iMTD (individualized maximal tolerated dose) protocol: A clinical strategy to address interindividual heterogeneity to antiangiogenic therapy

V. W. Li and W. W. Li
Angiogenesis Foundation, Cambridge, MA

Background: The determination of optimal biological dose is critical to the successful development of antiangiogenic agents. Recent studies suggest that genetic heterogeneity of angiogenesis and interindividual variations in efficacy response to angiogenic inhibitors and their side effects exist. Imiquimod, approved to treat skin cancer, is a topical immune response modifier with antiangiogenic effects mediated by interferons and interleukins. Although efficacy is associated with increased dosing frequency, adverse events are dose limiting. In clinical studies, imiquimod had a 75% efficacy rate in treating basal cell carcinoma (BCC) when dosed 5x/week x 12 weeks, but moderate to severe local inflammation was seen in up to 50%. Methods: The dose frequency that results in gross clinical skin inflammation is one marker of individual heterogeneity. To optimize efficacy while minimizing side effects, we devised a treatment algorithm termed Individualized Maximal Tolerated Dose (iMTD) to determine the optimal treatment frequency per patient. Imiquimod was applied in an incremental titrating fashion to BCC neoplasms (N=52): 2x/wk x 2 wks escalating to 3x/wk x 2 wks, then M-F x 2 wks, then daily x 2 wks. Dose frequency was increased until the threshold of inflammation, then lowered to the last best-tolerated dose. Tumor response and the maximal required/tolerated dose frequency (MTD) for each patient was recorded. Results: The iMTD protocol resulted in 52/52 complete responses with 0/52 cases of undesired inflammation. In order to achieve these results, a significant interindividual variation in dose tolerance was observed: 62% (32/52) required/tolerated 3x/week dosing for complete clearance, 29% (15/52) daily treatment, and 8% (4/52) 5x/week treatment. Conclusions: Because interindividual heterogeneity to response is not addressed in most clinical trial protocols, a single dose frequency among study cohorts generates outcomes that includes both responders and non-responders. When therapy is titratable by dose scheduling, the iMTD strategy may optimize clinical results while minimizing toxicities, a goal of antiangiogenic therapy.

No significant financial relationships to disclose.