Effect of Telomere Targeted 8-Oxoguanine Stress in Combination With DNA Damage Response Inhibitors on Genomic Instability in Cancer

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Cancer is the second leading cause of death worldwide. In 2021 almost 10 million people died of cancer. Numerous conditions and factors can be attributed to the formation of cancer. A critical factor is telomere shortening, with oxidative stress (OS) being the most commonly cited underlying cause. Telomeres are hypersensitive to 8-oxoguanine stress (8-oxoG), a type of OS that leads to G:C to 8-oxoG:A transversion mutations. In 2019, the FAP-TRF1 tool was created, which selectively induces 8-oxoG at telomeres through local production of singlet oxygen. Telomere repeat factor 1 (TRF1) protein is tagged with a fluorogen activating peptide (FAP). FAPs have a high affinity for the photosensitizer dye di-iodinated malachite green (MG2I). MG2I produces singlet oxygen upon FAP binding and subsequent excitation with 660-nm light. It was hypothesized the combination of induced telomere 8-oxoG and the inhibition of ATM, ATR, and WEE1, DNA damage repair checkpoints, would result in an increase in genomic instability, measured by micronuclei formation, chromosome fragments that remain outside of the nucleus after cell division. To test this hypothesis, 8-oxoG was induced and the cells were grown in the appropriate drug solution for 24 hours. The number of micronuclei per 100 cells were quantified. Assays showed a significant increase in the number of micronuclei when cells were subjected to 8-oxoG and ATRi, and no increase when using ATMi. The inhibition of WEE1 with 8-oxoG is still being investigated. The ATRi used in this study is currently in clinical trials.

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