



Clonal Hematopoiesis and Myeloid Neoplasms in the Context of Telomere Biology Disorders

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Abstract

Purpose of Review Telomere biology disorders (TBDs) are cancer-predisposing multisystemic diseases that portend a higher risk of transforming into myeloid neoplasms (MNs). Due to the rarity and high variability of clinical presentations, TBD-specific characteristics of MN and the mechanisms behind this predisposition are not well defined. Herein, we review recent studies on TBD patient cohorts describing myeloid transformation events and summarize efforts to develop screening and treatment guidelines for these patients.

Recent Findings Preliminary studies have indicated that TBD patients have a higher prevalence of somatic genetic alterations in hematopoietic cells, an age-related phenomenon, also known as clonal hematopoiesis; increasing predisposition to MN. The CH mutational landscape in TBD differs from that observed in non-TBD patients and preliminary data suggest a higher frequency of somatic mutations in the DNA repair mechanism pathway. Although initial studies did not observe specific features of MN in TBD patients, certain events are common in TBD, such as hypocellular bone marrows. The mechanisms of MN development need further elucidation.

Summary Current management options for MN-TBD patients need to be individualized and tailored as per the clinical context. Because of the high sensitivity to alkylator chemotherapy and radiation conferred by short telomeres, non-cytotoxic targeted therapies and immunotherapy are ideal therapeutic options, but these therapies are still being tested in clinical trials. Defining the mechanisms of CH evolution in TBD and identifying risk factors leading to MN evolution will allow for the development of screening and treatment guidelines for these patients.

Keywords Telomere biology disorders · Clonal hematopoiesis · Myeloid neoplasm

Introduction

Telomeres are nucleoprotein structures at the end of chromosomes that provide genome stability and protection against DNA damage response [1]. Telomere length (TL) progressively gets shorter with age due to cell division and the end replication problem (i.e., failure of the DNA polymerase to replicate the complete DNA ending), but there are specific circumstances (e.g., alterations in the genes involved in TL regulation or external stressors) when telomeres shorten at faster rates than usual and result in a multisystemic group of diseases called “telomere biology disorders” (TBDs) [2, 3].

The classical TBD is dyskeratosis congenita (DC), which presents with mucocutaneous triad of reticular skin pigmentation, nail dysplasia, and oral leukoplakia, and is predominantly a pediatric disease. TBDs, especially in adults, have a broad phenotypic variability and can present with hematological (cytopenias), pulmonary (idiopathic

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pulmonary fibrosis), gastrointestinal (cirrhosis), or immunodeficiency phenotypes, and present with a variable constellation of symptoms, penetrance, inheritance, and age of onsets (genetic anticipation) [3, 4]. Currently, the clinical approach to identify TBD patients includes telomere length measurement by flowFISH and/or identification of a pathogenic variant in one of the genes affecting telomere structural integrity and maintenance specifically, *DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *ACD*, *TINF2*, *POT1*, *CTC1*, *STN1*, *WRAP53*, *RTBL1*, *PARN*, *NAF1*, and *ZCCHC8* [3]. Genetic etiology (single nucleotide variants, indels, and somatic copy number alterations) is found in only 40% of patients, especially in adults, which suggest unidentified genetic or epigenetic events [3, 5]. In addition, there is still limited awareness of these disorders among clinicians, thereby making recognition of TBDs particularly challenging.

Patients with TBDs are susceptible to develop cancer at an overall frequency of around 10%, most commonly myeloid neoplasms (MNs) such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), but also squamous cell carcinomas of the head and neck (commonly HPV-driven) [6•, 7••]. Myeloid neoplasms have one of the highest observed/expected (O/E) incidence ratios, and development of these cancers in patients with TBDs needs further elucidation [8]. The specific pathological and genetic characteristics of MN in the TBD context are not fully defined and guidelines for clinical management of these patients are still lacking. Additionally, TBD patients have been recently described to have increased predisposition to develop clonal hematopoiesis (CH) [7••, 9, 10••], defined as a clonal expansion of somatic mutations in myeloid genes such as *DNMT3A*, *TET2*, and *ASXL1* in hematopoietic stem and progenitor cells, and a precursor stage for developing MDS/AML [11–13].

