INTRODUCTION

Imetelstat, a telomerase inhibitor, has shown clinical activity in patients with Myeloproliferative Neoplasms (MPN), including primary myelofibrosis (PMF) and essential thrombocythemia (ET). 1,2,3 Imetelstat is an oligonucleotide with a nucleotide sequence that is complementary to and therefore specifically binds to the template region of the RNA component of human telomerase with high affinity and acts as a potent, competitive inhibitor of telomerase enzymatic activity. Although inhibition of telomerase by imetelstat leads to telomere length (TL) shortening, its mechanisms to induce responses in MPN need further elucidation.

OBJECTIVES

1. To analyze the MPN mutation profile during a two-year course of imetelstat treatment as a means to assess clonal evolution and disease progression in a patient with MF.

2. To study mechanistic differences of imetelstat response in MPN cells harboring JAK2V617F versus CALRdel52 mutations in vitro.

METHODS

1) A high-risk PMF patient with multiple disease-related mutations who had been heavily pre-treated (e.g., ruxolitinib and hydroxyurea combination) when enrolled into imetelstat clinical trial MYF2001

2) TL was measured via flow-FISH during 30 months of imetelstat treatment

3) Mutational profile was assessed during 7.5 years pre- and post-imetelstat treatment

4) Reprogramming of patient-derived peripheral blood mononuclear cells (PBMCs), generation of disease-specific induced pluripotent stem cells (iPSCs)

5) Imetelstat response was analyzed in human TF-1MPL and murine 32D-MPL cells stably expressing JAK2V617F or CALRdel52

RESULTS

Clonal evolution of PMF during over 7 years of treatment. 373

1. Imetelstat and its metabolites induce significant changes in cellular phenotype and telomere length in a subset of MPN cells harboring both JAK2V617F and CALRdel52 mutations.

2. Imetelstat reduces clongenic capacity of primary CD34+ cells, while iPSC-derived CD34+ cells and iPSC-derived megakaryocytes remained unaltered.


CONCLUSIONS

Our data demonstrate that imetelstat reduces TL and targets JAK/STAT signaling, particularly in CALRmutated cells. Imetelstat reduced clongenic growth of the patient’s primary but not iPSC-derived CD34+ cells, suggesting that the iPSC reprogramming-associated TL increase (from 5.8 kb and 5.49 kb in lymphocytes and granulocytes, respectively, to 13.9 kb ± 1.85 in iPSC-derived HSPC) lowers the cells’ sensitivity to telomerase inhibition. In addition, we observed the expansion of a KRAST581 mutated clone during imetelstat treatment, and thus the role of KRAS mutations in the cellular response to imetelstat needs further investigation. Importantly, although the exact patient subpopulation who will benefit most from imetelstat is still to be defined, our data propose that CALR-mutated clones are highly vulnerable to imetelstat.

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