TUMOR BIOLOGY

Inhibition of ornithine decarboxylase to facilitate pegylated arginase treatment in lung adenocarcinoma xenograft model.

James C. M. Ho, Sze Kwan Lam, kin Pong U, Paul Ning-Man Cheng

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University of Hong Kong, Hong Kong, China; The University of Hong Kong, Hong Kong, Hong Kong; Bio-Cancer Treatment International Limited, Hong Kong, Hong Kong; 813 Medical Centre Ltd, Central, Hong Kong

Abstract Disclosures

Abstract

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Background: Arginine depletion has shown promising anticancer effects among arginine auxotrophic cancers that are deficient in argininosuccinate synthetase (ASS) and/or ornithine transcarbamylase (OTC). Pegylated arginase (PEG-BCT-100 (rhArg1peg5000)) works as an arginine depletor by converting arginine to ornithine. However, accumulated ornithine can be channeled via ornithine decarboxylase (ODC) to produce polyamines that are known to promote tumor growth. We postulate that ODC inhibition enhances anticancer effects of BCT-100 in lung adenocarcinoma. **Methods:** The activity of BCT-100 was tested in a panel of lung adenocarcinoma cell lines (H23, H358, HCC827, H1650, H1975, HCC2935 and HCC4006). Cell viability was measured using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Protein expression was evaluated by Western Blot. Nude mice subcutaneous xenograft models(XMs) derived from these cell lines were used for *in vivo*study. An ODC inhibitor (α-difluoromethylornithine or DFMO given orally) was combined with BCT-100 (intraperitoneal) in treatment of XMs. **Results:** BCT-100 reduced *in vitro*cell viability across different cell lines. However, BCT-100 could only suppress tumor growth in HCC4006 XM, while paradoxical growth stimulation was observed in H358, HCC827, H1650 and H1975 XMs. ASS was expressed in all XMs but OTC was found only in HCC827 XM. Upon BCT-100 treatment, ODC was induced in two solid tumor XMs (H1650 and H1975), while unaltered in cystic tumor XMs (H358 and HCC827) and the remaining solid tumor (HCC4006) XM. Using H1975 XM (tumor growth and ODC induced by BCT-100), combined BCT-100 and DFMO significantly suppressed tumor growth compared with control or single arm treatments (44% of control, 53% of DFMO and 30% of BCT-100 on day 12), with median survival doubled in BCT-100/DFMO (25 days) compared with control (12 days) ($p < 0.0001$). Apoptosis (cleavage of PARP and downregulation of survivin) and G1 (downregulation of cyclin E1, E2 and H) and G2/M arrest (downregulation of cyclin B1 and CDK7) were evident in the combination arm. **Conclusions:**Inhibition of ODC by DFMO is essential in BCT-100 treatment in lung adenocarcinoma.