Dynamics of Telomere Length Reflect the Clonal Suppression Seen with the Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocythemia

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BACKGROUND

Telomerase Inhibition in Essential Thrombocythemia (ET)

In a phase-2 study, patients with ET treated with imetelstat demonstrated rapid and durable hematologic and molecular responses and suppression of clones with non-driver mutations (Baerlocher et al. NEJM 2015; Oppliger et al. ASH 2015).

The median JAK2 V617F mutant allele burden was reduced by 71% at month 3, and MPL W515L/K and CALR mutant allele burdens were reduced by 15 to 60%. Most additional mutations in ASXL1, CBL, DNMT3A, EZH2, IDH1, SF3B1, U2AF1, CALR, JAK2, TP53, POT1, TP73, TP73, TP90, and TP90 mutations.

Telomerase and Telomere Length

Telomerase is transiently expressed in normal stem and progenitor cells and can maintain or elongate telomere length. In most human somatic cells, however, telomerase is physiologically suppressed and telomere repeats are lost with each cell division. Telomere length (TL) can therefore be used to describe clonal dynamics of hematopoietic cells. In contrast, telomerase is reactivated in 90% of human cancer cells, as in neoplastic cells of myeloproliferative neoplasms (MPN). Despite telomerase activity neoplastic cells with a high mitotic rate typically display low telomere length values (TLV).

Telomerase Inhibitor Imetelstat in Patients with Essential Thrombocythemia

In the ET imetelstat cohort, driver mutation burden at baseline and best reduction during treatment correlate significantly with baseline telomere length.

In patients with shorter baseline telomere length, driver mutation burden at baseline was significantly higher (p=0.03) and best reduction in driver mutation burden was significantly less (p=0.03).

AIMS

To measure TLV in subsets of leukocytes from ET patients treated with imetelstat in comparison to patients with MPN on standard of care (SOC) and healthy individuals.

To assess the TL dynamics in patients with ET treated with imetelstat and to correlate TLV with hematologic and molecular responses.

METHODS

17 patients with ET treated with imetelstat (IM-ET) who were resistant or intolerant to prior therapies and 63 patients with MPN (16 ET, 34 PV, 13 MF) untreated or treated with standard of care (SOC-MPN) were included in the study. 44% were treated with hydroxyurea, 43% with SOC-MP and 6% with SOC-MF (N=16). In all IM-ET patients, driver mutation burden at baseline and best reduction during treatment correlate significantly with baseline telomere length.

PATIENT CHARACTERISTICS

Changes of dTLV Correlate with Molecular Response to Imetelstat

The higher dTLV at BR reflects the reduction in neoplastic clones in relation to normal hematopoietic cells.

CONCLUSIONS

Higher dTLV after Treatment with Imetelstat in 10 Patients

The lower TLV found in granulocytes of patients with MPN and especially with MF compared to healthy individuals reflect the higher mitotic history of malignant clones.

In the ET imetelstat cohort, driver mutation burden at baseline and best reduction during treatment correlate significantly with baseline telomere length.

We demonstrate higher TLV after 9-10 months of therapy and a significant correlation with the reduction in the driver mutational burden.

TL dynamics analyzed in subsets of leukocytes by flow-FISH depict clonal behavior. Our data suggest that imetelstat treatment in ET patients can suppress neoplastic clones and favors recovery of normal hematopoiesis.

RESULTS

Features of IM-ET Patients by Baseline TLV

Features

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We demonstrate higher TLV after 9-10 months of therapy and a significant correlation with the reduction in the driver mutational burden.

TL dynamics analyzed in subsets of leukocytes by flow-FISH depict clonal behavior. Our data suggest that imetelstat treatment in ET patients can suppress neoplastic clones and favors recovery of normal hematopoiesis.