance rate strongly supports the ECIL guidelines recommendation on performing routine DST.

In the current analysis treatment success was obtained in 76% of patients. This success rate is lower than the one expected in the general population (approximately 85% as reported by WHO) (28), but is similar to the 75.8% response rate among allo-HCT patients in Chinese study (7). It cannot be excluded that this is the result of MTB drug-resistance, which was however not tested and hence not included in the decision-making process of protocol choice. Patients were treated with a variety of different classical combinations. Patients with the extrapulmonary disease were treated substantially longer i.e. median 12 months, as recommended (29). This led to similar outcomes in terms of survival in patients with extrapulmonary TB (HR=0.55, 95% CI 0.15-2.03, p=0.4) in comparison to pulmonary TB. None of the patients received bedaquiline-based treatment (30).

The overall survival of patients with TB in our study was dismal. The estimated 1-year OS rate was 75.7%, and the cumulative incidence of TB-associated death after 1 year was 18.1%. The dismal outcome of TB in the current report seems to remain unchanged in comparison to the earlier studies, where the TB-associated death rate amounted at approximately 15% (4, 5). Interestingly Zeng et al (7) in their report using propensity score matching analysis did not detect any significant differences in prognosis between the TB and control groups.

We were not able to identify any factors predictive of OS in patients with TB after HCT, although there was a trend for shorter OS in patients on corticosteroids at the time of TB diagnosis (HR=3.24, 95% CI 0.97-10.8; p=0.06) and patients transplanted more recently (≥2016 vs <2016; HR=4.41, 95% CI 0.96-20.19; p=0.06). This can be due to immune suppressive effect of steroids that affect control on infection on treatment and ameliorate the symptoms of infection and delay diagnosis,

as shown in in the previous EBMT report (4). On contrary, patients treated with other protocols than the 4-drug combination of INH-RIF-PZA-EMB did have a trend for better OS (HR=0.29, 95% CI 0.08-10.4); probably as the more severely ill patients received a 4-drug protocol as compared to a 3-drug protocols in a less severely ill.

Despite the fact that drug-drug interactions between RIF and calcineurin inhibitors (CNI) (31, 32) as well as other drugs, e.g. antibiotics, are well known, there is little data in the published literature on the impact of RIF administration on the outcome of transplantation. Temporary subtherapeutic plasma CNIs concentration caused by CYP3A4 activation by RIF can potentially lead to the development of graft versus host disease (GvHD) (5, 33). In our group of TB patients, we did not observe a clear tendency for avoiding RIF in the treatment (strategy used in some solid organ transplantation (SOT) patients(34, 35)), with 83% of patients being exposed to RIF. RIF, however, was the most frequently interrupted anti-TB drug, mostly for side effects. Unfortunately, we were not able to analyze the impact of RIF dosing on the GvHD occurrence.

The incidence of IRIS in the analyzed population amounted at 6% and was lower than the respective frequency of 14% reported for SOT (36) or allo-HCT population(6). IRIS is a complication of TB treatment known mostly from the treatment of human immunodeficiency virus (HIV) infected patients (37), and poorly described in HCT patients. It may be hypothesized that continued immunosuppression/ corticosteroid exposure contributed to its low incidence in our study.

This study has several limitations. First, it is a retrospective study. Second, the real TB relative frequency is possibly underestimated, due to the possibility of underreporting of the TB cases, especially those diagnosed in the earlier years of the analysis and those diagnosed later after HCT, when patients were not under the surveillance of the transplant center anymore. Third, the lack of a control group does not allow to identify risk factors associated with the development of TB. Additionally, the significant proportion of clinically diagnosed TB and the unavailability to differentiate between MTB and nontuberculous mycobacteria is also an important limitation. Nevertheless, we believe the study provides important and updated information on the frequency, clinical presentation, resistance pattern, and outcome of TB in the modern era based on the largest international cohort of patients with TB developing after HCT reported so far.

To conclude, TB can develop anytime from HCT, with most cased identified during the first months after transplantation when the patients stay under an active surveillance by transplant centers,

but probably also with late onset cases diagnosed when the patients are already outside the transplant centers. TB manifests frequently as an extrapulmonary disease and contributes substantially to the death of the affected patients. A significant proportion of patients are diagnosed with MTB strains resistant to anti-TB drugs, which warrants susceptibility testing and choosing appropriate treatment protocol based on it.

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AUTHOR CONTRIBUTIONS

JDS, JS, MM, AWG designed the study. JDS, DA, IV wrote the manuscript. IV, LW, NK managed data, GT did the statistics. DA, JS and RC supervised the study. MK, NBA, AC, MA (Mahmoud Aljurf), NK, GO, JP, MG, MP, LLC, AT, AP, MA (Mohsen Alzahrani), MCA, GB, ACEB, KC, AC, MF, PJ, GK, SDL, SM, JN, FP, KP, JAS, IY, MZ, AWG, RC, LG, MM, JS critically revised the paper and approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL

This retrospective study was approved by the Infectious Diseases Working Party (IDWP) of the EBMT and was performed in accordance with the Declaration of Helsinki.

