



Endothelin B receptor agonist, IRL 1620, enhances the anti-tumor efficacy of paclitaxel in breast tumor rats.

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Pharmacological agents that increase tumor blood flow could be utilized to promote the delivery of anti-cancer drugs. We have demonstrated that administration of endothelin-1 (ET-1) to breast tumor bearing rats transiently increased tumor blood flow by stimulating endothelin B (ET(B)) receptors. The present study evaluated the effect of ET(B) receptor agonist, IRL 1620, on breast tumor perfusion, concentration of [3H]paclitaxel in tumor and tissues, and efficacy of paclitaxel in N-methyl nitrosourea induced breast tumor bearing rats. Administration of IRL 1620 (3 and 9 nmol/kg) significantly increased (203 and 140%, respectively) breast tumor perfusion. BQ 788, an ET(B) receptor antagonist, pretreatment completely abolished IRL 1620 induced increase in tumor perfusion. Tumor [3H]paclitaxel concentration was increased by 308% when [3H]paclitaxel was administered 15 min after IRL 1620 (3 nmol/kg) compared to vehicle treated rats. However, IRL 1620 did not increase [3H]paclitaxel concentrations in other organs. Efficacy study showed that paclitaxel (5 mg/kg) administration on every third day for a total of five doses produced 60.0, 4.5 and 0% reduction in tumor volume, tumor progression and complete tumor remission, respectively, compared to saline treated rats. However, paclitaxel (5 mg/kg) when administered 15 min after IRL 1620 (3 nmol/kg) produced 268.9, 210.3 and 20% reduction in tumor volume, tumor progression and complete remission of tumors, respectively, compared to saline treated rats. In conclusion, IRL 1620 significantly enhanced delivery and effectiveness of paclitaxel in an animal model of breast cancer.