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Bevacizumab has differential and dose-dependent effects on glioma blood vessels and tumor cells.

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Abstract

PURPOSE: Bevacizumab targets VEGF-A and has proved beneficial in glioma patients, improving clinical symptoms by reducing tumor edema. However, it remains controversial whether or not bevacizumab exerts anti-tumor effects in addition to (and potentially independent of) its effects on tumor vessels, and unknown what doses are needed to achieve this.

EXPERIMENTAL DESIGN: We established a novel orthotopic glioma mouse model allowing to simultaneously study the kinetics of morphologic and functional vascular changes, tumor growth, and viability of individual tumor cells during the course of anti-VEGF therapy in the same microscopic tumor region in real-time. Three doses of bevacizumab were compared: a subclinical dose, and two clinical doses (medium and high).

RESULTS: Low (subclinical) doses of bevacizumab led to a significant reduction of total vascular volume without affecting tumor cell viability or overall tumor growth rates. Medium and high doses triggered a similar degree of vascular regression, but significantly decreased tumor growth and prolonged survival. Remaining vessels revealed morphological features of vascular normalization, reduced permeability, and increased blood flow velocity; the latter was dose-dependent. We observed an uncoupling of the anti-tumoral and the anti-vascular effects of bevacizumab with the high dose only, which showed the potential to cause microregional glioma cell regression. In some tumor regions, pronounced glioma cell regression occurred even without vascular regression. In vitro, there was no effect of bevacizumab on glioma cell proliferation.

CONCLUSIONS: Regression of glioma cells can occur independently from vascular regression, suggesting that high doses of bevacizumab have indirect anti-cancer cell properties in vivo.

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