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603

Table 1 Patients and hematopoietic cell transplant (HCT) characteristics at the time of HCT (allo-HCT – allogeneic hematopoietic cell transplantation, auto-HCT – autologous hematopoietic cell transplantation, ATG – anti-thymocyte globulin, BEAM – bendamustine, etoposide, cytarabine, melphalan, CML – chronic myeloid leukemia, CMV – cytomegalovirus, CR – complete response, CsA – cyclosporine A, GvHD – graft versus host disease, Gy – gray, HLA – human leukocyte antigen, LEAM - lomustine, etoposide, cytarabine, melphalan, MAC – myeloablative conditioning, MDS – myelodysplastic syndrome, MMF – mycophenolate mofetil, MPN – myeloproliferative neoplasm, MTX – methotrexate, PR – partial response, PT-CY – post-transplantation cyclophosphamide, RIC – reduced intensity conditioning, TAC – tacrolimus, TB – tuberculosis, TBI – total body irradiation, TCD – T-cell depletion)

Table 2 Patients and tuberculosis (TB) characteristics at the time of TB diagnosis (AFB - acid-fast bacilli, allo-HCT – allogeneic hematopoietic cell transplantation, auto-HCT – autologous hematopoietic cell transplantation, BAL – bronchoalveolar lavage, CARV – community acquired respiratory viral infections, CMV – cytomegalovirus, CNS – central nervous system, CR – complete response, CSF – cerebrospinal fluid, EMB – ethambutol, GvHD – graft versus host disease, HCT - hematopoietic cell transplantation, IGRA - interferon-γ release assay, INH – isoniazid, NAAT - nucleic acid amplification test, PR – partial response, PZA – pyrazinamide, RIF – rifampicin, RSV - respiratory syncytial virus)

[1] Aspergillus (5, 10%), invasive fungal infection (2, 4%), Candida Guilliermondii (1, 2%);

[2] respiratory syncytial virus (2, 4%), bocavirus (1, 2%); rhinovirus (1, 2%);

[3] hepatitis C virus (1, 2%), herpes simplex virus (1, 2%), picornavirus (1, 2%), varicella-zoster virus (1, 2%);

[4] Klebsiella (1, 2%), Pseudomonas (1, 2%);

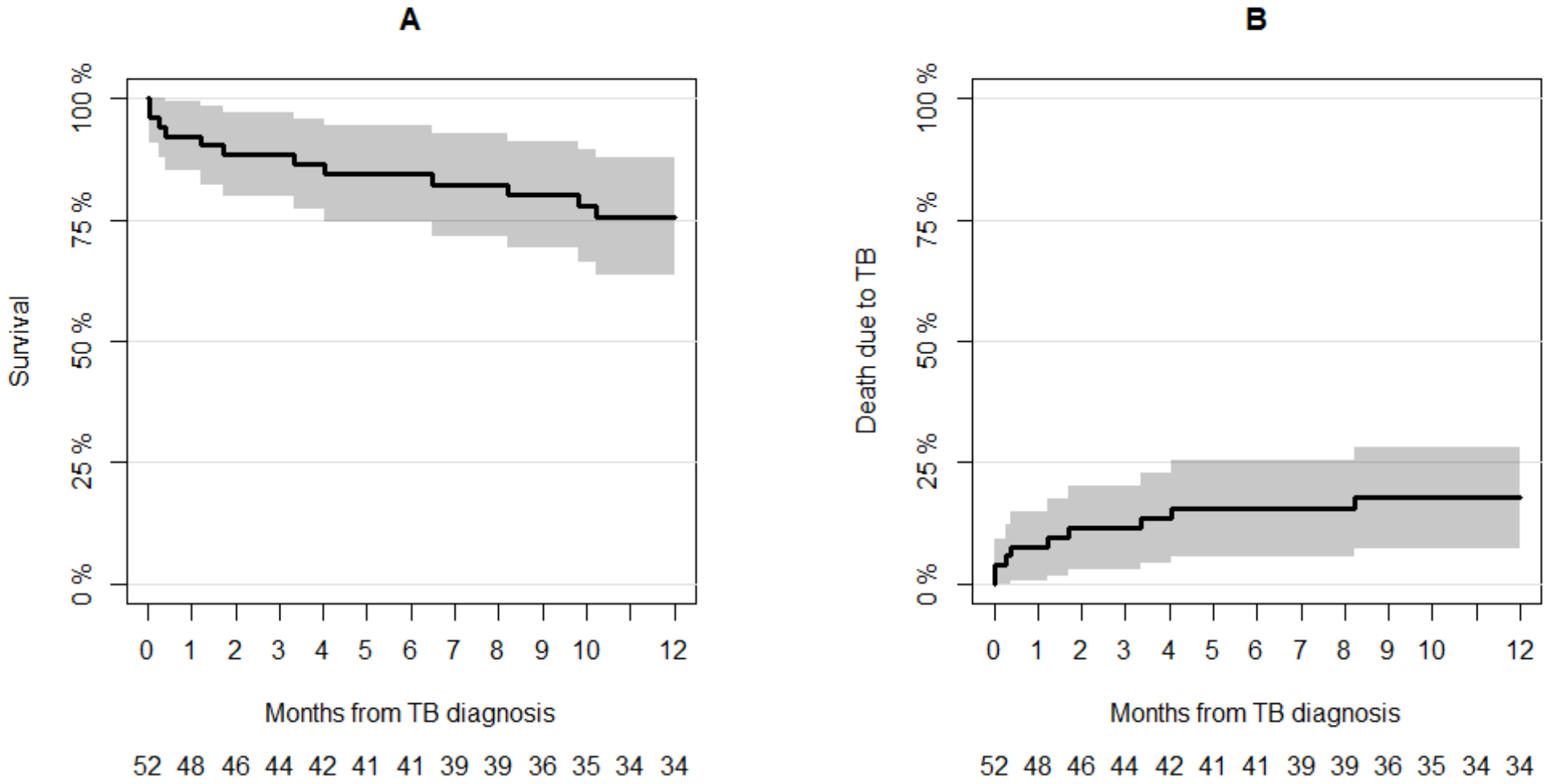
[5] Aspergillus + Candida Guilliermondii (1, 2%), Aspergillus + Pseudomonas + rhinovirus (1, 2%), cytomegalovirus + varicella-zoster virus (1, 2%), hepatitis C virus + invasive fungal infection (1, 2%), respiratory syncytial virus + picornavirus (1, 2%)

