Endogenous arginase 2 as a biomarker for PEGylated arginase 1 treatment in squamous cell lung carcinoma xenograft models.

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Abstract Disclosures

Abstract

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Background: Arginine depletion induced by PEGylated arginase 1 (BCT-100, PEG-BCT-100 or rhArg1peg5000) has shown promising anticancer effects among arginine auxotrophic cancers that are deficient in argininosuccinate synthetase (ASS1) and ornithine transcarbamylase (OTC). High endogenous arginase 2 (ARG2) was previously found in human lung cancers. Although high ARG2 does not induce immunosuppression nor affect disease progression, it may potentially affect the efficacy of BCT-100 treatment. ARG2 was highly expressed in H520 squamous cell lung carcinoma (lung SCC) xenograft while undetectable in SK-MES-1 and SW900 lung SCC xenografts. We postulated that high endogenous ARG2 expression might hamper anticancer effect of PEGylated arginase 1 in lung SCC. **Methods:** The *in vivo* effect of PEGylated arginase 1 was studied using 3 lung SCC xenograft models (SK-MES-1, SW900 and H520). Protein expression, arginine concentration and apoptosis were investigated by Western blot, ELISA and TUNEL assay respectively. ARG2 in H520 xenograft was knocked down using shRNA technique. **Results:** PEGylated arginase 1 (60 mg/kg) suppressed tumor growth in SK-MES-1 and SW900 but not in H520 xenograft. Serum arginine level was decreased significantly by BCT-100 in all xenografts. On the other hand, intratumoral arginine level was reduced by BCT-100 treatment in SK-MES-1 and SW900 xenografts. In H520 xenograft, intratumoral arginine level in control arm could not be further lowered in BCT-100 treatment arms. G1 arrest was indirectly evidenced by downregulation of cyclin A2, B1, D3, E1 and CDK4 with BCT-100 in SK-MES-1 xenograft only. Moreover, activation of apoptosis was induced by BCT-100 in SK-MES-1 and SW900 xenografts. Knockdown of ARG2 in H520 xenograft restored sensitivity to BCT-100 treatment partially induced by G1 arrest via arginine depletion. **Conclusions:** PEGylated arginase 1 treatment was effective in lung SCC xenograft with low endogenous ARG2 expression. High endogenous ARG2 level may explain resistance of BCT-100 treatment in lung SCC xenograft. ARG2 may serve as an additional predictive biomarker, other than ASS1 and OTC, in BCT-100 treatment in lung SCC.