TRILACICLIB, AN INTRAVENOUS CYCLIN-DEPENDENT KINASE 4/6 INHIBITOR, ENHANCES ANTITUMOR RESPONSES BY MODULATING T CELLS

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Background Cyclin-dependent kinase (CDK)4/6 inhibitors, including trilaciclib, have been shown to augment antitumor immunity.1,2 In an open-label, phase 2 trial in patients with metastatic triple-negative breast cancer (mTNBC), administration of trilaciclib prior to gemcitabine plus carboplatin improved overall survival, potentially through protection and direct activation of immune function.3,4 Here, we report the effects of transient, trilaciclib-mediated CDK4/6 inhibition on immune function in vitro.

Methods Peripheral blood mononuclear cells (PBMCs) or naïve CD4+ and CD8+ T cells were purified from 6 healthy human donors and activated with CD2/3/28 beads with or without trilaciclib. To visualize phenotypic and functional changes, trilaciclib was added to naïve CD4+ and CD8+ T cells 0-, 1-, and 3-days post-activation. Activated T cells were collected and stained for flow cytometric analyses 3-, 7-, and 14-days post-activation. Supernatant from activated PBMCs was harvested after 72 hours and added to human breast cancer cells. Following 24 hours’ incubation, levels of programmed death-ligand 1 (PD-L1) and human leukocyte antigen (HLA) class I and II were quantified by flow cytometry, and CXCL9 and CXCL10 chemokines by enzyme-linked immunosorbent assay.

Results Irrespective of when trilaciclib was added to CD4+ and CD8+ T cells, significant increases in the frequency of CD45RO+ memory T cells were observed. Within CD45RO+ memory T cells, T cells incubated with trilaciclib had increased frequencies of CD62LloCD69hi effector CD4+ and CD8+ T cells, with increases in CD62LloCCR7lo effector memory T cells also observed. Furthermore, trilaciclib significantly increased CXCL9 and CXCL10 levels (P=0.0001). Surface expression of PD-L1 and HLA class I and II was increased in breast cancer cell lines cultured with supernatant from T cells activated in the presence of 50 and 100 nM of trilaciclib, resulting in a greater frequency of cells being double-positive for HLA class I and II or HLA class I and PD-L1.

Conclusions Trilaciclib may enhance antitumor immunity by modulating essential steps in the cancer-immunity cycle. Our data suggest trilaciclib may increase antigen presentation by promoting HLA class I and II expression and the recruitment of T cells to the tumor site via CXCL9 and CXCL10. Trilaciclib also augments the differentiation of T cells by promoting the formation of memory T cells. These data support a role for trilaciclib in improving antitumor efficacy, as observed in the phase 2 trial in mTNBC, and provide a rationale to combine trilaciclib with immunotherapy to enhance immunogenicity within the tumor microenvironment.

Acknowledgements We thank Dr. Jason Grayson for immune profiling services.

REFERENCES

Ethics Approval This study was approved by the Wake Forest University School of Medicine’s Ethics Board under IRB #00080511.