[6] chest infection/ bone marrow; diffuse bone pain; pleural effusion; swelling at right supraclavicular region

Table 3 Number of isolates tested for specific drug susceptibility and the number of resistant isolates (INH – isoniazid, RIF – rifampicin, EMB – ethambutol, PZA – pyrazinamide, FQ – fluoroquinolone)

633 **Table 4** Published data on tuberculosis (TB) after hematopoietic cell transplantation (HCT), including
634 the frequency, frequency of drug-resistance, outcome of treatment and mortality attributable to TB.
635 Only papers reporting 10 or more patients are included. (allo-HCT - allogeneic hematopoietic cell
636 transplantation; auto-HCT – autologous hematopoietic cell transplantation; MBI – mycobacterial
637 infection; MDR – multi-drug resistant; NA – not available; OS – overall survival; TB – tuberculosis;
638 XDR – extensively drug resistant)
639 *not clear whether pulmonary cases are not included in this category
640 **no detailed description of the patients; data from medical records used to calculate the incidence

641 **Figure 1** Outcomes after tuberculosis (TB) diagnosis. 1A) Overall survival of patients who developed
642 TB; 1B) Cumulative incidence of TB associated death. Numbers below the graphs show the number of
643 patients at risk. Areas between the dotted lines show the 95% confidence intervals.


A
Survival
100 %
75 %
50 %
25 %
0 %
0 1 2 3 4 5 6 7 8 9 10 12
Months from TB diagnosis
52 48 46 44 42 41 41 39 39 36 35 34 34
B
Death due to TB
100 %
75 %
50 %
25 %
0 %
0 1 2 3 4 5 6 7 8 9 10 12
Months from TB diagnosis
52 48 46 44 42 41 41 39 39 36 35 34 34

Variable	Whole group	Localization			Certainty of diagnosis			Age group		
		Pulmonary TB	Extra-pulmonary TB	*p*	Bacterio-logically confirmed	Clinically diagnosed	*p*	Adults	Pediatrics	*p*
Number of patients with TB	52	34 (65%)	18 (35%)		40 (77%)	12 (23%)		37 (71%)	15 (29%)	
Sex										
Male	35 (67%)	24 (71%)	11 (61%)	*0.5*	29 (73%)	6 (50%)	*0.2*	26 (70%)	9 (60%)	*0.5*
Female	17 (33%)	10 (29%)	7 (39%)		11 (28%)	6 (50%)		11 (30%)	6 (40%)	
Age at HCT (years): median (range)	30.8 (0.5-66.8)	35.9 (5.7-66.8)	9.1 (0.5-57.5)	*0.003*	32.8 (0.5-66.8)	23.7 (0.6-61.1)	*0.1*	38.5 (17.9-66.8)	0.8 (0.5-16.0)	-
Number of patients ≤18 years	15 (29%)	5 (15%)	10 (56%)	*0.002*	10 (25%)	5 (42%)	*0.3*			
Year of HCT										
2000-2004	3 (6%)	1 (3%)	2 (11%)	*0.2*	2 (5%)	1 (8%)	-			
2005-2009	10 (19%)	9 (26%)	1 (6%)		7 (18%)	3 (25%)				
2010-2014	8 (15%)	6 (18%)	2 (11%)		6 (15%)	2 (17%)				
2015-2019	31 (60%)	18 (53%)	13 (72%)		25 (63%)	6 (50%)				
Year of HCT										

2000-2014	21 (40%)	16 (47%)	5 (28%)	*0.2*	15 (38%)	6 (50%)	*0.5*	19 (51%)	2 (13%)	*0.01*
2015-2019	31 (60%)	18 (53%)	13 (72%)		25 (63%)	6 (50%)		18 (49%)	13 (87%)	
Type of HCT										
auto-HCT	5 (10%)	5 (15%)	0 (0%)	*0.15*	2 (5%)	3 (25%)	*0.07*	3 (8%)	2 (13%)	*0.6*
allo-HCT	47 (90%)	29 (85%)	18 (100%)		38 (95%)	9 (75%)		34 (92%)	13 (87%)	
More than 1 HCT										
2 HCTs	6(12%)	6 (18%)	0 (0%)	-	3 (8%)	3 (25%)	-	6 (16%)	0 (0%)	
3 HCTs	2 (4%)	1 (3%)	1 (6%)		2 (5%)	0 (0%)		1 (3%)	1 (7%)	
2 or 3 HCTs	8 (15%)	7 (21%)	1 (6%)	*0.2*	5 (13%)	3 (25%)	*0.4*	7 (19%)	1 (7%)	*0.4*
Baseline disease										
Acute leukaemia	20 (38%)	18 (53%)	2 (11%)	-	17 (43%)	3 (25%)				
Chronic leukaemia	2 (4%)	1 (3%)	1 (6%)		1 (3%)	1 (8%)				
MDS or MPN	8 (15%)	3 (9%)	5 (28%)		7 (18%)	1 (8%)				
Lymphoma	8 (15%)	8 (24%)	0 (0%)		6 (15%)	2 (17%)				
Plasma cell disorders	2 (4%)	2 (6%)	0 (0%)		1 (3%)	1 (8%)				

