Chapter 12

Myelodysplastic Syndromes and Acute Myeloid Leukemia

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Introduction

Telomere biology disorders (TBDs), specifically disorders associated with short telomeres such as dyskeratosis congenita (DC) are cancer prone conditions. Among these cancers, there is a significantly increased risk of myeloid neoplasms such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). DC/TBD patients who develop MDS/AML need specialized management with unique clinical considerations. In this chapter, we will review MDS/AML in TBDs with a focus on clinical management in adults.

Background

Telomere biology disorders (TBDs), specifically disorders associated with short telomeres such as dyskeratosis congenita (DC) are cancer prone conditions (see also Chapter 9, Solid Tumors). Studies from the National Cancer Institute (NCI) and Johns Hopkins University have indicated an overall incidence of cancer in patients with TBDs to be around 10% [1-3]. Among these cancers, there is a significantly increased risk of myeloid neoplasms such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), as well as squamous cell carcinomas of the head and neck [1].

Telomere length regulation is very tightly regulated in all cells (see also Chapter 2, Why Telomeres Matter). The overall increased frequency of cancer in TBDs is somewhat inconsistent with the theory that telomere shortening-induced replicative senescence and senescence-independent autophagy are mechanisms of tumor suppression [4, 5]. There are several studies in support of the hypothesis that telomere shortening offers protection against neoplastic transformation. Cancers such as malignant melanoma,

chronic lymphocytic leukemia [6-9] have been associated with “long telomere” states, and myeloproliferative neoplasms are associated with *TERT* polymorphisms which elongate leukocyte telomeres [10]. Additionally, targeting the telomerase enzyme in myelofibrosis has shown some efficacy in cancer treatment [11]. However, there are some noteworthy exceptions to this hypothesis. Firstly, loss of tumor suppressor mechanisms such as *p53-p21* or *p16-pRB*-mediated DNA repair can induce genetic instability in cells with critically short telomeres, and thereby induce neoplastic transformation [4]. Additionally, emergence of clonal hematopoiesis in the hematopoietic compartment (one of the sites where telomerase is most active) can confer a fitness advantage to mutant clones on the background of accelerated stem cell pool depletion and can result in evolution of MDS and/or AML through serial acquisition of additional somatic variants [3, 12]. Recent work has shown that telomere erosion leads to formation of unstable dicentric chromosomes and chromosomal crisis, a phenomenon called “chromothripsis” or “Kataegis”, which is commonly associated with MDS/AML [13]. Another potential mechanism is adaptive immune dysregulation in TBDs [14], which has been shown to accelerate clonal evolution in other contexts [15]. These studies highlight both stem-cell intrinsic and extrinsic impact of telomere dysfunction in the development of MDS/AML.

Due to the unique nature of TBDs, affected individuals who develop MDS/AML need specialized management with unique clinical considerations. In recognition of this unique entity, the recent iteration of the World Health Organization classifies MDS/AML associated with TBDs as a separate entity under “myeloid neoplasms with germline predisposition and other organ dysfunction” [16]. In this chapter, we will review MDS/AML in TBDs with a focus on clinical management in adults. For practical purposes, MDS and AML are grouped together as ‘myeloid neoplasms’, and their precursor states such as clonal hematopoiesis and clonal cytopenias of undetermined significance (CCUS) are defined as in Table 1 [12, 16]. Since this is an emerging area, there is limited evidence for TBD-specific clinical decision-making. In describing our

recommendations, we clarify the level and grade of recommendation as outlined in Table 2, adapted from reference [17].

Table 1: Terminology used to describe various types of myeloid conditions.

Clonal hematopoiesis (CH)	Somatic pathogenic variants associated with hematologic malignancy in hematopoietic cells at a variant allele frequency of ≥2% in the absence of cytopenias and without any other diagnostic criteria for hematologic malignancy.
Clonal cytopenias of undetermined significance (CCUS)	CH plus cytopenia in one or more lineages.
Myelodysplastic syndromes (MDS)	Group of clonal hematopoietic stem cell disorders characterized by cytopenias, bone marrow biopsy showing dysplasia in ≥10% in one or more myeloid lineage, and <20% blasts in bone marrow aspirate.
Acute myeloid leukemia (AML)	≥20% blasts in peripheral blood or bone marrow aspirate.

