High-dose vitamin C in BRAF inhibitor resistant melanoma cells *in vitro* and *in vivo*

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Abstract:

Introduction: In recent years, we and others have discovered that high-dose vitamin C paradoxically acts as a pro-oxidant, causing large amounts of hydrogen peroxide that cannot be compensated by tumor cells, especially melanoma cells. Therefore, high-dose vitamin C may be an attractive approach for supportive care of refractory melanoma resistant to established modern therapies, such as BRAF inhibitors in BRAF-mutated melanoma.

Methods: Several BRAF-mutated melanoma cell lines were treated with either pharmacological doses of vitamin C alone or in combination with the BRAF inhibitor vemurafenib. Viability, cell cycle distribution, formation of reactive oxygen species and protein levels of GLUT-1 and HIF1alpha as well as phosphorylation levels of ERK1/2 were assessed. To study in vivo effects, BL6 mice subcutaneously bearing a D4M.3A (BRAFV600E) melanoma were treated with intraperitoneal injections of vitamin C (2 g/kg body weight), vemurafenib (30 mg/kg body weight), or a combination thereof.

Results: Both, vemurafenib sensitive and resistant BRAF mutated melanoma cell lines were sensitive to the treatment with pharmaceutically active amounts of vitamin C. Treatment of mice with BRAFV600E melanoma resulted in short-term ascorbate serum levels in the millimolar range. Furthermore, the therapeutic effect of BRAFV600E inhibition was markedly improved by high-dose vitamin C in terms of reduced tumor growth, which was reflected in a lower proliferation rate and an increased proportion of apoptotic cells.

Conclusion: High-dose vitamin C therapy can be combined with standard targeted melanoma therapies without severe toxicities or loss of efficacy.