Effects of Anti-Human Papillomavirus (HPV) Disease Agents on HPV Episome Levels In Vitro: Cidofovir, Podophyllotoxin, and Pyrrole-Imidazole Polyamides

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Many in vitro studies of anti-HPV agents have misguidedly focused upon cells maintaining integrated rather than episomal copies of human papillomaviruses (HPV). HPV displays genotype-specific tissue tropism and causes hyperproliferative diseases of both cutaneous and mucosal epithelia. Persistent infection with “high risk” HPVs may lead to malignancy. We have taken a novel approach to design a series of pyrrole-imidazole polyamides against the sequences located in the ori of high-risk HPV genotypes. The compounds specifically reduce HPV episome levels in cells maintaining high-risk HPV genomes. In this study, we compared the effects of our targeted polyamides against Cidofovir, which is currently being used off label for treatment of HPV-related disease including recurrent respiratory papillomatosis (RRP), and podophyllotoxin which is commonly used to treat cutaneous warts. Monolayer cultures of human foreskin keratinocytes maintaining HPV31 were treated for 48 hours with a range of doses of each compound. The effect of this treatment on HPV31 episome levels was measured via Q-PCR normalized to DNA input. Cell viability was also assessed in parallel using an MTT assay. A 50% reduction in HPV31 genome copy number was achieved at a concentration of 1uM of polyamide NV1020 with no observable cytotoxicity up to the highest dose tested (10uM). Cidofovir caused a dose-dependent decrease in HPV31 DNA at high doses of compound, although a 50% reduction in viral genomes was never reached for this compound up to 500uM. The observable loss of HPV31 episomes due to Cidofovir correlated with losses in cell viability. Podophyllotoxin had no effect on HPV31 episome levels, however there was a significant dose-dependent reduction in cell viability (TD50 = 80uM). These studies demonstrate the following: that podophyllotoxin does not effect HPV episome levels but acts primarily via a cytotoxic mechanism; that Cidofovir appears to have an anti-HPV effect that is associated with cytotoxic activity; and that NV1020 effects on HPV episome levels occur in the absence of measurable cytotoxicity.