Table 2: Levels and grades of evidence used in this chapter.

Level of evidence	
Type I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
Type II	Evidence obtained from at least one well-designed experimental study.
Type III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time, or matched case-control series.
Type IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.
Type V	Evidence from case reports and clinical examples.
Grade for recommendation	
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.
B	There is evidence of types II, III, or IV and findings are generally consistent.
C	There is evidence of types II, III, or IV but findings are inconsistent.

Incidence

In the NCI cohort of individuals with DC/TBD with a 15-year follow-up, the overall incidence of cancer was 10%; 3% for AML and 11% for MDS. The authors also calculated an observed-to-expected (O/E) incidence ratio based on data from Surveillance, Epidemiology, and End Results after adjustment for age, sex, race and birth

cohort. The O/E ratio was 578 for MDS and 73 for AML, while the overall cancer ratio was 4.2 [1]. This suggests that MDS and AML are among the most frequent cancers in DC patients, along with head and neck squamous cell cancers. Further, the median age of presentation for any cancer is approximately 38 (range: 18-63) years; 40 (range: 28-56) years for AML, and 31 (4-73) years for MDS [1]. The median age of presentation in the Johns Hopkins University cohort was higher at 53 (range: 12-71) years [3]. In both datasets, the age-at-onset is younger than expected in the general population.

Genetic Patterns

TBDs are characterized by a unique constellation of multisystemic clinical features such as nail dystrophy, skin pigmentation, oral leukoplakia, bone marrow failure, and/or pulmonary or hepatic fibrosis [18, 19]. Late or adult onset TBDs are often associated with *TERT* and *TERC* heterozygous variants, predominantly presenting with bone marrow failure, idiopathic pulmonary fibrosis, or hepatic disease without the classical DC-associated findings. Individuals with *RTEL1* or *PARN* heterozygous variants seem to present with bone marrow failure less frequently. With respect to MDS/AML, an association with specific germline telomere biology gene pathogenic variants has not been found, which suggests that short telomeres rather than gene-specific impairment may be the main driver of leukemogenesis in these individuals [1]. Larger cohorts are needed to further clarify whether any specific germline telomere gene defect is associated with a higher risk of MDS/AML development, and whether that risk is independent of the two common genetic variants (single nucleotide variants or SNPs, rs2853669 and rs2736100) in *TERT* that may be associated with AML [20, 21].

Clonal evolution and MDS/AML in TBDs are often characterized by acquired monosomy 7, but also trisomy 8, similar to other germline bone marrow failure syndromes [19, 22]. In conventional clinical practice, monosomy 7 is considered a “high risk” abnormality predicting a poor prognosis. Despite these specific abnormal cytogenetic associations, a study showed that the mutational spectrum of TBD-associated MDS/AML is not

significantly different from an unselected population of MDS/AML patients, although the sampled cohort had a relatively small sample size [3]. The somatic mutations include epigenetic regulators (*DNMT3A, TET2, ASXL1*), splicing factor variants (*SF3B1, U2AF1*), DNA repair (*TP53, ATM*), transcription factors (*BCORL1, ETV6, RUNX1*) and cell signaling (*CBL, GNAS* and *MPL*).

It is also worth noting that the rate of clonal hematopoiesis (precursor to MDS/AML) was about three times higher in TBD patients compared with healthy individuals [3]. This suggests that evaluation for CH may identify TBD patients at higher risk of MDS/AML development and should be prospectively studied as a future screening strategy.

Screening

In the absence of prospective data, it is not known whether it is appropriate to screen for MDS/AML, what tools to use for screening, and what is the appropriate age to start the screening in TBD patients. As mentioned above, the reported median ages of AML and MDS presentation in adult patients with TBDs range from 40-52 years. Our approach is to selectively consider screening for MDS/AML in patients <40 years in patients by following blood counts over time. In patients ≥ 40 years of age with a documented germline telomere gene variant and short telomeres, we recommend that patients should be screened for clonal evolution through annual bone marrow exam (type IV level of evidence, grade B recommendation). An alternative screening approach is to annually test peripheral blood for myeloid-specific gene variants; however, diagnostic utility is not established, and thus reimbursement from insurance agencies may pose a challenge (type V level of evidence, grade C recommendation). Significant family history of MDS/AML in two or more first or second relatives, and their ages of presentation may provide individualized guidance on screening. 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 (type V level of evidence), we recommend screening because the appearance of clonal evolution may prompt a time-sensitive preparation for allogeneic hematopoietic cell transplantation (HCT) (grade B recommendation) (see also Chapter 13, Hematopoietic Stem Cell Transplantation). 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 [24, 25]. 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#01659606). However, appearance of clonal evolution and MDS/AML may necessitate intensification of the conditioning regimen which can lead to increased toxicity in TBD patients [26]. 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 AML therapy is promising as it offers a relatively less intense alternative without compromising efficacy significantly, but this needs to be studied in patients with TBDs [27].

