Anti-tumor activity of novel nuclear export inhibitors (NEIs) in multiple murine leukemia models

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**ABSTRACT #5688**

NEIs are a novel class of compounds that possess potent antiproliferative activity in a variety of human leukemia and solid tumor cell lines. They are believed to inhibit tumor growth through 1) the induction of apoptosis in cancer cells and 2) by blocking the nuclear export of oncoproteins. NEIs are currently undergoing Phase I clinical trials in mice and humans. Their mechanisms of action suggest that they could also be useful as anti-infective agents. We have previously shown that NEIs inhibit growth of leukemia cell lines, including K562, MOLT-4, and MV-4-11. We further evaluated the potential of NEIs as novel agents to treat leukemia in vivo. The efficacy of NEIs in multiple murine leukemia xenograft models was evaluated. Both mice bearing xenografts of K562 and MOLT-4 leukemia cells were treated with KOS-1815, an NEI analog, using a weekly dosing schedule. Mice bearing K562 xenografts were treated with KOS-1815, KOS-2464, or saline at the indicated doses for 4 weeks. Single doses of KOS-2464 or KOS-1815 were also administered to mice bearing MOLT-4 xenografts. The results showed that both KOS-1815 and KOS-2464 significantly inhibited growth of K562 and MOLT-4 xenografts. In addition, KOS-2464 was well-tolerated, and mice bearing K562 xenografts treated with KOS-2464 showed improved survival compared to control mice. These results suggest that NEIs could be useful as novel agents to treat leukemia in vivo.