Similarly, the mechanism behind this increased predisposition also needs to be elucidated. For example, shortened telomeres below a certain threshold (termed the Hayflick limit) force the cell to enter a state called senescence that eliminates its replicative capacity and has been hypothesized to be a defense mechanism against cancer [14]. Thus, the higher risk of developing MN in a situation with short telomeres such as TBD diseases is counterintuitive to this theory, and full explanation of this phenomenon is still not known.

In this review, we will summarize recent findings about the significance of somatic genetic variants in TBD patients at different stages of MN evolution, from the identification of CH to the development of MDS/AML. We will discuss the different screening options offered by these findings, and finally, we will comment on clinical management options being currently used and in development.

CH Is More Frequent in TBD and Is Likely Associated with a Characteristic Mutational Landscape

CH denotes the presence of a blood clonal population because of acquired pathogenic variants in genes associated with hematologic malignancies within hematopoietic stem and progenitor cells [11, 15]. Depending on whether the mutation is accompanied or not by persistent cytopenias, CH can be further classified as CH of indeterminate potential (CHIP, where the variant allele fraction is $\geq 2\%$) or clonal cytopenia of unclear significance (CCUS), respectively [16, 17]. The interest of CH and CCUS in clinical practice has increased over the years not only due to the fact that carriers present higher risk of evolving to hematological neoplasms (about 1% per year risk, hazard ratio, 11.1; 95% confidence interval [CI], 3.9 to 32.6), but also because more recently, CH presence has been associated with increased risk of all-cause mortality (hazard ratio, 1.4; 95% CI, 1.1 to 1.8), largely due to cardiovascular diseases [15], inflammation, immune deregulation, type 2 diabetes [18], or response to infection with SARS-CoV-2 [19], among others. The role of CH in non-TBD individuals has been discussed elsewhere in both the hematological [20] and non-hematological [21] contexts. This review will specifically focus on CH occurring in the context of TBD.

CH is considered a precursor feature that increases the risk to develop MDS or AML. In a seminal study from 2014, Genovese et al. [11] identified CH in 10% of persons older than 65-year-old in an unselected cohort which was associated with a strong risk factor for subsequent hematologic malignancy (HR = 12.9, 95% interval 5.8 to 28.7). Similar results have been described in subsequent studies [22, 23]. Although the list of CH-associated genes exceeds 200, over 80% of CH cases arise from mutations involving epigenetic regulators (*DNMT3A*, *TET2*, *ASXL1*), DNA damage repair genes (*TP53*, *PPM1D*), mRNA splice processing components (*SF3B1*, *SRSF2*), or *JAK2*. Nevertheless, different studies have identified variable enrichment of mutations in different pathways depending on the population studied, likely caused by the different selective pressures in the bone marrow for each situation. Thus, in age-related CH (ARCH), mutations tend to cluster in the epigenetic regulator pathway [11, 24], while in therapy-related CH, the DNA repair response pathway presents higher percentage of mutations [25, 26].

Very few studies have tried to define the role of CH in TBD to date [6•, 7••, 10••]. Schratz and colleagues tested 20 TBD individuals (median age 59 years, range: 45–76) negative for MDS/AML and found that 30% presented with CH (Fig. 1A), higher than the 6–10% observed in non-TBD patients, even at older ages (~70 years) [7••].

