UNIVERSITÄT LEIPZIG

Medizinische Fakultät

Universitätsklinikum Leipzig

Medizin ist unsere Berufung.

Enhanced Radiation Effects by combined Treatment with Decitabine and Abacavir in a murine Model of human pediatric Medulloblastoma

Gringmuth M., Patties I., Böhme L., Kortmann R.D., Glasow A.

University of Leipzig, Department of Radiooncology, Stephanstraße 9a, 04103 Leipzig

Background and Objective:

Medulloblastoma (MB) is the most common malignant pediatric brain tumor. Standard therapy consists of surgical excision followed by radio-chemotherapy. The 5-year overall survival for children is between 45 % (Group 3 MB) and 95 % (WNT MB) depending on molecular subgroup. Our previous *in vitro* studies showed a significant combinatorial enhancement of radiotherapy (RT), DNA-demethylating agent decitabine (DEC), and telomerase inhibitor abacavir (ABC) on clonogenic MB cell death with no increased neurotoxicity on murine hippocampal slice cultures. Here, we translate those results in an orthotopic PDX model using Group 3 medulloblastoma cells.

Method:

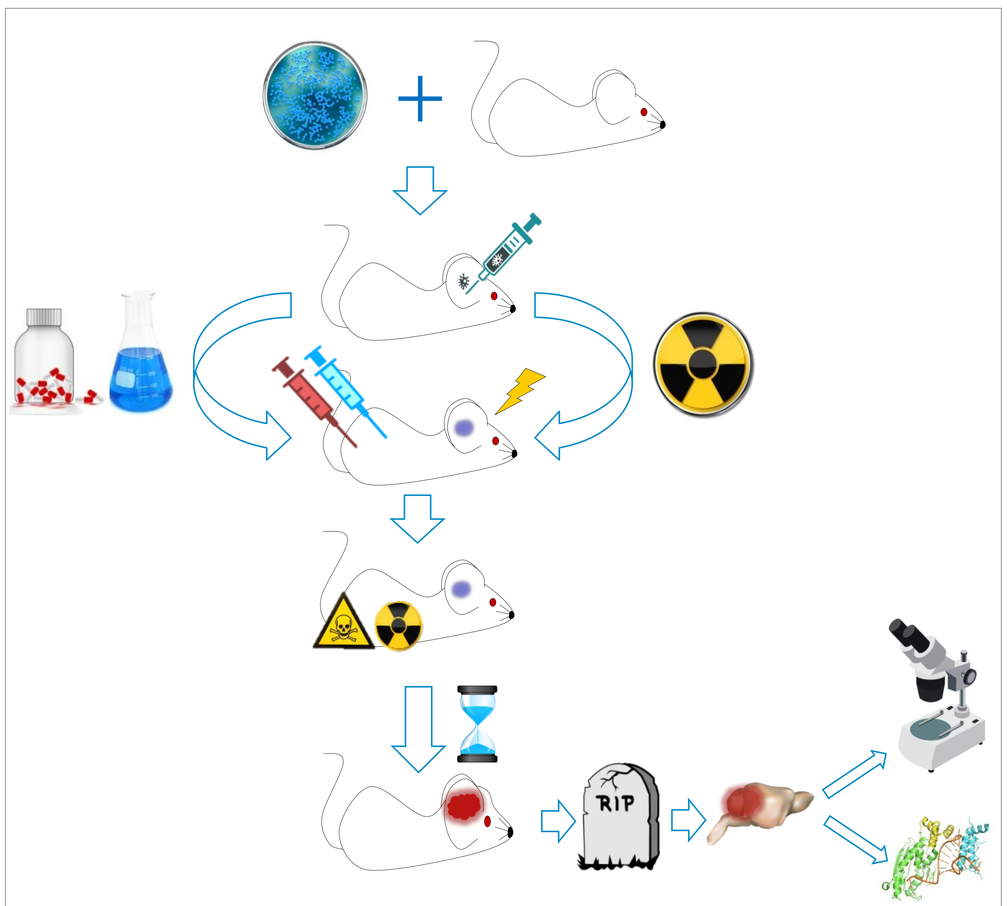

Figure 1: Treatment procedure using NSG mice and Group 3 medulloblastoma PDX cells: Mice were injected, treated with 0.1mg/kg DEC and/or 50 mg/kg ABC daily for 14 days and/or with 2 Gy single dose RT at day 8. After euthanasia, brains were preserved for histological staining.

