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The response of human papillomavirus associated head and neck squamous cell carcinoma cell lines on standard therapy and treatment with an experimental alpha-particle emitter immunoconjugate targeting EGFR (Bi-213-Cetuximab)

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. Despite considerable improvements in surgery, radio- and chemotherapy over the last decades, the five-year overall survival has not changed significantly. Radio resistance is a frequent issue that impedes success in therapy. Tumor hypoxia often is causing this resistance, hence targeted therapy with oxygenation-independent alpha-emitters could be a effective strategy for therapy of HNSCC. Another emerging factor for treatment response is infection with human papillomavirus (HPV). HPV associated HNSCC is known to have a better prognosis and therefore is described as distinct entity within HNSCC. Still there are contrary experimental studies on response to therapy and the underlying molecular mechanisms.

Objectives

Characterizing the relevance of HPV status of HNSCC cell lines for response to standard and experimental therapy with alpha-particle emitter immunoconjugate targeting EGFR (^{213}Bi-Cetuximab).

Materials & Methods

We analyzed proliferation, colony forming capability, cell cycle and DNA double strand brakes (yH2AX) in six HNSCC cell lines (3 HPV pos./3 HPV neg.) after treatment with chemotherapeutics, alpha-particle emitter ^{213}Bi-Cetuximab (9.25-111 kBq/mL) and irradiation by X-Rays (0.5-14 Gy). We also performed Western blot analysis and determined the impact of knockdown of DNA repair factors (RAD51, LIG4 or XRCC1) on proliferation.

Results

HPV-positivity was significantly associated with a more pronounced antiproliferative response to treatment with various chemotherapeutics, ^{213}Bi-Cetuximab as well as X-Ray irradiation with single or fractionated doses. Colony forming capability of the cells after treatment was also significantly correlated with HPV status. After treatment with ^{213}Bi-Cetuximab cells accumulated in the G2-Phase. After X-Ray therapy this effect could be seen in the HPV-positive cell lines only. Treatment with ^{213}Bi-Cetuximab (37 kBq/mL) resulted in a delayed, stronger and more persistent peak level of the DNA double strand break marker yH2AX compared to X-Ray therapy (2 Gy). HPV-positive cell lines showed slightly stronger yH2AX intensity changes with both treatments. Cleavage of PARP and phosphorylation of Erk1/2 after irradiation correlated with HPV-positivity. Rad51 protein level was HPV-independently upregulated, most notably with ^{213}Bi-Cetuximab treatment. Knockdown of RAD51 had an antiproliferative effect on the cells - especially in HPV-positive cells –whereas knockdown of LIG4 or XRCC1 did not affect proliferation. Irradiation-induced antiproliferative effects could be enhanced by knockdown of these DNA-repair factors, noticing the strongest effect with knockdown of RAD51.

Conclusion

HPV associated HNSCC showed a better response to all forms of therapy tested. Our results are suggesting a more pronounced G2-arrest to be responsible for this observation. Compared to X-Rays, the experimental therapy with the alpha-particle emitter ^{213}Bi-Cetuximab is a remarkably more effective approach to attenuate the proliferation potential of HNSCC. Since this superior response is also true for more radioresistant HPV-negative cell lines, targeted ^{213}Bi-Cetuximab treatment of HNSCC is a promising option and should be further developed.

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