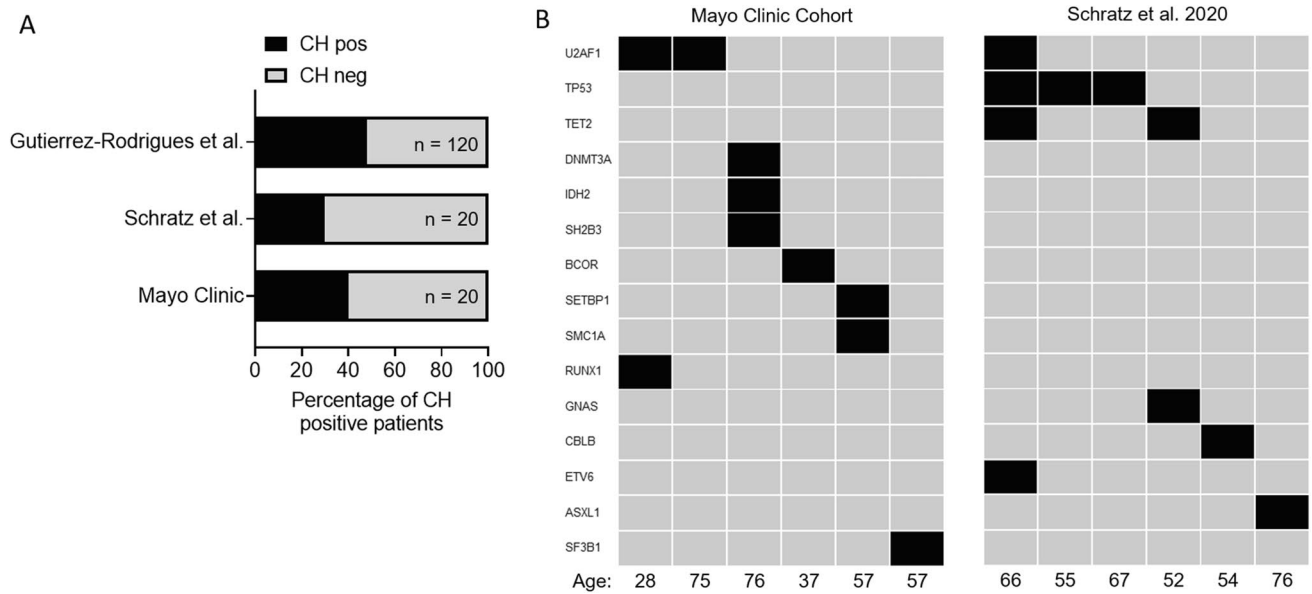


Fig. 1 Telomere biology disorder patients present increased percentage of clonal hematopoiesis that suggest a characteristic mutational signature. **A** Comparison of the two previous reports and our own data showing a percentage of clonal hematopoiesis in TBD patients around 40%. **B** Oncoplot with the mutational landscape described by

Schratz et al. (adapted from Schratz et al. 2020) and the Mayo Clinic cohort. Mutations found impact splicing and DNA repair pathways, while age-related mutations are less frequent than described in non-TBD cohorts. CH, clonal hematopoiesis

Since only 6 patients were CH positive with distinct TB germline variants, the authors could not conclude if the increased CH percentage was associated with any particular germline alteration or identify a somatic mutational pattern characteristic of TBD that could differentiate this stage from therapy-related CH or ARCH. Nevertheless, none of these patients had a *DNMT3A* variant, while 2 presented with *TET2* mutations (p.Gln275Ilefs*18, p.Ala1341Cysfs*3, and p.Pro1115Leufs*2 co-occurring in one patient, and Gln810Ter in another patient) and only 1 carried an *ASXL1* mutation (p.Gly646Trpfs*12), while *TP53* mutations (p.Arg282Trp, p.Gly245Ser, and Leu265Pro) were seen in 3 patients (Fig. 1B), indicating that TBD-CH may cluster in the DNA damage response pathway [7••].

Consistent results of increased CH in TBD were reported in a more recent study by Gutierrez-Rodriguez et al. in which 48% of a cohort of 120 patients (median age: 29 years) presented with CH-related mutations (Fig. 1A) [10••]. The larger number of patients, however, allowed this group to identify mutations in *PPM1D* (30% of CHIP carriers), the promoter of *TERT* (24%), *POT1* (21%), and *U2AF1* (21%) as the most frequent in TBD, and the authors were able to correlate germline variants to specific somatic mutations [10••]. According to this data, TBDs caused by germline *TINF2* variants are enriched in *POT1* somatic mutations, while *TERT* promoter and *PPM1D* somatic mutations were exclusively found among *TERT/TERC* germline variant carriers. Again, it is notable

the low percentage of variants in *DNMT3A*, *TET2*, and *ASXL1*.

Finally, our own unpublished data from the CHIP Clinic at Mayo Clinic also supports these results: in 20 TBD patients with lymphocyte TL below the 10th percentile of healthy controls, we found that 40% of these patients presented CH (Fig. 1A), while in 10 age-matched patients with TL above the 10th percentile, no CH was identified. Due to the limited number of patients in our cohort, and the variability in the germline mutation identified (one patient each with *TERT*, *TERC*, and *RTEL1* while no germline mutation was identified in the rest), we could not identify a pattern either, but similar to previous studies, only 1 patient presented with a variant in an ARCH-related gene (*DNMT3A*), while the remaining mutations impacted other pathways such as splicing (*U2AF1*, *SF3B1*) or DNA repair (*SMC1A*) (Fig. 1B). In parallel to this study, in a different analysis currently under review, we observed that in an unselected cohort of patients undergoing genetic testing at our institution, *TERT* germline variants predicted to be deleterious were more commonly co-occurring with somatic variants in *TP53*. However, none of these patients presented with symptoms of TBD.