Results (I): Survival analyses

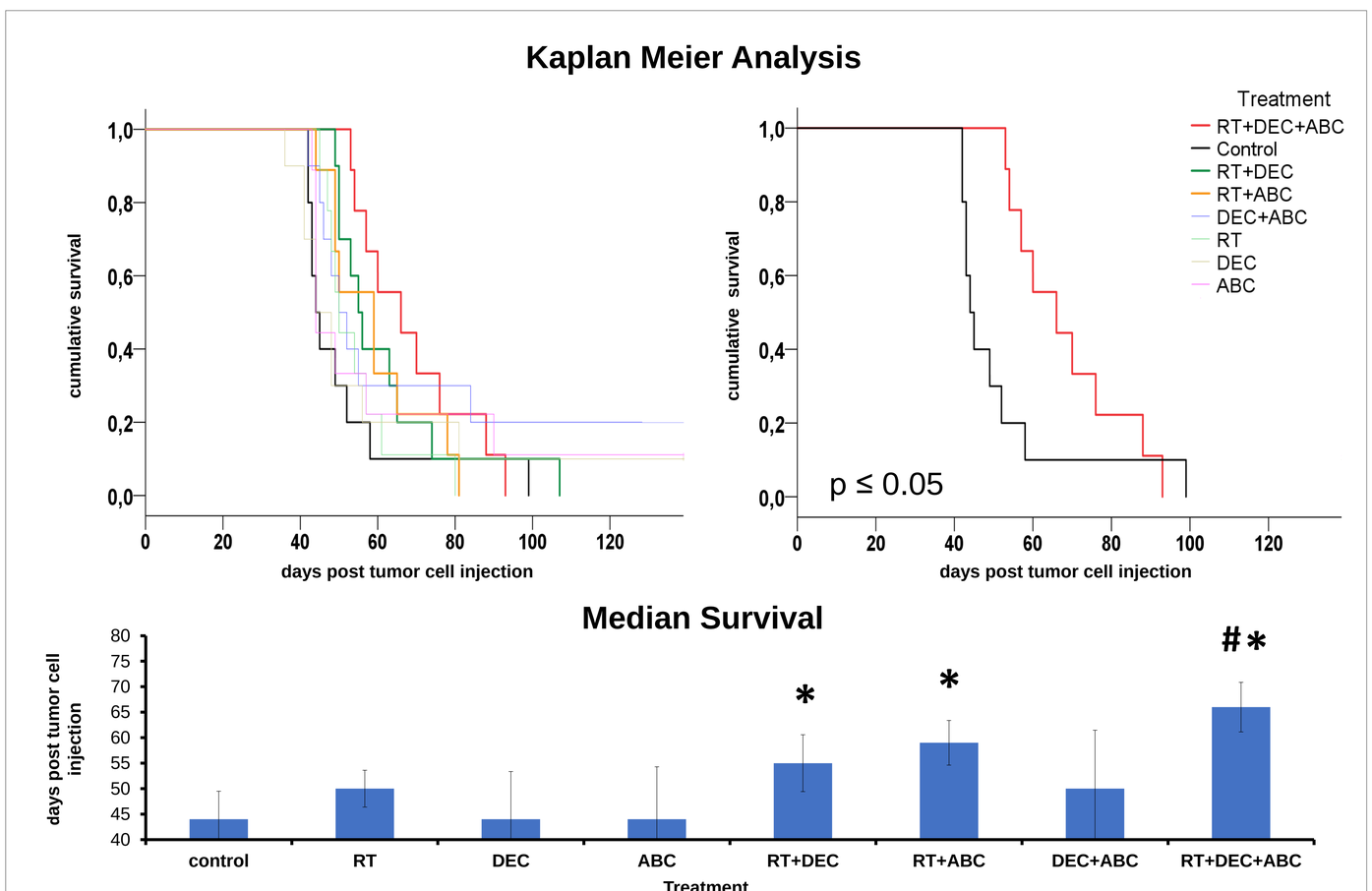

Figure 2: Survival analyses of MB-bearing mice after multimodal treatment with 0.1 mg/kg/d Decitabine (DEC), 50 mg/kg/d Abacavir (ABC), and 2 Gy local radiotherapy (RT), Kaplan-Meier survival curves and Median survival +/-SEM, n = 10,; * p ≤ 0.05, compared to untreated control; # p ≤ 0.05 compared to radiation control

Survival analysis revealed significantly prolonged median survival after multimodal treatment (RT, DEC, ABC; 66 ± 9 days) compared to untreated control group (44 ± 2 days) and RT-only-treated group (50 ± 1 days). Both combinations of RT + DEC and RT + ABC resulted in significantly longer survival compared to untreated control, but not to radiation control. (**figure 2**) Tissue analysis revealed tumor tissue of triple-treated group has significantly lower amounts of blood vessels (14 %) (**figure 3a**) compared to control group and 15 % less proliferative cells (**figure 3b**).

