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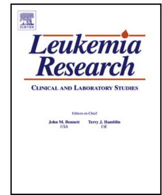

Meeting report

Telomere length and associations with somatic mutations and clinical outcomes in acute myeloid leukemia

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ABSTRACT

We examined the genetic implications and clinical impact of telomere length (TL) in 67 patients with acute myeloid leukemia (AML). There was a trend toward improved survival at 6 months in patients with longer TL. We found that patients with activating mutations, such as *FLT3-ITD*, had shorter TL, while those with mutations in epigenetic modifying enzymes, particularly *IDH1* and *IDH2*, had longer TL. These are intriguing findings that warrant further investigation in larger cohorts. Our data show the potential of TL as a predictive biomarker in AML and identify genetic subsets that may be particularly vulnerable to telomere-targeted therapies.

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1. Introduction

Perturbations of telomere homeostasis have been implicated in the pathogenesis of aplastic anemia, myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML) [1,2], but it is unknown if telomere length (TL) is associated with clinical outcomes or somatic mutations in AML. Critical loss of telomeric DNA in hematopoietic stem cells can lead to genomic instability and cytogenetic abnormalities, such as gain or loss of chromosomes and non-reciprocal translocations [3]. Over half of AML patients present with an abnormal karyotype [4], and patients with complex cytogenetic abnormalities have shorter TL [5]. Hematopoietic stress—such as chemotherapy and ionizing radiation—can accelerate physiological, age-related, telomere attrition leading to telomere crisis and chromosomal instability as reported in therapy-related myeloid neoplasms [6,7]. Hypofunctional germ-line mutations in telomere-specific reverse transcriptase (*TERT*), the enzymatic component of the telomere repair complex, have also been identified in patients with cytogenetically-abnormal AML [8]. While there are data suggesting that shorter TL may correlate with worse outcomes in MDS and acute promyelocytic leukemia [9,10], the degree to which TL is associated with clinical outcome in AML is unknown.

There are at least 30 recurrently mutated genes in AML that cannot be detected by routine cytogenetic testing [11,12]. Many of these mutations are enriched in patients with normal karyotype-AML (NK-AML), which accounts for ~45% of AML [4]. Outcomes in NK-AML can vary markedly, and it is not known why certain mutations or mutation combinations, such as *FLT3*-ITD mutations—particularly if co-occurring with *TET2* or *DNMT3A* mutations—are associated with a poor prognosis, while others, such as *NPM1/IDH* co-mutations in the absence of *FLT3*-ITD, are associated with a much more favorable prognosis [11]. Such mutations, by enhancing proliferation or through epigenetic alterations affecting telomerase expression or function, may be associated with short-

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ened or preserved telomeres. This may account in part for the variations in outcome seen across genetically-defined AML subsets. The potential association between TL and specific mutations or mutation groups in AML has not been adequately studied.

2. Methods

We analyzed tumor samples from 67 AML patients treated at Memorial Sloan Kettering Cancer Center (MSKCC). Patients were consented for sample collection under a hematologic oncology tissue banking protocol approved by the MSKCC Institutional Review Board (IRB). DNA extraction was performed using viably frozen peripheral blood and bone marrow mononuclear cells. Targeted sequencing for exons of a set of 27 genes commonly mutated in AML was performed as previously described [13]. TL was measured as mean telomere content by qPCR [2].

FLT3 and *NPM1* mutations, as well as cytogenetics by metaphase karyotyping, were extracted by clinical chart review.

For newly diagnosed (ND) patients, survival outcomes were assessed from sample collection. ND patient samples were collected during the initial diagnostic period and before any anti-leukemia therapy was given. Relapsed or refractory (RR) patient samples were collected from patients who had received prior AML chemotherapy, and either relapsed or had refractory disease. Patients with secondary AML were defined as having therapy-related AML or AML evolved from an antecedent hematologic disorder. Overall survival (OS) were calculated using standard Kaplan-Meier methods, with survival distributions compared using a log-rank test. Differences in TL across patient characteristics were evaluated by the Wilcoxon rank-sum test. All p-values presented are unadjusted for multiple comparisons unless otherwise noted.

3. Results

In the 67 patient AML cohort, 45 patients were ND (67.2%) and 22 RR (32.8%) at the time of sample collection. Median age was 64.1 years (range 26.2–84.4), and 36 (53.7%) of patients were female. Median WBC was 16.2×10^9/L (range 0.9–136.1). Twenty-three (34.3%) patients had secondary AML (therapy related or antecedent hematologic disorder). Cytogenetic risk groups included 5 (7.5%) patients with favorable risk, 43 (64.2%) patients with intermediate risk, 18 (26.9%) patients with adverse risk, and 1 (1.5%) patient with missing data [14].