Despite the small number of studies and the limitations discussed above, current data points to a higher predisposition of TBD patients to develop CH, and that this mutational signature is different than CH caused by aging, as indicated by the low observed frequency of variants in *DNMT3A*,

ASXL1, and *TET2*. However, whether TBDs present with a unique somatic mutational signature in hematopoietic stem and progenitor cells and their relationship to myeloid transformation remains to be elucidated.

Clinical Significance of CH in TBD Is Still Unclear

The clinical significance and associated risk of developing MDS/AML in TBD patients with CH is still unknown. In the study by Schratz et al. [7••], none of the patients was reported to have MDS/AML and most patients died of TBD-related non-hematological complications, while the study by Gutierrez-Rodriguez et al. did not report clinical outcomes [10••].

An interesting theory formulated in recent years regarding these somatic mutations is that they could constitute a genetic rescue mechanism [27•, 28]; in other words, the somatic events would provide a clonal advantage by correcting the germline defect either directly or indirectly by impacting other components of the same pathway, as opposed to CH in which the selective clonal advantage would be mediated by means independent of the original germline alteration causing the disease (e.g., modifying gene methylation).

The first reported and more common event supporting this idea happens in two positions of the *TERT* promoter (c.-124C and c.-146C) in cis with the wild type allele of TBD patients carrying a pathogenic variant in *TERT* [29, 30]. These changes create de novo ETS-binding sites that result in a higher transcription of the wild type allele that increases the telomerase activity in these cells. In a more recent study using a deep sequencing approach (detection limit of 0.5% VAF) in TBD patients with and without MDS/AML, it was observed that similar somatic rescue events were not only limited to the *TERT* promoter but also found in members of the sheltering complex (*POT1*, *TERF2IP*) and the telomerase RNA processing pathway (*DIS3*, *SKIV2L2*, and *RBM7*) [27•]. Although unfortunately these somatic events were not accompanied by any measurable improvement in blood counts or telomere lengths, they were more common in the MDS/AML-negative TBD individuals (35% vs 10% in MDS/AML positive) which suggests that they could provide protection against evolution to malignancy. Relevantly, the authors noticed that these somatic mutations were mutually exclusive with acquired monosomy of chromosome 7, which is considered a “high risk” abnormality in MDS/AML conferring poor prognosis, and is a common feature seen in TBD-related MDS/AML (see below) [5]. Therefore, the authors hypothesize that at a certain point in time, cells suffer a fate-deciding event in which they either acquire a rescue event or alternatively evolve into MDS/AML.

Both mechanisms (genetic rescue or CH) are not necessarily exclusive and could happen in TBD patients at the same time. More studies with additional cohorts and mechanistic experiments are critically needed to clarify the impact of somatic mutations in clinical outcomes and management of these patients.

MDS/AML Are the Most Common Malignancies in TBD

Cohort studies have reported a higher risk of overall cancer development in TBD patients, of which, MNs are the leading malignancies observed [6•, 9]. Alter et al. found that in the NCI cohort ($n = 197$), 11% of patients were diagnosed with MDS and 3% with AML, translating into an O/E ratio of 578 and 73, respectively. These results were in line with those from the Johns Hopkins TBD cohort (180 patients) where MDS was observed in 8% of the entire cohort and AML in 2% (O/E ratio for MDS was 142 and 21 for AML). Within all malignancies reported, MDS/AML were the most common (85% for both MDS/AML in the NCI cohort and 75% in Johns Hopkins). Similarly, in both cohorts, the median age of presentation was younger than expected for non-TBD individuals: 31 (range: 4–73) years old for MDS and 40 years old (range: 28–65) for AML in the case of the NCI cohort, and 53 years old (12–71) for MDS/AML diagnosis in the Johns Hopkins cohort.