Results (II): Tumor vascularization and proliferation

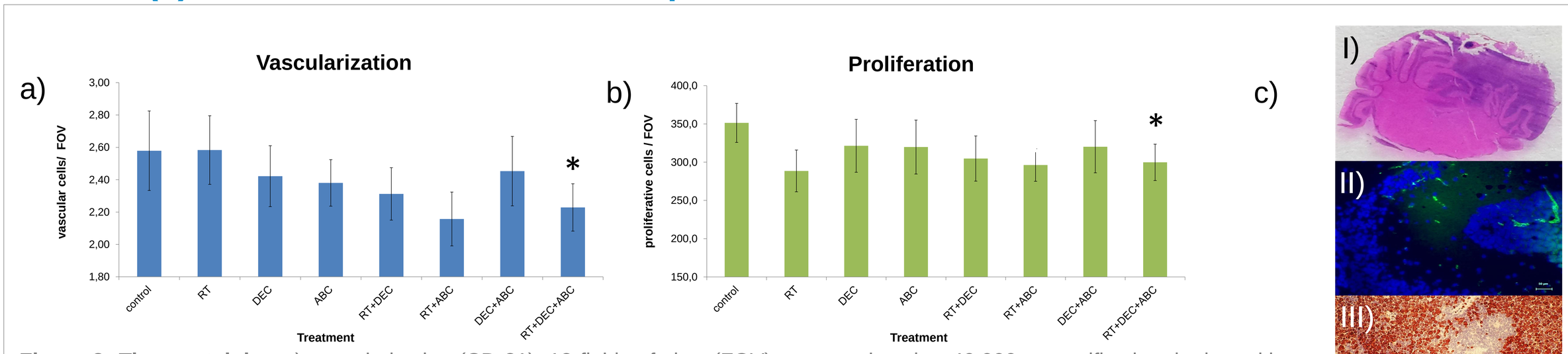

Figure 3: Tissue staining a) vascularization (CD 31): 12 fields of view (FOV) were analyzed at 40.000x magnification, both positive single cells (capillaries) and cell clusters (larger vessels) were counted. b) proliferation (Ki-67): 6 FOV were analyzed in 40.000x magnification, *p ≤ 0,05, n = 10 c) Representative images from hematoxylin/eosine staining (I), CD 31 immunofluorescence (II), Ki-67 immunohistochemistry (III)

Conclusion:

The multimodal therapy with decitabine, abacavir, and RT significantly prolongs the survival of mice with an orthotopic PDX Group 3 medulloblastoma. Tumor tissue vascularization and cell proliferation was significantly lower in triple-treated compared to control tumors. In further studies we will evaluate if the treatment is also effective in a SHH/p53-mutated MB PDX mouse model.