VIII-Ⅱ-3. Original Research

OR1

Reducing Intratumor Acute Hypoxia through Bevacizumab Treatment, Referring to Distant Metastatic Potential

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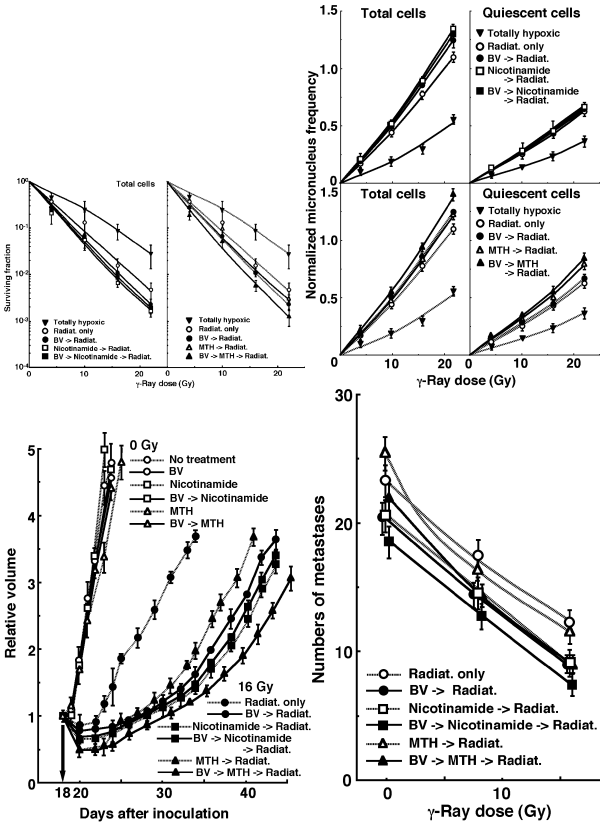
BACKGROUNDS AND PURPOSES: It was believed that antiangiogenic therapy prevents the tumor vascular growth and proliferation, thus depriving the tumor of oxygen and nutrients necessary for survival [1]. Subsequent study, however, suggested that antiangiogenic therapy may also "normalize" the tumor vasculature for a short period of time, thereby providing a window of opportunity for improved drug delivery and enhanced sensitivity to radiation [1,2]. Tumor hypoxia results from either limited oxygen diffusion (chronic hypoxia) or limited perfusion (acute hypoxia) [3]. Further, it was reported that acute and cyclic, but not chronic, hypoxia significantly increased the number of spontaneous lung metastases, and that this effect was due to the influence of acute hypoxia treatment on the primary tumor [4,5]

Here, we tried to analyze on hypoxia in solid tumors after the administration of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, using the acute hypoxia-releasing agent nicotinamide combined with γ-ray irradiation, in terms of both local tumor response and lung metastasis compared with irradiation combined with mild temperature hyperthermia (MTH), already shown to have the potential to release tumor cells from diffusion-limited chronic hypoxia [6,7]. In addition, concerning the local tumor response, the effect not only on the total (= proliferating (P) + quiescent (Q)) tumor cell population but also on the Q cell population was evaluated using our original method for detecting the response of Q cells in solid tumors [8].

MATERIALS AND METHODS: B16-BL6 melanoma tumor-bearing C57BL/6 mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all proliferating (P) cells. They received γ-ray irradiation following treatment with the acute hypoxia-releasing agent nicotinamide or MTH with or without the administration of bevacizumab under aerobic conditions or totally hypoxic conditions achieved by clamping the proximal end of the tumors. Immediately after the irradiation, cells from some tumors were isolated and incubated with a cytokinesis blocker. The responses of the Q and total cell populations were assessed based on the frequency of micronuclei using immunofluorescence staining for BrdU. In other tumor-bearing mice, 17 days after irradiation, macroscopic lung metastases were enumerated.

RESULTS: Three days after bevacizumab administration, acute hypoxia-rich total cell population in the tumor showed the remarkably enhanced radio-sensitivity to γ-rays, and the hypoxic fraction (HF) was reduced, even after MTH treatment. However, the HF was not reduced after nicotinamide treatment. With or without γ-ray irradiation, bevacizumab administration showed some potential to reduce the number of lung metastases as well as nicotinamide treatment.

CONCLUSION: Bevacizumab has the potential to reduce the perfusion-limited acute hypoxia and some potential to cause the decrease in the number of lung metastases as well as nicotinamide [9].



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ベバシツマブ処置による腫瘍内急性低酸素細胞分画低下作用と遠隔肺転移抑制効果について　独自研究
（京大・原子炉）増永慎一郎、田中浩基、櫻井良憲、鈴木実、近藤夏子、楢林正流、丸橋　晃、小野公二