4th International Conference on

HEMATOLOGY AND BONE MARROW TRANSPLANTATION

July 25-26, 2019 | Amsterdam, Netherlands

GLOBAL HEMATOLOGY 2019



KEYNOTE FORUM
DAY 1

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Varsha Gandhi, Hematol Blood Disord 2019, Volume 2

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SCIENTIFIC RATIONALE FOR LOWER DOSE OF IBRUTINIB IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Ibrutinib (Imbruvica®) is a revolutionary and FDA approved agent for chronic lymphocytic leukemia (CLL). This oral drug covalently and irreversibly binds to the C481 residue of Bruton's tyrosine kinase (BTK); a pivotal enzyme in the B-cell receptor pathway. The standard ibrutinib dose for CLL is 420 mg/d, which was selected from a Phase I study of ibrutinib in patients with relapsed/refractory B-cell malignancies. Although ibrutinib is well tolerated, intolerance and adverse events (AEs) are major causes of discontinuation of ibrutinib. In addition to the issues of safety and tolerability, the cost of ibrutinib in the United States exceeds $130,000/year for patients with CLL. Furthermore, since complete remissions with ibrutinib are rare, either indefinite administration of the drug or combination strategies are required. Previously they demonstrated a decline in BTK protein levels in CLL cells after cycle 1 of ibrutinib, suggesting that the ibrutinib dose could be lowered after the first cycle without loss of biological effect. To test this postulate, a pilot study was designed to systematically reduce ibrutinib dosing within the same patient with CLL over three 28-day cycles. Following an initial cycle of 420 mg/d, the dose was reduced to 280 mg/d in cycle 2 and then to 140 mg/d in cycle 3. Eleven patients began study treatment, and nine completed the 3 cycles. Plasma and intracellular levels of ibrutinib were dose-dependent and even the lowest dose was sufficient to occupy on average >95% of BTK protein. In concert, BTK downstream signalling inhibition was maintained with 140 mg/d ibrutinib in cycle 3, and there were comparable reductions in total and phospho-BTK (Tyr223) protein levels across the 3 cycles. Reductions of plasma chemokine CCL3 and CCL4 levels, considered to be biomarkers of ibrutinib response, were similar over the 3 cycles. These pharmacokinetics and pharmacodynamics data demonstrate that following one cycle of ibrutinib at the standard 420 mg/d dose, the dose can be reduced without losing biological activity. Real-world experiences (Four different studies in US, UK, Poland and Sweden) with ibrutinib further support this notion; no difference in progression free or overall survival between patients that had ibrutinib dose reductions and those that did not. In conclusion, their investigations provide a scientific basis for dose-reduction which should be tested in a prospective randomized trial. Such dose reductions would lower drug cost, lessen untoward toxicity, and facilitate rationale-based combinations.

BIOGRAPHY

Varsha Gandhi is interim Chair for the Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Centre in Houston, Texas. She is also Professor and Rebecca Meyer Brown and Joseph Mellinger Brown Chair in Basic Science Research in the Department of Experimental Therapeutics. She has published more than 300 articles and serves as Associate Editor or Board Member of Clinical Cancer Research, Leukemia and Lymphoma. She designed and developed a new graduate education program "Experimental Therapeutics" which is now offered as Therapeutics and Pharmacology program at the Graduate School of Biomedical Science. She has several investigator-initiated peer-reviewed grant supports from NIH, Leukemia and Lymphoma Society and CLL Global Research Foundation and sponsored research agreements from AbbVie, Loxo Oncology and Sunesis.

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TRANSLATION OF PVSG/WHO INTO THE CLINICAL, LABORATORY, MOLECULAR AND PATHOLOGICAL (2018 CLMP) DEFINED MYELOPROLIFERATIVE NEOPLASMS CAUSED BY JAK2V617F JAK2EXON12, CALR, MPL AND TPO DRIVER MUTATIONS ARE DISTINCT BLOOD AND COAGULATION DISORDERS: PROGNOSTIC AND THERAPEUTIC IMPLICATIONS TOWARDS 2020 AND BEYOND

The JAK2V617F mutated tri-linear myeloproliferative neoplasms (MPN) include a broad spectrum of clinical laboratory and bone marrow features in essential thrombocythaemia (ET), prodromal polycythaemia vera (PV) and erythrocythemic PV, classical PV and advanced stages of masked PV and PV complicated by splenomegaly and secondary myelofibrosis (MF). Heterozygous JAK2V617F mutated ET is associated with low JAK2 allele and MPN disease burden and normal life expectance. In combined heterozygous and homozygous or homozygous JAK2V617F mutated tri-linear MPN, the JAK2 mutation load increases from less than 50% in prodromal and early stage PV to above 50% up to 100%in classical PV, advanced PV and PV with MF. Bone marrow histology features show various degrees of diagnostic erythrocytic, megakaryocytic and granulocytic (EMG) myeloproliferation in JAK2V617F mutated tri-linear MPN clearly differ from mono-linear megakaryocytic (M) in MPL or dual megakaryocytic granulocytic (MG) myeloproliferation in calreticulin (CALR) mutated thrombocythemia without features of PV. The morphology of clustered large pleomorphic megakaryocytes with hyper lobulated nuclei is similar in JAK2V67F thrombocythemia, prodromal PV and classical PV patients. Mono-linear megakaryocytic (M) myeloproliferation of large to giant megakaryocytes with hyper lobulated staghorn like nuclei is the hallmark of MPL515 mutated normocellular thrombocythaemia. CALR mutated thrombocythaemia usually presents with high platelet count around

1000x109/l and normocellular megakaryocytic (M) proliferation of immature megakaryocytes with cloud-like hyperchromatic nuclei or prefibrotic dual megakaryocytic granulocytic (MG) myeloproliferation followed by various degrees of bone marrow fibrosis. Natural history and life expectancy of MPN patients are related to the response to treatment and the degree of anaemia, splenomegaly, myelofibrosis and constitutional symptoms. The acquisition of epigenetic mutations at increasing age on top of MPN disease burden independently predicts unfavourable outcome in JAK2V617F, MPL515 and CALR mutated MPNs, which mutually exclude each other. Current treatment options in MPN include low dose aspirin in JAK2 and MPL mutated ET, phlebotomy on top of aspirin in PV, pegylated interferon in intermediate stages of PV and CALR and MPL mutated ET followed by hydroxyurea and or ruxolitinib in the hypercellular stages of PV and MF.