Of the 67 patients, median TL was 5.22 kb (range 3.73–8.76 kb). While in healthy cells TL shortens with age [15], we found no association between TL and age in our cohort ($R^2 = 0.043$, $p = 0.73$), validating that we were analyzing the leukemic population and that there was, as expected, no association between blasts TL and age of patients (Fig. 1). We found no difference in TL in ND vs. RR patients, or in patients with de novo vs. secondary AML. In the 45 ND patients, there was improved survival at 6 months in the longest TL tertile group compared to the middle and shortest tertiles groups (86.7% vs. 33.3% and 60.0%); however, this association was not statistically significant ($p = 0.662$) (Fig. 2A). When TL was separated into 2 groups, longer [range 6.02-8.76] and shorter [range 3.73–6.02], survival at 6 months was 86.7% vs. 46.7%, $p = 0.732$ (Fig. 2B). In the 22 RR patients, there was similar improved OS at 6 months in the longest TL tertile group (60.0% vs. 11.1% and 25.0%, $p = 0.284$). The lack of statistical significance may have been due to the number of subjects examined (45 ND and 22 RR patients).

Targeted sequencing data were available in 62 patients. Analysis of single mutation association with TL showed that patients with *IDH1* mutations had significantly longer TL than those without *IDH1* mutations (unadjusted $p = 0.02$; Bonferroni adjusted $p = 0.24$; Table 1). Patients with either *IDH1* or *IDH2* mutations had longer TL (unadjusted $p = 0.04$; Bonferroni adjusted $p = 0.48$). There was also a suggestion that mutations in a set of genes associated with epigenetic regulation (*IDH1/2*, *ASXL1*, *DNMT3A*, and *TET2*) were associated with longer TL when examined as a group ($p = 0.073$). As previously reported [5], we also found that *FLT3* mutations may be associated with shorter TL [*FLT3*-ITD $p = 0.084$; *FLT3*-ITD or *FLT3*-TKD mutation $p = 0.092$]. *FLT3*-mutated patients had a higher white blood cell count (WBC) than *FLT3* wild-type patients ($p < 0.001$).

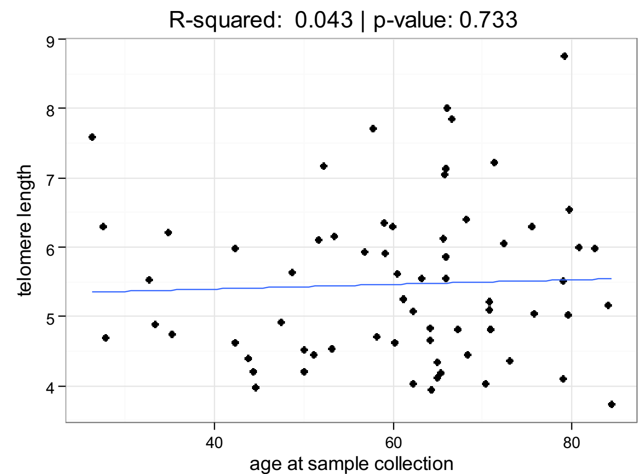

Fig. 1. Scatter plot showing no relationship between telomere length and age at sample collection in leukemia blast samples.

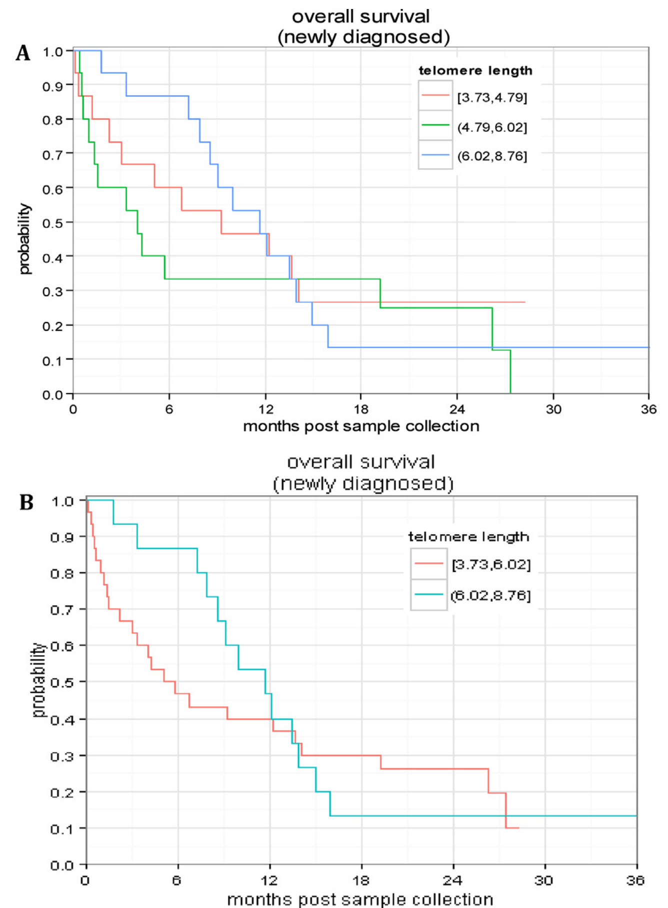

Fig. 2. Overall survival of newly diagnosed AML patients when stratified by telomere length divided into tertiles (A) or into 2 groups (short vs. long; B). OS for the entire cohort at 3 years was approximately 12%.

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