The therapeutic efficacy of anti vascular endothelial growth factor antibody, bevacizumab, and pemetrexed against orthotopically implanted human pleural mesothelioma cells in severe combined immunodeficient mice.

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PURPOSE: Malignant pleural mesothelioma (MPM) is an aggressive malignancy, which has a poor prognosis with a median survival of less than 1 year. The vascular endothelial growth factor (VEGF) has been reported to be an ideal therapeutic target, and a multitargeted antifolate, pemetrexed, has been clinically used for the treatment of MPM. EXPERIMENTAL DESIGN: We examined the therapeutic efficacy of the antihuman VEGF neutralizing antibody, bevacizumab, in combination with pemetrexed against two different human MPM cells, EHMES-10 and MSTO-211H, orthotopically inoculated into severe combined immunodeficient mice. RESULTS: Bevacizumab inhibited a VEGF-induced proliferation of the human endothelial cells in a dose-dependent manner, but it had no effect on the proliferation of the two MPM cell lines *in vitro*. The orthotopically inoculated EHMES-10 cells (VEGF high expressing) produced thoracic tumors and a large volume of bloody pleural effusion, whereas the MSTO-211H cells (VEGF low expressing) produced thoracic tumors and a small volume of bloody effusions. Treatment with bevacizumab effectively inhibited the production of thoracic tumors and dramatically prevented the production of pleural effusion by the EHMES-10 cells but not the MSTO-211H cells. Treatment with bevacizumab reduced the number of enlarged tumor-associated vessels and proliferating tumor cells. Moreover, treatment with bevacizumab in combination with pemetrexed more effectively suppressed the formation of the pleural effusion and prolonged the survival compared with the control and monotherapy in the EHMES-10 cell-bearing severe combined immunodeficient mice. CONCLUSIONS: These results suggest that the combined use of bevacizumab and pemetrexed may therefore be promising for controlling the progression of MPM highly expressing VEGF.