The specific SF1R inhibitor DCC-3014 exhibits immunomodulatory and anti-invasive activities in cancer models

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ABSTRACT

The role of tumor-associated macrophages (TAMs) in promoting an immune-suppressive tumor microenvironment is well established. TAMs mediate tumor growth, invasion, and immunosuppression through the secretion and response to a variety of factors.1-3 TAMs are dependent on SF1R kinase activity for proliferation and differentiation, thus making it an attractive target during cancer development. Many of these TAMs, however, also inhibit the closely related CSF1R family members KIT, PDGFRβ, and FLT3, which may limit their utility due to off-target toxicity. Antibodies targeting CSF1R have been reported in clinical studies, yet result in low levels of the ligand CSF1R. Thus, a therapeutic approach to address the challenges of targeting TAMs is needed.

This study evaluated the effects of DCC-3014 (a selective SF1R inhibitor) on TAMs in vitro and in vivo. DCC-3014 inhibits SF1R and is closely related to its target kinase (KIT, PDGFRβ, and FLT3), which tolerate normal tissue. Cells were exposed to 10 mg/kg PO QD or PD-1 inhibition. DCC-3014 had an IC50 of 1.1 nM and inhibited cell migration of human vascular smooth muscle cells (HVSMMs) with an IC50 of 49 nM. In vivo, DCC-3014 inhibited tumor growth of tumor-bearing mice and demonstrated reduced tumor growth and angiogenesis in a human xenograft model.

RESULTS - in vivo

To determine the effects of DCC-3014 on primary tumor growth, macrophages, and the adaptive immune system, the syngeneic immunocompetent MC38 colorectal cancer model was employed. As a single agent-treated for five days in the MC38 model, DCC-3014 (10 mg/PO, PD) significantly reduced CD11b+ cells in the circulation by 10-fold, as well as increased CD8+ T cells by 6-fold. DCC-3014 also inhibited growth of CD11b+/F4/80+ macrophages in vitro. DCC-3014 levels varied from 0.1 to 1.4 µM. In the presence of CD11b+/F4/80+ macrophages, DCC-3014 led to a 6-fold increase in the ratio of cytotoxic CD8+ T cells to regulatory T cells, indicating normalization of the adaptive immune system and improved tumor immunosuppression.

CONCLUSIONS

In vivo, DCC-3014 exhibited additive effects with anti-PD1 antibody to inhibit tumor growth and angiogenesis of the syngeneic MC38 colorectal cancer model. These results suggest that combination therapy of DCC-3014 and PD-1 inhibition may be a promising therapeutic approach to inhibit tumor growth, angiogenesis, and immune cell infiltration. Further studies are needed to determine the optimal dosing regimen for clinical trials.