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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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