A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies.


Source

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Abstract

Malignancies associated with latent Epstein-Barr virus (EBV) are resistant to nucleoside-type antiviral agents because the viral enzyme target of these antiviral drugs, thymidine kinase (TK), is not expressed. Short-chain fatty acids, such as butyrate, induce EBV-TK expression in latently infected B cells. As butyrate has been shown to sensitize EBV(+) lymphoma cells in vitro to apoptosis induced by ganciclovir, arginine butyrate in combination with ganciclovir was administered in 15 patients with refractory EBV(+) lymphoid malignancies to evaluate the drug combination for toxicity, pharmacokinetics, and clinical responses. Ganciclovir was administered twice daily at standard doses, and arginine butyrate was administered by continuous infusion in an intrapatient dose escalation, from 500 mg/(kg/day) escalating to 2000 mg/(kg/day), as tolerated, for a 21-day cycle. The MTD for arginine butyrate in combination with ganciclovir was established as 1000 mg/(kg/day). Ten of 15 patients showed significant antitumor responses, with 4 CRs and 6 PRs within one treatment cycle. Complications from rapid tumor lysis occurred in 3 patients. Reversible somnolence or stupor occurred in 3 patients at arginine butyrate doses of greater than 1000 mg/(kg/day). The combination of arginine butyrate and ganciclovir was reasonably
well-tolerated and appears to have significant biologic activity in vivo in EBV(+) lymphoid malignancies which are refractory to other regimens.

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