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A phase 1 study of mebendazole with bevacizumab and irinotecan in high-grade gliomas

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Abstract

Background: High-grade gliomas (HGG) have a dismal prognosis despite multimodal therapy. Mebendazole is an anti-helminthic benzimidazole that has demonstrated efficacy in numerous in vitro cancer models, and is able to cross the blood-brain barrier. We conducted a phase 1 trial (NCT01837862) to evaluate the safety of mebendazole in combination with bevacizumab and irinotecan in children and young adults with HGG.

Objective: To determine the maximally tolerated dose of mebendazole when given in combination with bevacizumab and irinotecan in children with HGG; to describe the progression-free survival (PFS) and overall survival (OS) for this group.

Design/method: Patients between 1 and 21 years of age with HGG were enrolled in a 3 + 3 design to escalating doses of mebendazole in combination with bevacizumab (10 mg/kg/dose) and irinotecan (150 mg/m^2 /dose). Subjects were eligible upfront after completion of radiation or at the time of progression. Mebendazole was taken orally twice per day continuously, and bevacizumab and irinotecan were given intravenously on Days 1 and 15 of 28-day cycles.

Results: Between 2015 and 2020, 10 subjects were enrolled at mebendazole doses of 50 mg/kg/day (n = 3), 100 mg/kg/day (n = 4), and 200 mg/kg/day (n = 3). One subject assigned to 100 mg/kg/day was not evaluable. Seven subjects had a diagnosis of diffuse midline glioma, one subject had anaplastic astrocytoma, and one subject had a spinal HGG. All subjects received radiation. There were no dose-limiting toxicities. The most frequent G3/4 adverse events were neutropenia (n = 3) and lymphopenia (n = 4). The overall response rate was 33%, with two subjects achieving a partial response and one subject achieving a complete response sustained for 10 months. The mean PFS and OS from the start of study treatment were 4.7 and 11.4 months, respectively.

Conclusion: Mebendazole was safe and well tolerated when administered with bevacizumab and irinotecan at doses up to 200 mg/kg/day. Further studies are needed to determine the efficacy of this treatment.

Keywords: high-grade glioma; mebendazole; phase 1 trial.