Bone marrow failure	5 (10%)	2 (6%)	3 (17%)		3 (8%)	2 (17%)				
Inherited disorders	7 (14%)	0 (0%)	7 (39%)	*0.0002*	5 (13%)	2 (17%)	*0.7*	0 (0%)	7 (47%)	*<0.0001*
Baseline disease										
Acute leukaemia	20 (38%)	18 (53%)	2 (11%)	*0.003*	17 (43%)	3 (25%)	*0.3*	17 (46%)	3 (20%)	*0.08*
Other	32 (62%)	16 (47%)	16 (89%)		23 (58%)	9 (75%)		20 (54%)	12 (80%)	
Disease status at HCT										
CR	24 (46%)	19 (56%)	5 (28%)	-	19 (48%)	5 (42%)	-	19 (51%)	5 (33%)	
PR	5 (10%)	4 (12%)	1 (6%)		4 (10%)	1 (8%)		5 (14%)	0 (0%)	
Refractory/ active disease	5 (10%)	3 (9%)	2 (11%)		4 (10%)	1 (8%)		4 (11%)	1 (7%)	
Relapse or progression	2 (4%)	0 (0%)	2 (11%)		2 (5%)	0 (0%)		1 (3%)	1 (7%)	
Other	16 (31%)	8 (24%)	8 (44%)		11 (28%)	5 (42%)		8 (22%)	8 (53%)	
Disease status at HCT										
CR	24 (46%)	19 (56%)	5 (28%)	*0.053*	19 (48%)	5 (42%)	*0.7*	19 (51%)	5 (33%)	*0.2*
Other	28 (54%)	15 (44%)	13 (72%)		21 (53%)	7 (58%)		18 (49%)	10 (67%)	
Conditioning (for **allo**-HCT)	**n = 46**	**n = 28**	**n = 18**		**n = 38**	**n = 8**		**n = 34**	**n = 12**	

RIC	15 (33%)	11 (39%)	4 (22%)	*0.2*	12 (32%)	3 (38%)	*0.7*	14 (41%)	1 (8%)	*0.07*
MAC	29 (63%)	16 (57%)	13 (72%)		25 (66%)	4 (50%)		19 (56%)	10 (83%)	
No conditioning	2 (4%)	1 (4%)	1 (6%)		1 (3%)	1 (13%)		1 (3%)	1 (8%)	
Conditioning (for **auto**-HCT)	**n = 5**	**n = 5**			**n = 2**	**n = 3**				
BEAM	2 (40%)	2 (40%)	NA		2 (100%)	0 (0%)				
LEAM	2 (40%)	2 (40%)	NA		0 (0%)	2 (67%)				
Melpahalan	1 (20%)	1 (20%)	NA		0 (0%)	1 (33%)				
TBI in conditioning (only for **allo**-HCT)	**n = 47**	**n = 29**	**n = 18**		**n = 38**	**n = 9**		**n = 34**	**n = 13**	
Yes	10 (21%)	10 (34%)	0 (0%)	*0.008*	9 (24%)	1 (11%)	*0.7*	8 (24%)	2 (15%)	*0.7*
No	37 (79%)	19 (66%)	18 (100%)		29 (76%)	8 (89%)		26 (76%)	11 (85%)	
Dose of TBI (only for **allo**-HCT)	**n = 10**	**n = 10**			**n = 9**	**n = 1**				
2 Gy	3 (30%)	3 (30%)	NA	-	2 (22%)	1 (100%)	-			
12 Gy	6 (60%)	6 (60%)	NA		6 (67%)	0 (0%)				
20 Gy	1 (10%)	1 (10%)	NA		1 (11%)	0 (0%)				
Type of donor (only for **allo**-HCT)	**n = 45**	**n = 27**	**n = 18**		**n = 38**	**n = 7**		**n = 33**	**n = 12**	

HLA-identical sibling	14 (31%)	8 (30%)	6 (33%)	*0.9*	11 (29%)	3 (43%)	*0.9*	11 (33%)	3 (25%)	*0.1*
Unrelated	22 (49%)	14 (52%)	8 (44%)		19 (50%)	3 (43%)		18 (55%)	4 (33%)	
Mismatched related	9 (20%)	5 (19%)	4 (22%)		8 (21%)	1 (14%)		4 (12%)	5 (42%)	
Stem cell source	**n = 50**	**n = 33**	**n = 17**		**n = 39**	**n = 11**		**n = 37**	**n = 13**	
Peripheral blood	38 (76%)	25 (76%)	13 (76%)	*1*	28 (72%)	10 (91%)	*0.3*	31 (84%)	7 (54%)	*0.06*
Bone marrow	12 (24%)	8 (24%)	4 (24%)		11 (28%)	1 (9%)		6 (16%)	6 (46%)	
TCD (only for **allo**-HCT)	**n = 45**	**n = 27**	**n = 18**		**n = 37**	**n = 8**				
ATG	18 (40%)	12 (44%)	6 (33%)	-	14 (38%)	4 (50%)	-			
Other than ATG	4 (9%)	1 (4%)	3 (17%)		4 (11%)	0 (0%)				
No TCD	21 (47%)	13 (48%)	8 (44%)		18 (49%)	3 (38%)				
TCD yes, type unknown	2 (4%)	1 (4%)	1 (6%)		1 (3%)	1 (13%)				
TCD (only for **allo**-HCT)	**n = 45**	**n = 27**	**n = 18**		**n = 37**	**n = 8**		**n = 32**	**n = 13**	
Yes	24 (53%)	14 (52%)	10 (56%)	*0.8*	19 (51%)	5 (63%)	*0.7*	14 (44%)	10 (77%)	*0.04*
No	21 (47%)	13 (48%)	8 (44%)		18 (49%)	3 (38%)		18 (56%)	3 (23%)	
GvHD prophylaxis (only for **allo**-HCT)	**n = 44**	**n = 27**	**n = 17**		**n = 36**	**n = 8**				

