Pegylated arginase treatment in mesothelioma xenograft models.

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Abstract Disclosures

Abstract

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Background: Cancers with deficient argininosuccinate synthetase (ASS) and/or ornithine transcarbamylase (OTC) are biologically vulnerable to arginine depletion. Preliminary clinical data had suggested a therapeutic role of arginine depletion in malignant pleural mesothelioma (MPM). Pegylated arginase (PEG-BCT-100 (rhArg1peg5000)) works as an arginine depletor with ongoing clinical trials. We postulate that BCT-100 can exert anticancer effect on MPM. **Methods:** The activity of BCT-100 was tested in a panel of mesothelioma cell lines (H28, 211H, H226, H2052 and H2452). Cell viability was measured using crystal violet staining. Protein expression was evaluated by Western Blot. Arginine concentration was detected by ELISA. Nude mice subcutaneous xenograft models(XMs) derived from 211H and H226 cells were used for *in vivo* study. BCT-100 was administered via intraperitoneal injection in XMs. **Results:**BCT-100 reduced *in vitro* cell viability (13-24 mU/ml) across different cell lines and suppressed tumor growth in both XMs. ASS was expressed in H28, H226, H2452 cells as well as 211H and H266 XMs. OTC was undetectable in all cell lines and XMs. BCT-100 (60 mg/kg) significantly suppressed tumor growth (41% of control on day 20 in 211H XM, 44% of control on day 35 in H226 XM), with increased median survival (from 22 to 38 days in 211H XM ($p < 0.001$) and from 36.5 to 50.5 days in H226 XM ($p < 0.01$)). BCT-100 decreased serum arginine concentration (100 mm to < 20 mM, $p < 0.001$). Moreover, intratumoral arginine content was decreased with 20 mg/kg BCT-100 treatment ($p < 0.001$ compared with control), which was further reduced in 60 mg/kg arm (20 Vs 60 mg/kg, $p < 0.01$). Apoptosis (PARP cleavage in 211H XM and Bcl-2 downregulation and cleavage of PARP and caspase 3 in H226 XM) and G1 arrest (downregulation of cyclin A2, D3, E1 and CDK4 in 211H and suppression of cyclin A2, E1, H and CDK4 in H226 XM) were evident with BCT-100 treatment. **Conclusions:** BCT-100 (pegylated arginase) reduced cell viability *in vitro*, suppressed growth of tumor xenografts and increased median survival in XMs of MPM. The mechanisms were mediated by arginine depletion resulting in apoptosis and G1 arrest.