Systemic administration of 3-bromopyruvate in treating disseminated aggressive lymphoma.


Source

Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287-0817, USA.

Abstract

The Warburg hypothesis states that aggressive cancers obtain much of their adenosine triphosphate (ATP) by metabolizing glucose directly to lactic acid. As a result of its high tumor selectivity, 3-bromopyruvic acid (3-BrPA), a well-known inhibitor of energy metabolism, has been proposed as a specific anticancer agent. We investigated the effect of 3-BrPA in a mouse model of aggressive metastatic lymphoma. Epstein-Barr-virus-infected human Raji lymphoma cells with lentivirally transfected green fluorescent protein and luciferase were incubated with RPMI/fetal bovine serum, and various concentrations of 3-BrPA were used to determine the LD50 in vitro. In total, 18 severely combined immunodeficient mice were injected with 1 million human Raji lymphoma cells via the tail vein. Using bioluminescent imaging, tumor growth was measured daily for 12 days to determine the tumor burden. At day 0 (start of treatment), the mice were randomized. Six mice received 10 mg/kg 3-BrPA i.p. daily for 7 days, 6 mice received 1 treatment at day 0, and 6 mice received the control buffer. Tumor growth was assessed daily from day 0 until day 7 using bioluminescent imaging. All data were normalized to acquisition time (luminescence/second; L/s). Body weight was measured daily to determine the toxicity of 3-BrPA. The LD50 for Raji lymphoma cells exposed to 3-BrPA in vitro was 11 μM with an extremely steep dose response curve. At day 0, tumor activity medians in the group with daily treatment was 2131 L/s (244-12,725), with a 1-day dose of 3095 L/s (523-9650) and in the nontreated control group, 2997 L/s (1521-6911). In mice treated with a daily dose of 10 mg/kg 3-BrPa for 7 days, a significant reduction in tumor activity was found during the whole treatment period compared with the control mice (P = 0.0043 at day 7). In mice with a single treatment at day 0, growth delay was only evident at day 2 (P = 0.0152 at day 2) but not for the rest of the observation period. The only manifestation of toxicity of the daily administration of 10 mg/kg 3-BrPA was a reduction in body weight. Body weight at day 0 was 17.22 g ± 0.84 g in the treatment group and 17.58 g ± 0.86 g in the control group. Body weight at day +6 was 15.02 g ± 2.04 g in the treated group and 19.4 g ± 0.63 g in the control
group. 3-BrPA demonstrated a significant positive tumor response both in vitro and in vivo. This, to our knowledge, is the first report of the use of 3-BrPA in a systemic tumor model. Based on these data, 3-BrPA holds promise for treatment of systemic metastatic cancers.

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