Role of BTK Inhibitors as Facilitators of Cellular Immunotherapies

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The past 4 years have highlighted immunologic aspects of patients with B-cell malignancies: the COVID pandemic underscored the vulnerability of immunodeficient patients and the challenge of achieving protective immune responses to vaccines, while the widespread use of inhibitors of Bruton-tyrosine kinase (BTK) and adoption of cellular immunotherapies opened new treatment avenues. I will discuss principles how BTK inhibitors (BTKi) impact vaccine responses and their potential for improving success of cellular immunotherapies primarily in patients with CLL. Early successes with CAR-T cell therapy in CLL, have been difficult to replicate given immune dysfunction that hampers efficacy of cellular immunotherapies. We identified a beneficial effect of BTKi on response to T-cell engaging bispecific antibodies. In vitro, bispecific antibodies induced superior T cell activation and cytotoxicity in PBMCs from patients on BTKi. Transcriptomic data pre and during BTKi therapy revealed downregulation of an immunosuppressive program in tumor cells, including CTLA4 and CD200. ITK inhibition was not required. Bispecific antibodies were also effective in PBMCs from patients progressing on BTKi. In contrast, cellular immune response to recombinant vaccines was reduced in patients on BTKi compared to that observed in treatment-naïve patients. Combination therapy of immunotherapy and BTKi appears promising, while vaccine responses might be enhanced by short treatment interruptions.