Safety Evaluations of Rapamycin Perfluorocarbon Nanoparticles in Ovarian Tumor Bearing Mice

Adam Mitchell, Qingyu Zhou, Antonina Akk, John Harding, Luke E. Springer, Joseph P. Gaut, Ping Fan, Ivan Spasojevic, Christine T. Pham, Samuel Wickline, Daniel Rauch, Katherine Fuh, and Hua Pan

1Washington Univ School of Medicine in St. Louis; 2Univ of South Florida College of Pharmacy; 3Washington University School of Medicine in St. Louis; 4Duke University School of Medicine; 5Morsani College of Medicine; 6Washington University School of Medicine; and 7University of California San Francisco School of Medicine

Abstract ID 50713 Poster Board 455

In the US, ovarian cancer is the 2nd most common gynecologic cancer of the female reproductive system and claims more lives than any other gynecologic cancer. Cisplatin is used as part of the first-line of treatment for ovarian cancer and has demonstrated better therapeutic outcomes than carboplatin. Independent reports indicated that about 40% of ovarian cancer patients developed acute kidney injury (AKI) after cytoreductive surgery and cisplatin-based hyperthermic intraperitoneal chemotherapy. Although efforts to protect kidney function from cisplatin induced toxicity were initiated in the 1970's, current clinical managements remain as supportive measures, such as hydration and/or magnesium replacement. Our recent studies demonstrated the benefits of rapamycin perfluorocarbon nanoparticles (PFC NP) in mitigating cisplatin induced AKI and favorable safety profiles in normal mice. Here, we report the safety evaluations of rapamycin PFC NP in ovarian tumor bearing mice. Fourteen Athymic nu/nu mice received a subcutaneous implantation of 1 million OVCAR-8-eGFP cells. Two weeks after the implantation, palpable tumors were observed, and the mice were treated with either rapamycin PFC NP or saline administered intravenously twice a week for two weeks. Seventy-two hours post last treatment, mice were euthanized for blood testing and histopathological evaluations. The results demonstrated that rapamycin PFC NP treatment reduced the tumor burden (8±3 mg) by 89% compared with the control (72±22 mg) (p=0.012). The immunofluorescent evaluation on tumors illustrated that tumors from the control group exhibited a well-established blood vessel network from the peripheral to the core, which did not exist in the tumors from rapamycin PFC NP treated mice. Consistent with our previous report, the rapamycin PFC NP treatment (Rx) didn’t impair the kidney function (BUN: 26.11±1.86 vs 22.67±1.67 mg/dL; Creatinine: 0.20±0.03 vs 0.26±0.03 mg/dL; control vs Rx), liver function (Total protein: 5.18±0.10 vs 5.48±0.19 g/dL; AST: 142.70±20.03 vs 150.56±14.00 U/L; ALT: 38.60±1.68 vs 46.44±1.99 U/L; ALP: 95.20±7.93 vs 100.33±4.68 U/L; control vs Rx), nor affect blood glucose (177.89±10.48 vs 186.22±8.17 mg/dL; control vs Rx) and blood electrolytes (Sodium: 153.67±0.76 vs 153.86±0.34 mmol/L; Potassium: 3.77±0.10 vs 3.54±0.07 mmol/L; Chloride: 113.00±1.00 vs 112.00±0.82 mmol/L; control vs Rx). Moreover, the rapamycin PFC NP treatment didn’t alter the total number of splenocytes (28.43±4.27 x10⁶ vs 30.57±5.37 x10⁶; control vs Rx) or splenocyte subpopulations (B cells: 22.24±3.32 x10⁶ vs 23.70±4.76 x10⁶; PMN: 3.41±0.77 x10⁶ vs 3.20±0.39 x10⁶; Monocytes: 2.38±0.61 x10⁶ vs 3.78±0.86 x10⁶; control vs Rx). All the results were reported as mean±SEM. In conclusion, our results suggested that rapamycin PFC NP treatment didn’t alter normal vital organ function nor normal immune system but inhibited ovarian tumor progress partially due to preventing tumoral blood vessel establishment. These observations suggested that rapamycin administered in PFC NP format is effective against ovarian cancer in a preclinical model without exhibiting significant toxic effects.

The work is supported by NIH, R01DK125322.

Supported by NIH, R01DK125322