Combination therapy with Trifluridine/Tipiracil and ATR–CHK1–WEE1 pathway inhibition against *TP53*–mutant esophageal cancer

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Abstract

Unresectable or recurrent esophageal squamous cell carcinoma (ESCC) is a highly aggressive malignancy with poor survival and limited treatment options. *TP53* gene, a part of the ATM– Checkpoint Kinase 2 (CHK2)–p53 pathway, is the most frequently (83–92%) mutated in ESCC, and *TP53*–mutant ESCC is thought to rely on the ATR–Checkpoint Kinase 1 (CHK1)–WEE1 pathway to maintain DNA integrity. We found that targeting the ATR–CHK1–WEE1 pathway with combination therapies involving trifluridine/tipiracil (FTD/TPI), a thymidine–based nucleoside analog that induces DNA damage, and inhibitors of CHK1 or WEE1 induced potent antitumor effects in *TP53*–mutant ESCC *in vitro* and *in vivo*, acting through synthetic lethality. We also found that the combinations of CHK1 / WEE1 inhibitors and FTD/TPI increased abortion of cell cycle arrest, increased double–strand DNA breaks, and suppressed tumor growth compared to monotherapy or control groups. Our results suggest that the inhibition of ATR–CHK1–WEE1 pathway can enhance the efficacy of chemotherapy by exploiting the vulnerability to DNA damage in *TP53*–mutant ESCC.