THE NOVEL TELOMERASE-DIRECTED TELOMERE-TARGETED ANTICANCER AGENT 6-THIO-DG (THIO) DEMONSTRATES POTENT ACTIVITY AND INDUCES ANTITUMOR IMMUNITY IN HEPATOCELLULAR CARCINOMA (HCC) MODELS

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Background

HCC is one of the leading causes of cancer-related deaths worldwide. Low response rates with current treatments for HCC demonstrate an urgent unmet need for more effective systemic therapies. However, development of novel treatments for HCC has been challenging due to a lack of functionally druggable targets. The nucleoside prodrg analogue THIO is a first-in-class telomerase-directed, telomere-targeted, anticancer agent that has shown potent activity in other tumor types, including colorectal, lung, melanoma, and brain cancer models. In cancer cells, THIO is converted into the corresponding 5'-triphosphate, which is efficiently incorporated into telomeres by telomerase, activating DNA damage responses and pro-apoptotic pathways. We hypothesized that telomerase-targeting agents may be effective in HCC given the high rate of mutations in the telomerase reverse transcriptase (hTERT) promoter. Moreover, since >90% of HCCs reactivate telomerase to drive escape from senescence-induced growth arrest, treatment with THIO or second-generation telomere-targeted analogues is likely highly selective for telomerase-positive cancer cells relative to nonmalignant hepatocytes.

Methods

Activity of THIO and second-generation analogues was evaluated in vitro using telomerase-positive HCC cells and in vivo using syngeneic mouse models of aggressive HCC. HCC cells treated with or without THIO were analyzed for cell proliferation and stained with markers of replicative stress or cell cycle arrest, followed by confocal microscopy and/or flow cytometry. Immunophenotyping of tumor-infiltrating T cells in mice treated with THIO was performed by measuring the frequencies of MDSCs (Ly6C+Ly6G-), NK cells (NK1+), CD4 T cells (Ki67+/CD4+), and CD8 T cells (Ki67+/CD8+). Antitumor activity was assessed by serial measurements of tumor volume in mice sequentially treated with therapeutically relevant doses of THIO ± checkpoint inhibitors compared to control mice and mice treated with checkpoint inhibitors alone.

Results

THIO treatment induced replicative stress, followed by cell cycle arrest and apoptosis in telomerase-reactivated HCC cells. In syngeneic mouse models of aggressive HCC, treatment with THIO activated pathways associated with innate and adaptive immunity (eg, cGAS-STING pathway and infiltration of CD8+ T cells into the tumor microenvironment) and altered the immune-suppressive tumor microenvironment. THIO treatment enhanced the response to checkpoint inhibitors, yielding complete responses in some HCC model systems with no dose-limiting toxicities. Similar results were observed with second-generation THIO analogues.

Conclusions

Results of this study indicate that THIO, a first-in-class telomerase-directed, telomere-targeted agent, and its analogues may enhance the overall therapeutic efficacy of current immune checkpoint inhibitor-based treatments for HCC.

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Ethics Approval

All in vivo studies were approved by the animal ethics committee of UT Southwestern, Dallas, Texas.