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Co-inhibition of mitotic kinesins and kinases with BCL-2 family inhibitors enhances cytotoxicity of oral cancer cells

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Abstract

Background: Head and neck cancer is the seventh most prevalent cancer worldwide and it includes oral cancer [1]. Approximately 90% of all oral cancers are oral squamous cell carcinomas [2,3]. Despite their promising preclinical results, the inhibitors of mitotic kinesins and kinases failed in clinical trials, probably because they are not too effective in inducing apoptosis when used in monotherapy [4,5]. Thus, apoptotic pathway in cell treated with mitotic kinesin and kinase inhibitors may be a strategy to improve the effectiveness of these antimitotic agents. **Objective:** Kinesin spindle protein (KSP) is involved in chromosome segregation and its inhibition results in the formation of monopolar spindles, inducing a mitotic delay. Aurora B is involved in correcting errors in chromosome attachment to the mitotic spindle, and its inhibition leads to mitotic exit with chromosome missegregation. The objective of this study is to assess the antitumor potential of combining a KSP or an Aurora B inhibitor with a BCL-2 family inhibitor in oral cancer. **Methods:** To evaluate the cytotoxic activity of the inhibitors, the IC_{50} was determined by the MTT assay. Using the Combenefit software, the combinations corresponding to the lowest concentration of the drugs that resulted in the greatest cytotoxic effect were selected. Cell death was assessed by flow cytometry, using annexinV/PI staining. Cell fate after combination treatment was monitored and characterized by time-lapse microscopy. **Results:** Both anti-KSP/anti-BCL2 and anti-Aurora B/anti-BCL2 combinations showed synergistic effects with increased cytotoxic activity. The anti-KSP/anti-BCL2 combination showed an exacerbation of apoptosis during mitotic arrest, while the anti-Aurora B/anti-BCL2 combination led to increased postmitotic death. **Conclusions:** Our data demonstrate that the combination of a BCL2 family inhibitor with either a KSP or an Aurora B inhibitor may be potentially useful as treatment strategies against oral cancer.

Keywords: antimitotics; BCL-2 family inhibitor; apoptosis; combination therapy; oral cancer

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