TBD-Related MDS/AML Clinical Features Show Similarities and Differences with Non-TBD MDS/AML

No preferential type of MDS (according to the morphology-based WHO classification) has been seen in TBD [8, 9]. However, some characteristics that are not as common in unselected MDS/AML cohorts were observed at a higher percentage by Schratz et al. Half of the MDS patients presented hypocellular marrow and all the normo- and hypercellular patients presented with bone marrow ring sideroblasts [7••]. By contrast, these two conditions are reported each in 10–15% of the general MDS population. All MDS/AML patients presented with karyotypic abnormalities, with monosomy 7 being the most frequent event [5, 9].

An additional difference reported by the Johns Hopkins group was seen in the flowFISH performed on these patients. TBD individuals with MDS/AML presented with shorter telomeres in the granulocyte compartment when compared to age-matched non-MDS/AML TBD patients (0.9 kb shorter, $p = 0.001$). This distinction was not seen in the lymphocytic compartment of affected patients. However, the authors

clarify that this marker is not sensitive enough since it was observed only in half of MDS/AML patients.

Regarding genotype–phenotype correlation, the germline mutations reported in both cohorts impacted mostly the same genes (*TERT*, *TERC*, *RTEL1*, *DKC1*, only *TINF2* and *NAF1* differed between studies), although similarly to the CH reports mentioned above, the numbers were too low and the spectrum too wide to conclude on specific correlations. Importantly, the somatic mutational configuration found in MN did not show differences between TBD and non-TBD patients. This is in contrast with observations regarding the somatic landscape found in CH and suggests that different somatic compositions can differentially impact the risk of myeloid clonal evolution and could serve as a risk predictor marker.

Screening Approaches Recommendations

In the absence of prospective data, it is not known whether it is appropriate to screen for MDS/AML and if so, what tools should be used for screening. As suggested by these preliminary reports, it is possible that TBD patients acquire a characteristic landscape of somatic variants, and this could be connected to specific germline alterations. If these results are confirmed, this could pave the way to segregate these patients into high and low risk of MN development according to this pattern. Similarly, identifying the specific telomere shortening in granulocytes mentioned by the Johns Hopkins groups may help in certain situations, but this too needs to be validated before adopting it as a screening tool.

It is still debatable as to what is the appropriate age to start screening TBD patients for MDS/AML. As indicated above, the reported median ages of AML and MDS presentation in adult patients with TBDs range from 40 to 52 years. Our approach is to follow blood counts every 3–6 months and conduct annual bone marrow examinations (Fig. 2). An alternative screening approach is to annually test peripheral blood for myeloid-specific gene variants; however, the diagnostic utility of this approach has not been established, and thus reimbursement from insurance agencies may pose a challenge. Genetic anticipation, that is, occurrence of phenotype at an earlier age when compared to the previous generation due to inheritance of both the telomere gene-related mutation and short telomeres, can occur in TBDs and should be considered when making these decisions.

Although there is lack of evidence for either approach, we recommend screening because the appearance of clonal evolution may prompt a time-sensitive preparation for allogeneic hematopoietic cell transplantation (HCT). Further, the type of allogeneic HCT, including the choice of donor and conditioning regimen, varies and may need to be different for patients with or without clonal evolution [31]. To be

specific, TBD patients without clonal evolution may benefit from a conditioning regimen with lower doses of alkylator or total body irradiation and preferably, a total body irradiation-free and alkylator-free regimen which is currently under clinical trial investigation (NCT#01,659,606). However, appearance of clonal evolution and MDS/AML may necessitate intensification of the conditioning regimen which can lead to increased toxicity in TBD patients. The specific types of cytotoxic therapies used in the treatment of MDS/AML associated with short telomeres are discussed below, both in the HCT and non-HCT setting. The advent of venetoclax plus hypomethylating agent therapy in adult AML treatment protocols is promising as it offers a relatively less intense alternative without significantly compromising efficacy, but this needs to be prospectively studied in patients with TBDs.