CsA + MTX	20 (45%)	13 (48%)	7 (41%)	-	16 (44%)	4 (50%)	-			
MMF + TAC	1 (2%)	1 (4%)	0 (0%)		1 (3%)	0 (0%)				
PT-CY	6 (14%)	4 (15%)	2 (12%)		6 (17%)	0 (0%)				
Other	17 (39%)	9 (33%)	8 (47%)		13 (36%)	4 (50%)				
GvHD prophylaxis (only for **allo**-HCT)	**n = 44**	**n = 27**	**n = 17**		**n = 36**	**n = 8**		**n = 33**	**n = 11**	
CsA + MTX	20 (45%)	13 (48%)	7 (41%)	*0.7*	16 (44%)	4 (50%)	*1*	16 (48%)	4 (36%)	*0.5*
Other	24 (55%)	14 (52%)	10 (59%)		20 (56%)	4 (50%)		17 (52%)	7 (64%)	
CMV serostatus of the recipient	**n = 47**	**n = 30**	**n = 17**		**n = 37**	**n = 10**				
Positive	38 (81%)	23 (77%)	15 (88%)	*0.5*	30 (81%)	8 (80%)	*1*			
Negative	9 (19%)	7 (23%)	2 (12%)		7 (19%)	2 (20%)				
CMV serostatus of the donor (only for **allo**-HCT)	**n = 45**	**n = 28**	**n = 17**		**n = 37**	**n = 8**				
Positive	33 (73%)	18 (64%)	15 (88%)	*0.1*	26 (70%)	7 (88%)	*0.4*			
Negative	12 (27%)	10 (36%)	2 (12%)		11 (30%)	1 (13%)				
Hematopoietic recovery										
Neutrophil reconstitution: ≥ 0.5 x 10^9/L	49 (94%)	33 (97%)	16 (89%)	*NA*	37 (93%)	12 (100%)	*NA*	36 (97%)	13 (87%)	*NA*

Time to neutrophil reconstitution days, median, range	15 (1-66)	16 (1-25)	15 (7-66)		15 (8-66)	14 (1-28)				
No	1 (2%)	(0%)	1 (6%)		1 (3%)	0 (0%)				
Neutrophil never: < 0.5 x 10^9/L	2 (4%)	1 (3%)	1 (6%)		2 (5%)	0 (0%)				
	n = 51	**n = 33**	**n = 18**		**n = 40**	**n = 11**		**n = 36**	**n = 15**	
Lymphocyte reconstitution: ≥ 0.5 x 10^9/L	46 (90%)	30 (91%)	16 (89%)	*NA*	38 (95%)	8 (73%)	*NA*	32 (89%)	14 (93%)	*NA*
Time to lymphocyte reconstitution days, median, range	28 (8-253)	28 (8-253)	27 (10-107)		28 (10-253)	28 (8-89)				
No	3 (6%)	2 (6%)	1 (6%)		2 (5%)	1 (9%)				
Lymphocyte never: < 0.5 x 10^9/L	2 (4%)	1 (3%)	1 (6%)		0 (0%)	2 (18%)				

Table 1 Patients and hematopoietic cell transplant (HCT) characteristics at the time of HCT (allo-HCT – allogeneic hematopoietic cell transplantation, auto-HCT – autologous hematopoietic cell transplantation, ATG – anti-thymocyte globulin, BEAM – bendamustine, etoposide, cytarabine, melphalan, CML – chronic myeloid leukemia, CMV – cytomegalovirus, CR – complete response, CsA – cyclosporine A, GvHD – graft versus host disease, Gy – gray, HLA – human leukocyte antigen, LEAM - lomustine, etoposide, cytarabine, melphalan, MAC – myeloablative conditioning, MDS – myelodysplastic syndrome, MMF – mycophenolate mofetil, MPN – myeloproliferative neoplasm, MTX – methotrexate, PR – partial response, PT-CY – post-transplantation cyclophosphamide, RIC – reduced intensity conditioning, TAC – tacrolimus, TB – tuberculosis, TBI – total body irradiation, TCD – T-cell depletion)

Variable	Whole group	Localization			Certainty of diagnosis			Age groups		
		Pulmonary TB	Extra-pulmonary TB	*p*	Bacterio-logically confirmed	Clinically diagnosed	*p*	Adults	Pediatrics	*p*
Number of patients	52	34 (65%)	18 (35%)		40 (77%)	12 (23%)		37 (71%)	15 (29%)	
Age at TB diagnosis (years): median (range)	32.0 (0.7-68.5)	36.7 (6.1-68.5)	9.3 (0.7-57.8)	*0.002*	34.9 (0.7-68.5)	24.3 (0.9-62.2)	*0.3*	39.0 (18.8-68.5)	1.9 (0.7-17.7)	-
Number of patients <18 years	15 (29%)	5 (15%)	10 (56%)	*0.002*	10 (25%)	5 (42%)	*0.3*			
Time from HCT to TB diagnosis (days): median (range)	135 (16-3225)	184 (33-3225)	97 (16-949)	*0.03*	133 (16-3225)	344 (48-1271)	*0.1*	160 (33-3225)	111 (16-761)	*0.2*
Certainty of diagnosis					-	-				
Bacteriologically confirmed	40 (77%)	26 (76%)	14 (78%)	-	-	-	-	30 (81%)	10 (67%)	*0.3*
Clinically diagnosed	12 (23%)	8 (24%)	4 (22%)		-	-		7 (19%)	5 (33%)	
Contact with active respiratory tract TB-positive patient	4/49 (8%)	4/31 (13%)	0/18 (0%)	*0.3*	4/38 (11%)	0/11 (0%)	*0.6*	3/34 (9%)	1/15 (7%)	*1*
Disease status at TB diagnosis	**n = 48**	**n = 32**	**n = 16**		**n = 37**	**n = 11**				
CR	36 (75%)	23 (72%)	13 (81%)	-	28 (76%)	8 (73%)	-			
PR	3 (6%)	3 (9%)	0 (0%)		2 (5%)	1 (9%)				
Relapse/refractory or active disease	8 (17%)	6 (19%)	2 (13%)		6 (16%)	2 (18%)				