Management

Initial Therapy

The initial therapy of MDS/AML in patients with TBDs is not well studied and needs to be individualized to the patient. Toxicity from conventional cytotoxic chemotherapy containing anthracycline and cytarabine may be excessive given the short telomere-associated hypersensitivity of rapidly dividing cells to total body irradiation and alkylator chemotherapy [26]. 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 [28] and Shwachman-Diamond Syndrome [29]. Additionally,

TBD-specific extra-hematopoeitic complications such as pulmonary fibrosis and hepatopulmonary syndrome need consideration prior to aggressive therapies [3]. In addition to standard evaluation, in TBD patients with MDS/AML, we recommend testing for liver stiffness with a magnetic resonance elastrography (MR elastogram) and pulmonary function with spirometry/diffusion capacity testing and high-resolution computed tomography (HRCT) scan prior to initiating MDS/AML-directed therapy (level IV/V, grade B recommendation).

In pediatric and adult MDS patients, HMA remains the standard choice for cytoreduction (BM blast ≤ 10%) followed by an allogeneic HCT in intermediate-high risk patients (type V level of evidence, grade C recommendation) [30, 31]. For AML therapy, intensive cytotoxic therapy is still the standard of care in young, otherwise fit patients. The regimen of venetoclax plus hypomethylating agent therapy (HMA) is promising for older adults with co-morbidities as it offers a relatively less intense alternative without compromising excessively on efficacy [27]. The optimal approach in patients with TBDs presenting with MDS/AML is unknown, but depending on the clinical context and if available, clinical trials with non-cytotoxic targeted therapies and immunotherapy may be offered to patients.

Allogeneic hematopoietic cell transplantation for MDS or AML

TBD patients presenting with MDS/AML should be considered candidates for allogeneic HCT if they fall under 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 increase risk for excessive transplant-associated toxicities as has been demonstrated in many studies [24, 32, 33]. Additional organ dysfunction such as pulmonary fibrosis and hepatic disease play 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#01659606, see also Chapter 13, Hematopoietic

Stem Cell Transplantation). When clonal evolution occurs, we recommend choosing a relatively more intensive but still reduced intensity conditioning (type V level of evidence, grade B recommendation). The choice of donors is also especially relevant as related or sibling donors can be carriers of germline variants without obvious phenotypic manifestations. Any potential related donor should undergo telomere length testing or genetic testing if a mutation is known. Choice of stem cell source is highly contextual and depends upon disease status prior to transplant. In pediatric patients, long-term effects of graft versus host disease are especially relevant, and bone marrow is the preferred stem cell source. Optimal choice of conditioning, donors, and stem cell source needs to be systematically studied. 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 (see also Chapter 9, Solid Tumors) including preventive measures such as human papillomavirus vaccination.

Summary

In summary, surveillance and intervention for MDS/AML is a challenge for patients, families, and medical professionals. The management is complicated by other TBD-associated medical problems and potential treatment-related toxicities. Future research efforts should include studying the biology of clonal evolution in the hematopoietic system of patients with TBDs. Single-cell technologies may clarify the question whether clonal evolution occurs specifically in hematopoietic stem cells with critically short telomeres and DNA repair defects, or emerge as separate clones due to proliferative advantage conferred as a consequence of stem cell pool depletion. Prospective studies evaluating optimal screening methods for MDS and AML in TBD patients and their prognostic value are also necessary. Although the focus should be on

prevention due to the challenges of management and poor outcomes associated with MDS/AML in TBDs, efforts should also be directed towards novel non-cytotoxic drug discovery.

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