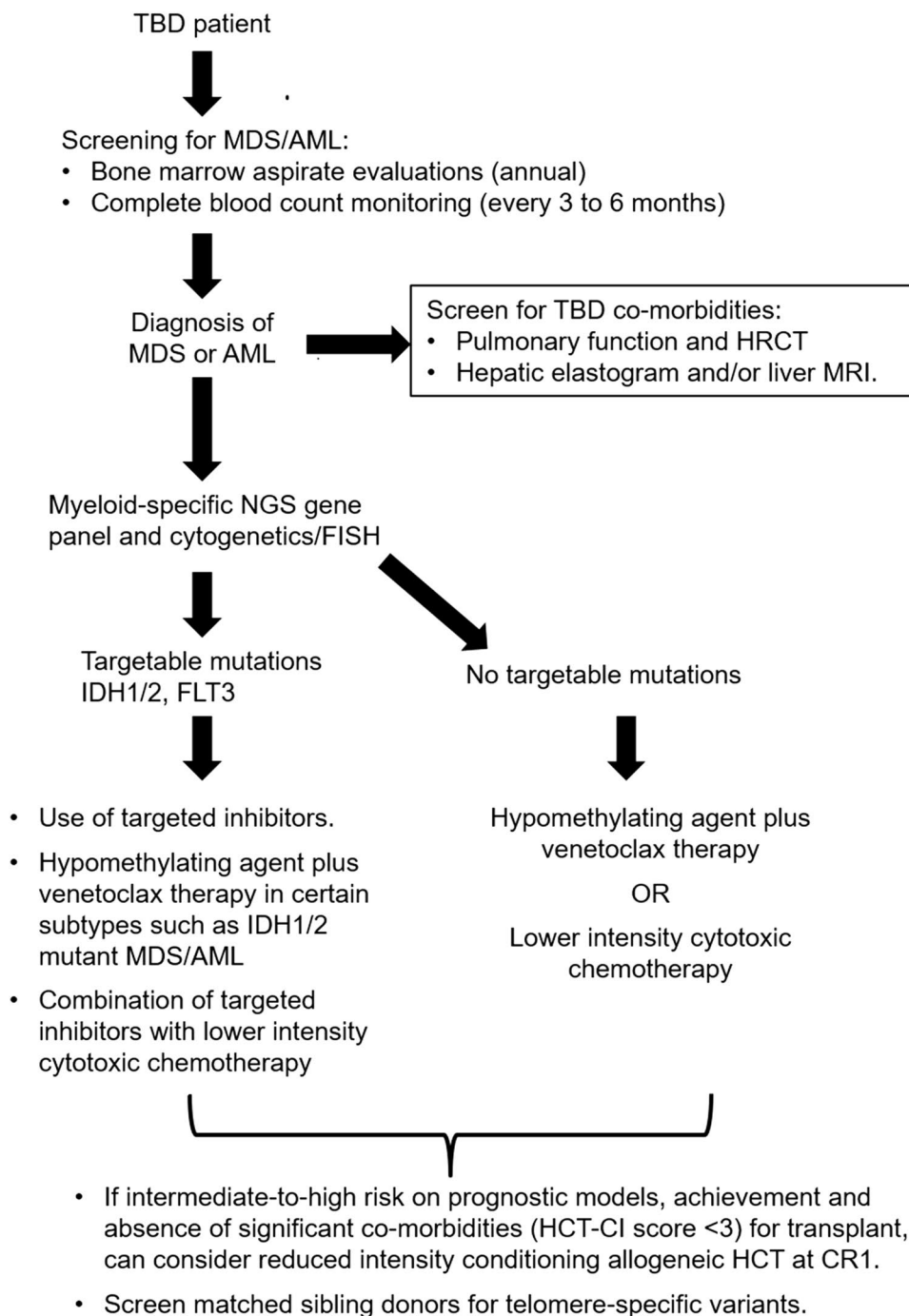
Management of MN in TBD

Due to the limited literature available on MN in TBD, there is not a well characterized treatment approach and management for each case needs to be individualized.

Toxicity from conventional cytotoxic chemotherapy containing anthracycline and cytarabine may be excessive, extrapolating from the short telomere-associated hypersensitivity of rapidly dividing cells to total body irradiation and alkylator-based chemotherapy. Similar patterns of excess total body irradiation and alkylator chemotherapy-associated toxicity, in particular, delayed count recovery and mucositis, have been described in other germline bone marrow failure syndromes such as Fanconi anemia and Shwachman-Diamond syndrome [32–34]. Additionally, TBD-specific extrahematopoietic complications such as pulmonary fibrosis and hepatopulmonary syndrome need consideration prior to aggressive therapies. In addition to standard evaluations, in TBD patients with MDS/AML, we recommend testing for liver stiffness with a magnetic resonance elastography (MR elastogram) and pulmonary function with spirometry/diffusion capacity testing and high-resolution computed tomography (HRCT) scan prior to initiating MDS/AML-directed therapy (Fig. 2). If abnormal, we recommend consulting with organ-specific expert and tailoring chemotherapy plan accordingly.

