Angiogenesis inhibitor dose: Dual function during cancer treatment

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In 2009, Ebos and Paez-Ribes reported that angiogenesis inhibitors could promote tumor metastasis. In previous experiments from Ebos' research group, the mice treated with sunitinib at the doses of 60 and 120 mg/kg exhibited an increased trend for host (mouse) and tumor (human) VEGF levels. In contrast, plasma levels in mice treated with sunitinib at the doses of 15 and 30 mg/kg did not exhibit the obvious increase. However, based on clinical application, the effective dose in mice should be 10-12 mg/kg, which suggested that higher than effective dose could promote the development of tumors. Therefore, the administration dose, frequency, and period of angiogenesis inhibitor drugs can result in significant impact on treatment efficacy. The high dose of angiogenesis inhibitors may interrupt the antitumor effect and induce the generation of tumor metastasis factors.

In our laboratory, we found that if a comprehensive investigation of the dosage of angiogenesis inhibitors such as HM-3 was not undertaken, an objective evaluation of angiogenesis inhibitors could not be achieved. We synthesized HM-3 and explored its anticancer activity in vitro and in vivo. The HM-3, a polypeptide containing 18 amino acids, was designed and synthesized in our laboratory. During the design process of HM-3, RGD integrin ligand sequence was added to improve its target capability to tumor cells with highly expressed integrin αvβ3. On the basis of the experimental results in vitro, HM-3 had no inhibitory effect on tumor cells, but significantly inhibited the migration of endothelial cells. Matrigel and aortic ring tests in rats demonstrated that HM-3 effectively inhibited angiogenesis, indicating that its antitumor effect was accomplished by inhibiting the migration of endothelial cells and angiogenesis. Meanwhile, the antitumor activity was dose dependent in the range 0.75-3 mg/kg. No obvious antitumor activity was observed when the dose of HM-3 was lower than 0.75mg/kg or higher than 6mg/kg. On the other hand, HM-3 at the dose higher than 6 mg/kg could promote the migration of endothelial cells and result in the overexpression of genes related to tumor metastasis.

Our investigations will provide a reference for further research of angiogenesis inhibitors: preclinical and clinical applications should consider administration dose, frequency, and period of angiogenesis inhibitors to achieve an objective evaluation.

Because angiogenesis and angiogenesis inhibition in the human body is a very delicate process, patient status, symptoms, and pathological mechanisms must be fully considered while using angiogenesis inhibitors. It is really necessary to understand the tumor mechanisms (whether the tumor is derived from increased tumor angiogenesis factor such as VEGF or decreased angiogenesis defense system); drug type, administration dose, treatment frequency, and period are the determinants for cancer treatments.