

Clinical Cancer Research



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Cancer Therapy: Clinical

Phase I Trial of VNP40101M (Clometazine) in Children with Recurrent Brain Tumors: A Pediatric Brain Tumor Consortium Study

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Purpose: VNP40101M (Clometazine), a novel DNA alkylating agent, was evaluated in a phase I study in children with recurrent brain tumors.

Experimental Design: VNP40101M was given i.v. daily for 5 consecutive days every 6 weeks for

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up to eight cycles. Dose escalation was done independently in patients stratified based on intensity of prior therapy (moderately pretreated, stratum I; heavily pretreated, stratum II). Correlative studies included pharmacokinetics and measurement of O^6 -alkylguanine-DNA alkyl transferase levels in peripheral blood mononuclear cells before and after treatment.

Results: Forty-one eligible patients (stratum I, 19; stratum II, 22) were enrolled on this study. The dose-limiting toxicity in 35 evaluable patients was myelosuppression, which occurred in 4 of 16 patients in stratum I and 3 of 19 patients in stratum II. Pharmacokinetic studies showed a median terminal half-life of 30 min (range, 14-39.5). The maximum tolerated dose in stratum I and II were 45 and 30 mg/m²/d daily for 5 days every 6 weeks, respectively. Peripheral blood mononuclear cells alkylguanine alkyl transferase levels did not decrease significantly after VNP40101M treatment. Central imaging review confirmed that three patients had stable disease for a median of 45 weeks (range, 37-61+) after therapy.

Conclusions: The recommended dose of VNP40101M for phase II studies in children with brain tumors is 45 mg/m²/d in moderately pretreated and 30 mg/m²/d in heavily pretreated patients when administered for 5 consecutive days every 6 weeks.

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