In pediatric and adult MDS patients, HMA remains the standard choice for cytoreduction (BM blast $\leq 10\%$) followed by an allogeneic HCT in intermediate-high risk patients. For AML therapy, intensive cytotoxic therapy is still the standard of care in young, otherwise fit patients. The regimen of venetoclax plus hypomethylating agent (HMA) therapy is promising for older adults with co-morbidities as it offers a relatively less intense alternative without compromising excessively on efficacy. The optimal approach in patients with TBDs presenting with MDS/AML is unknown, but

Fig. 2 Outline of the authors approach to clinical management of telomere biology disease patients and suggested screening strategy for MDS/AML in these patients



depending on the clinical context and if available, clinical trials with non-cytotoxic targeted therapies and immunotherapy may be offered to patients.

TBD patients presenting with MDS/AML should be considered candidates for allogeneic HCT if they fall in the intermediate- to high-risk categories as assessed by the revised international prognostic scoring system (IPSS-R) for MDS and European LeukemiaNet classification for AML. The presence of short telomeres increases risk for excessive transplant-associated toxicities as has been demonstrated in

many studies [35, 36]. Additional organ dysfunction such as pulmonary fibrosis and hepatic disease plays a critical role in the choice of conditioning regimen. Agarwal et al. have developed a novel conditioning protocol with lower toxicity which is under clinical trial investigation; however, this protocol excludes patients with cytogenetic abnormalities associated with MDS and AML (NCT#01,659,606). When clonal evolution occurs, we recommend choosing a relatively more intensive but still reduced intensity conditioning; however, prospective data on outcomes for such clinical

patients is lacking. The choice of donors is also especially relevant as related, or sibling donors can be carriers of germline variants without obvious phenotypic abnormalities. The advent of haploidentical donors with post-transplant cyclophosphamide has increased the availability of donors, but from the TBD-context, use of cyclophosphamide may be problematic due to toxicity. Although the use of cord blood units is declining, they may offer an attractive alternative for TBD patients due to theoretical benefit of longer telomeres in cord hematopoietic stem cells and avoiding use of cyclophosphamide [37]. However, this needs to be prospectively studied in trials. Any potential related donor should undergo telomere length testing or genetic testing if the variant is known. Optimal choice of conditioning, donors, and stem cell source needs to be systematically studied in prospective trials. Post-HCT care should involve monitoring for development of infections and secondary neoplasms such as squamous cell cancers, including appropriate cancer surveillance and vaccinations. Immune reconstitution may be impaired in some of patients with TBDs due to the inherent T cell immunodeficiency, placing them at risk for infections. Also, the rates of transplant-associated secondary malignancies, in particular head and neck, and genital squamous cell cancers are higher and need periodic screening including preventive measures such as human papillomavirus vaccination. University of Pittsburg has a combined lung and bone marrow transplant protocol for TBD patients with ILD and bone marrow failure (NCT03500731). Partial HLA matching and ABO matching between the hematopoietic stem cell product and cadaveric organ is done to prevent rejection and minimize graft versus host disease. Lung transplantation is performed prior to HCT, in order to ensure adequate pulmonary function prior to HCT. Post-transplant danazol can be used in case of excess cytopenias on account of stress-induced telomere crisis.

We outline in Fig. 2 our own approach in managing patients with TBD regarding MDS/AML. However, due to the aforementioned limitations and gaps in knowledge about these diseases, each situation has to be individualized and personalized.

Conclusions

The rarity of and the inherent clinical variability seen in TBD patients complicates their clinical management. TBD patients have a higher frequency of CH and MN, although precise mechanisms remain undefined. Future studies in particular single cell DNA sequencing and clonal tracking studies in in vivo models could provide mechanistic insights into the evolution of MN in TBD patients. Multi-center, prospective clinical studies to address important clinical questions such as ideal chemotherapy management, ideal conditioning

regimens for transplant, ideal timing for transplant, and optimal post-transplant care are necessary.

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Declarations

Conflict of Interest AF, AM, and MMP declare no potential conflict of interest. MMP has received research funding from Kura Oncology and Stem Line Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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