ET-60. ENHANCED THERAPEUTIC EFFICACY OF PRODRUG ACTIVATOR GENE THERAPY WITH A NON-LYTIC RETROVIRAL REPlicATING VECTOR (TOCA 511) COMBINED WITH RADIATION THERAPY IN EXPERIMENTAL GLIOMA

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A tumor-selective non-lytic retroviral replicating vector (RRV), Toca 511 (vocimagene amiretrorepvec), is being investigated in clinical trials in patients with recurrent high grade glioma (rHGG) (www.clinicaltrials.gov NCT01156584, NCT01470794, NCT01985256). Toca 511 encodes a modified yeast cytosine deaminase (CD), which converts oral prodrug 5-FC into the anticancer drug 5-fluorouracil (5-FU) within infected tumor cells. Since 5-FU is a radiosensitizer, we investigated in preclinical models the combination of Toca 511, 5-FU and radiation for treatment of human HGG. U87 and radioresistant U87EGFRvIII cells were infected in vitro with Toca 511 and subsequently irradiated with 0, 3, 6 or 9 Gy. In non-irradiated and irradiated cells, RRV infected >95% of cells by day 21 showing that radiation does not perturb viral spread. In vitro clonogenic survival assays showed significant radiosensitization with 5-FU in RRV-infected U87EGFRvIII cells. For in vivo survival studies, U87EGFRvIII cells (5 x 10^4) were stereotactically implanted into athymic mouse brain and Toca 511 (10^5 Transducing Units) was injected intratumorally 4 days later. Mice were treated with a single cycle of intraperitoneal PBS or 5-FU (500 mg/kg) for 5 days from day 10 to 14, with or without irradiation (2 Gy/fr/day; total 10 Gy, or 4 Gy/fr/day; total 20 Gy). Mice treated with 20 Gy and a single cycle of 5-FU showed significantly longer survival compared with the other two groups (p<0.0001) and median survival was >75 days. Next, mice were treated with multiple cycles of PBS or 5-FU (intraperitoneal, 5 days every 2 weeks, 5 cycles) with or without irradiation at the lower dose (total 10 Gy). Mice treated with 10 Gy and 5 cycles of 5-FU showed significantly longer survival (p<0.0001) and median survival was >89 days. These efficacy data support clinical investigation of Toca 511 and 5-FU in combination with radiation in the first-line setting for patients with HGG.