On treatment	1 (2%)	0 (0%)	1 (6%)		1 (3%)	0 (0%)				
Disease status at TB diagnosis	**n = 48**	**n = 32**	**n = 16**		**n = 37**	**n = 11**		**n = 35**	**n = 13**	
CR	36 (75%)	23 (72%)	13 (81%)	*0.7*	28 (76%)	8 (73%)	*1*	26 (74%)	10 (77%)	*1*
Other	12 (25%)	9 (28%)	3 (19%)		9 (24%)	3 (27%)		9 (26%)	3 (23%)	
Hematologic treatment after HCT and before TB other than immunosuppression	10 (19%)	8 (24%)	2 (11%)	*0.5*	10 (25%)	0 (0%)	*0.09*	10 (27%)	0 (0%)	*0.046*
Immunosuppression at TB diagnosis	33 (63%)	17 (50%)	16 (89%)		27 (68%)	6 (50%)		22 (59%)	11 (73%)	*0.3*
Immunosuppression at TB diagnosis **auto**-HCT	1/5 (20%)	1/5 (20%)	N.A.	*NA*	0/2 (0%)	1/3 (33%)	*NA*			
Immunosuppression at TB diagnosis **allo**-HCT	32/47 (68%)	16/29 (55%)	16/18 (89%)	*0.02*	27/38 (71%)	5/9 (56%)	*0.4*			
GvHD at TB diagnosis (only for **allo**-HCT)	**n = 47**	**n = 29**	**n = 18**		**n = 38**	**n = 9**		**n = 34**	**n = 13**	
Acute GvHD at TB diagnosis	3/47 (6%)	2/29 (7%)	1/18 (6%)	*1*	2/38 (5%)	1/9 (11%)	*0.5*	3/34 (9%)	0/13 (0%)	*0.6*
Chronic GvHD at TB diagnosis	4/46 (9%)	3/28 (11%)	1/18 (6%)	*1*	3/37 (8%)	1/9 (11%)	*1*	4/33 (12%)	0/13 (0%)	*0.3*
Concomitant infection at TB diagnosis	15 (29%)	9 (26%)	6 (33%)	*0.6*	11 (28%)	4 (33%)	*0.7*	12 (32%)	3 (20%)	*0.5*
Fungal coinfection[1]	7 (13%)	7 (21%)	0 (0%)		5 (13%)	2 (17%)				

CMV coinfection	3 (6%)	1 (3%)	2 (11%)		3 (8%)	0 (0%)				
Viral coinfection: CARV[2]	4 (8%)	2 (6%)	2 (11%)		3 (8%)	1 (8%)				
Viral coinfection: Other[3]	4 (8%)	2 (6%)	2 (11%)		3 (8%)	1 (8%)				
Bacterial coinfection[4]	2 (4%)	1 (3%)	1 (6%)		1 (3%)	1 (8%)				
>1 pathogen[5]	5 (10%)	4 (12%)	1 (6%)		4 (10%)	1 (8%)				
Clinical symptoms of TB (descending order)	**n = 51**	**n = 33**	**n = 18**		**n = 39**	**n = 12**		**n = 36**	**n = 15**	
Symptoms present	47 (92%)	29 (88%)	18 (100%)	-	36 (92%)	11 (92%)	-	33 (92%)	14 (93%)	
Fever	34 (67%)	22 (67%)	12 (67%)		25 (64%)	9 (75%)		25 (69%)	9 (60%)	
Cough	20 (39%)	19 (58%)	1 (6%)		13 (33%)	7 (58%)				
Weakness or fatigue	13 (25%)	9 (27%)	4 (22%)		8 (21%)	5 (42%)				
Dyspnoea	11 (22%)	11 (33%)	0 (0%)		9 (23%)	2 (17%)				
Weight loss	11 (22%)	7 (21%)	4 (22%)		8 (21%)	3 (25%)				
Lymph node enlargement	10 (20%)	2 (6%)	8 (44%)		9 (23%)	1 (8%)		2 (6%)	8 (53%)	
Sputum production	8 (16%)	8 (24%)	0 (0%)		5 (13%)	3 (25%)				
Acute respiratory syndrome	7 (14%)	7 (21%)	0 (0%)		5 (13%)	2 (17%)		5 (14%)	2 (13%)	

