Abstract

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Phase 1 Study of Vorinostat as a Radiation Sensitizer with 131I-Metaiodobenzylguanidine (131I-MIBG) for Patients with Relapsed or Refractory Neuroblastoma.

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Abstract

Purpose: 131I-metaiodobenzylguanidine (MIBG) is a radiopharmaceutical with activity in neuroblastoma. Vorinostat is a histone deacetylase inhibitor that has radiosensitizing properties. The goal of this phase 1 study was to determine the maximum tolerated doses of vorinostat and MIBG in combination. Experimental Design: Patients < 30 years with relapsed/refractory MIBG-avid neuroblastoma were eligible. Patients received oral vorinostat (dose levels 180 and 230 mg/m2) daily Days 1-14. MIBG (dose levels 8, 12, 15, and 18 mCi/kg) was given on Day 3 and peripheral blood stem cells on Day 17. Alternating dose escalation of vorinostat and MIBG was performed using a 3+3 design. Results: 27 patients enrolled to 6 dose levels, with 23 evaluable for dose escalation. No dose-limiting toxicities (DLT) were seen in the first three dose levels. At dose level 4 (15 mCi/kg MIBG / 230 mg/m2 vorinostat), 1 of 6 patients had DLT with grade 4 hypokalemia. At dose level 5 (18 mCi/kg MIBG / 230 mg/m2 vorinostat), two patients had dose-limiting bleeding (one grade 3 and one grade 5). At dose level 5a (18 mCi/kg MIBG / 180 mg/m2 vorinostat), 0 of 6 patients had DLT. The most common toxicities were neutropenia and thrombocytopenia. The response rate was 12% across all dose levels and 17% at dose level 5a. Histone acetylation increased from baseline in peripheral blood mononuclear cells collected on Days 3 and 12-14. Conclusions: Vorinostat at 180 mg/m2/dose is tolerable with 18 mCi/kg MIBG. A phase 2 trial comparing this regimen to single-agent MIBG is ongoing.

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