PRIMA-1met as a potential prostate cancer radiosensitizer under normoxia and hypoxia

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Background: Mutated p53 (Mutp53) induces increased radioresistance and reduction of apoptosis in advanced prostate cancer. PRIMA-1met is a new agent that reverses mutated p53 to a normal function therefore activating downstream p21 and apoptosis. We investigated whether PRIMA-1met could radiosensitize prostate cancer cell lines under oxia (21% O_2) or hypoxia (0.2% O_2).

Material and Methods: The effects of PRIMA-1met on p21WAF protein expression (Western Blot), on apoptosis (Hoechst 33342 and TUNEL staining) and on clonogenic survival (drug alone or combined with radiation) were studied using 2 prostate cancer cell lines that also form xenografts: DU145 (MTp53), 22RV1 (WTp53). To assess potential toxicity, the effects of the drug on normal fibroblasts (GM5757) in vitro and in a gut colony assay in vivo were also studied. Potential tumour radiosensitizing effects of the drugs were assessed by an ex vivo clonogenic assay and apoptosis staining of xenografts.

Results: PRIMA-1met reduced clonogenic survival of mutp53 cell line DU145 (IC50: 12 μM) but also on WTp53 cell line 22RV1 (IC50 3.8 μM). However, PRIMA-1met did not induce p21WAF activation in DU145 under oxia or hypoxia, nor did it induce apoptosis in vitro or in vivo. Under oxic conditions PRIMA-1met significantly radiosensitized the MTp53 cell line DU145 (Sensitizing Enhancement Ratio 1.2) but not WTp53 cell line 22RV1. Under hypoxia, PRIMA-1met induced a similar cell death for DU145 as under oxic conditions (54% survival for 10 μM), but did not radiosensitize DU145 cells. Clonogenic survival ex vivo was reduced (irradiation alone: 33%, irradiation plus PRIMA-1met: 28%). PRIMA-1met did not radiosensitize normal diploid fibroblasts in vitro nor gut colony forming cells in vivo.

Conclusion: PRIMA-1met is a potent radiosensitizer of Mutp53 prostate cancer cells under normoxia. The activity of PRIMA-1met against MTp53-expressing cells could involve p21WAF- and apoptosis-independent mechanisms and makes this agent an attractive adjunct to prostate radiotherapy.