Chest pain	7 (14%)	7 (21%)	0 (0%)		6 (15%)	1 (8%)				
Chills	6 (12%)	5 (15%)	1 (6%)		5 (13%)	1 (8%)				
Skin lesions	6 (12%)	0 (0%)	6 (33%)		5 (13%)	1 (9%)		0 (0%)	6 (40%)	
Back pain	3 (6%)	2 (6%)	1 (6%)		1 (3%)	2 (18%)				
Focal neurological signs	3 (6%)	1 (3%)	2 (11%)		3 (8%)	0 (0%)				
Headache	2 (4%)	0 (0%)	2 (11%)		1 (3%)	1 (8%)				
Seizures	2 (4%)	1 (3%)	1 (6%)		1 (3%)	1 (8%)				
Suppurative lymphadenitis	2 (4%)	0 (0%)	2 (11%)		2 (5%)	0 (0%)		0 (0%)	2 (13%)	
Arthralgia	1 (2%)	1 (3%)	0 (0%)		1 (3%)	0 (0%)				
Haematuria	1 (2%)	1 (3%)	0 (0%)		1 (3%)	0 (0%)				
Haemoptysis	1 (2%)	1 (3%)	0 (0%)		1 (3%)	0 (0%)				
Other[6]	4 (8%)	2 (6%)	2 (11%)		4 (10%)	0 (0%)				
Time from symptom to TB diagnosis (days); median (range)	14 (-5-347)	20 (-5-347)	13.5 (0-233)	*0.2*	14 (-5-290)	16.5 (0-347)	*0.5*	28 (-5-347)	9 (0-51)	*0.01*
Tuberculosis sites										
Lung(s)	34 (65%)	34 (100%)	0 (0%)		26 (65%)	8 (67%)		29 (78%)	5 (33%)	

Pleura	5 (10%)	4 (12%)	1 (6%)		5 (13%)	0 (0%)				
Lymph nodes	13 (25%)	4 (12%)	9 (50%)		12 (30%)	1 (8%)		5 (14%)	8 (53%)	
Liver/spleen	8 (15%)	3 (9%)	5 (28%)		6 (15%)	2 (17%)		4 (11%)	4 (27%)	
Joints/bones incl. vertebral column	6 (11%)	2 (6%)	4 (22%)		3 (8%)	3 (25%)		4 (11%)	2 (13%)	
Abscess	5 (10%)	0 (0%)	5 (28%)		4 (10%)	1 (8%)		1 (3%)	4 (27%)	
Skin/soft tissues	5 (10%)	1 (3%)	4 (22%)		4 (10%)	1 (8%)		2 (5%)	3 (20%)	
Blood	3 (6%)	3 (9%)	0 (0%)		3 (8%)	0 (0%)		2 (5%)	1 (7%)	
CNS	2 (4%)	1 (3%)	1 (6%)		2 (5%)	0 (0%)				
Genitourinary tract	2 (4%)	2 (6%)	0 (0%)		2 (5%)	0 (0%)				
Gastrointestinal tract	1 (2%)	1 (3%)	0 (0%)		1 (3%)	0 (0%)				
Pericardial effusion	1 (2%)	1 (3%)	0 (0%)		0 (0%)	1 (8%)				
>1 location	25 (48%)	16 (47%)	9 (50%)		21 (53%)	4 (33%)		15 (41%)	10 (67%)	
Type of material with positive TB tests results	**n positive/ n tested**	**n positive/ n tested**	**n positive/ n tested**		**n positive/ n tested**	**n positive/ n tested**		**n positive/ n tested**	**n positive/ n tested**	
BAL	15/23 (65%)	15/20 (75%)	0/3 (0%)		15/20 (75%)	0/3 (0%)		14/22 (64%)	1/1 (100%)	
Sputum	11/22 (50%)	10/16 (63%)	1/6 (17%)		11/16 (69%)	0/6 (0%)				

Blood	4/10 (40%)	4/8 (50%)	0/2 (0%)		4/8 (50%)	0/2 (0%)				
Pleural fluid	3/4 (75%)	2/3 (67%)	1/1 (100%)		3/4 (75%)	0/0 (0%)				
Urine	2/5 (40%)	2/3 (67%)	0/2 (0%)		2/5 (40%)	0/0 (0%)				
CSF	1/4 (25%)	0/3 (0%)	1/1 (100%)		1/3 (33%)	0/1 (0%)				
Other	4/5 (80%)	1/2 (50%)	3/3 (100%)		3/3 (100%)	1/2 (50%)				
TB diagnosis made solely based on the clinical picture and radiological findings	5 (9%)	4 (12%)	1 (6%)	*0.6*	0 (0%)	5 (42%)	-	2 (5%)	3 (20%)	*0.1*
Type of test with positive TB tests results	**n positive/ n tested**	**n positive/ n tested**	**n positive/ n tested**		**n positive/ n tested**	**n positive/ n tested**				
Culture	29/43 (67%)	23/30 (77%')	6/13 (46%)		29/36 (81%)	0/7 (0%)				
NAAT	29/33 (88%)	17/21 (81%)	12/12 (100%)		29/31 (94%)	0/2 (0%)				
Smear Zielh-Neelsen AFB staining	28/45 (62%)	16/29 (55%)	12/16 (75%)		22/35 (63%)	6/10 (60%)				
Histopathological sample	23/23 (100%)	10/10 (100%)	13/13 (100%)		17/17 (100%)	6/6 100%)				
IGRA	7/20 (35%)	7/11 (64%)	0/9 (0%)		7/17 (41%)	0/3 (0%)				
Treatment protocol (on patients who received treatment)	**n = 50**	**n = 33**	**n = 17**		**n = 38**	**n = 12**		**n = 35**	**n = 15**	
INH+RIF+ PZA+EMB	20 (40%)	18 (55%)	2 (12%)		15 (39%)	5 (42%)		15 (43%)	5 (33%)	

Other	30 (60%)	15 (45%)	15 (88%)		23 (61%)	7 (58%)		20 (57%)	10 (67%)	
Duration of treatment months; median (range)										
Whole treatment	8 (0.1-18)	6 (0.1-18)	12 (4-18)		8.9 (1.5-18)	6 (0.1-12)		8 (1-12)	12 (0.1-18)	
Intensive phase	3 (0.1-14)	2 (0.1-14)	6 (2-12)		3 (0.5-14)	3 (0.1-12)		2 (0.5-12)	6 (0.1-14)	
Continuation phase	3 (0-13)	3 (0-11)	4.5 (0-13)		4 (0-13)	0.5 (0-9)		3 (0-11)	4 (0-13)	

Table 2 Patients and tuberculosis (TB) characteristics at the time of TB diagnosis (AFB - acid-fast bacilli, allo-HCT – allogeneic hematopoietic cell transplantation, auto-HCT – autologous hematopoietic cell transplantation, BAL – bronchoalveolar lavage, CARV – community acquired respiratory viral infections, CMV – cytomegalovirus, CNS – central nervous system, CR – complete response, CSF – cerebrospinal fluid, EMB – ethambutol, GvHD – graft versus host disease, HCT - hematopoietic cell transplantation, IGRA - interferon-γ release assay, INH – isoniazid, NAAT - nucleic acid amplification test, PR – partial response, PZA – pyrazinamide, RIF – rifampicin, RSV - respiratory syncytial virus)

[1] Aspergillus (5, 10%), invasive fungal infection (2, 4%), Candida Guilliermondii (1, 2%);

[2] respiratory syncytial virus (2, 4%), bocavirus (1, 2%); rhinovirus (1, 2%);

[3] hepatitis C virus (1, 2%), herpes simplex virus (1, 2%), picornavirus (1, 2%), varicella-zoster virus (1, 2%);

[4] Klebsiella (1, 2%), Pseudomonas (1, 2%);

[5] Aspergillus + Candida Guilliermondii (1, 2%), Aspergillus + Pseudomonas + rhinovirus (1, 2%), cytomegalovirus + varicella-zoster virus (1, 2%), hepatitis C virus + invasive fungal infection (1, 2%), respiratory syncytial virus + picornavirus (1, 2%)

[6] chest infection/ bone marrow; diffuse bone pain; pleural effusion; swelling at right supraclavicular region

	Phenotypic testing *(resistant isolates/ isolates tested)*	Genotypic (molecular) testing *(resistant isolates/ isolates tested)*	Phenotypic and genotypic testing *(resistant isolates/ isolates tested)*	Type of test unknown *(resistant isolates/ isolates tested)*	Total number of isolates tested	Total number of resistant isolates
INH	2/13	1/8	0/1	0/1	**23**	**3 (13%)**
RIF	1/13	0/8	0/1	1/1	**23**	**2 (8.7%)**
EMB	1/13	0/5	0/1	0/1	**20**	**1 (5%)**
PZA	1/10	0/4	0/1	0/1	**16**	**1 (6.3%)**
FQ*	0/1	0/2	0/0	1/1	**4**	**1 (25%)**
Amikacin	0/0	0/0	0/0	0/1	**1**	**0**
Linezolid	0/0	0/0	0/0	0/1	**1**	**0**
Streptomycin	0/8	0/1	0/0	0/0	**9**	**0**

** Testing was not specified other than fluoroquinolone; 10 patients were treated with moxifloxacin, 5 patients were treated with levofloxacin, 2 patients were treated with ciprofloxacin*

Table 3 Number of isolates tested for specific drug susceptibility and the number of resistant isolates (INH – isoniazid, RIF – rifampicin, EMB – ethambutol, PZA – pyrazinamide, FQ – fluoroquinolone)

	Number of patients	Time	Allo-HCT/ auto-HCT	Relative frequency (%)	Extra-pulmonary TB (%)	Drug-resistant TB (%)	Treatment success (%)	Death attributed to TB (%)
Current EBMT analysis	52	2000-2019	47/5	Allo-HCT: 0.21%; Auto-HCT: 0.025%	35%	22% (MDR 4%)	76%	1-year mortality 18.1%
Cordonnier, 2004 (EBMT)(4)	20	1994-1999	16/4	Allo-HCT 1.06%; Auto-HCT 0.13%	40%	0%	NA	3/20 (15%)
de la Camara, 2000 (Spain)(5)	20	1976-1998	12/8	Allo-HCT: 0.42%; Auto-HCT: 0.16%	20%	NA	NA	Allo-HCT: 25%; Auto-HCT: 0%
Fan, 2015 (Taiwan)(25)	39	1997-2006	32/7	Allo-HCT: 2.34%; Auto-HCT: 0.91%	12.8%*	NA	NA	Death rate during the study period: 51.3% (TB group) vs. 39.3% (non-TB-group)
Lee, 2017 (Korea)(6)	21	2004-2011	21/0	Allo-HCT: 2.45%	47.6%	1/6 (17%) (mono-resistant)	Cured/ improved 91%	10%
Zeng, 2020 (China)(7)	33	2008-2018	33/0 (haplo-identical 78.8%)	Allo-HCT: 0.53%	18.2%	0% MDR/XDR	75.8%	No impact of TB on OS
Kapoor, 2021 (India)(9)	15	2012-2020	381	Allo-HCT: 3.9%	26.7%	0%	86.7%	0%
Hyun, 2024 (South Korea)(3)	276**	2008-2020	188/88	Allo-HCT: 1.68%;	NA	NA	NA	NA

				Auto-HCT: 0.95%				