An Implantable Intraperitoneal Drug Delivery Device for the Treatment of Advanced Ovarian Cancer

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Statement of Purpose:

Ovarian cancer carried a 70.3% mortality rate in the United States in 2011, largely due to late-stage detection (Ovarian Cancer National Alliance, Ovarian Cancer Statistics, 2012). The current standard of care for ovarian cancer is tumor-debulking surgery followed by alternating rounds of chemotherapy with cisplatin and paclitaxel three times a week, for six cycles. The drug is administered intravenously (IV) or intraperitoneally (IP) through an indwelling catheter. Women who received IP chemotherapy had longer survival than those who received IV injections. Catheter-related complications and side effects also lead to early termination of IP therapy in many cases. These challenges led to the proposal of an implantable device to achieve controlled-release of chemotherapeutic agents into the peritoneal cavity over the entire duration of treatment. This device has the potential to improve treatment efficacy in patients with ovarian cancer while minimizing discomfort, catheter-related complications and systemic toxicity.

Methods:

The poly-L-lactic acid devices were injection molded by MicroPEP (RI, USA) and orifices micromachined in the devices to achieve various drug release rates. Nu/nu mice obtained from Charles River (MA, USA) were injected with 10^6 human SKOV-3 ovarian cancer cells and treatment was administered on day 14. The mice were either implanted with devices (device group), injected once per week with 10mg/kg cisplatin solution (IP bolus cisplatin injection group), or administered no treatment (control). An intraperitoneal injection of daily saline was administered for hydration of animals receiving a bolus injection or treatment with the device. Animals were euthanized upon 20% weight loss, according to procedures established by the MIT Committee on Animal Care. The study was terminated on day 56 and tissues were harvested for histological analysis.

Results:

Preliminary results from the *in vivo* study comparing the implantable cisplatin release device to IP bolus administration and no treatment demonstrate that the device provides effective treatment while reducing systemic toxicity. Figure 1 demonstrates that the implanted device significantly reduces the visible tumor mass at the point of euthanasia compared to the no treatment control group. The IP bolus treatment did not have any visible tumor mass; however, most of the animals lost 20% weight before the termination of the study, when tumor burden in the controls was likely significantly lower than at day 56. Figure 2 illustrates the significant weight loss that follows each bolus dose of cisplatin, indicating accompanying systemic toxicity from the cisplatin, whereas animals treated with the device maintain a more stable weight throughout the duration of

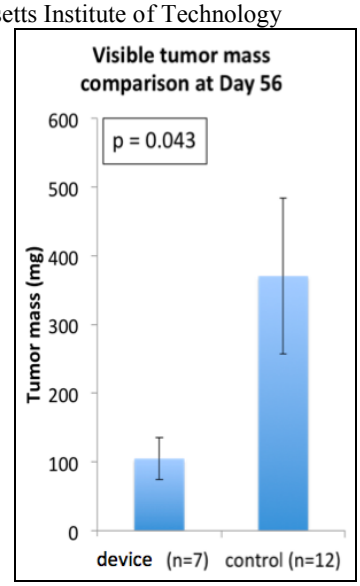

Figure 1. Comparison of visible tumor mass at point of animal euthanasia

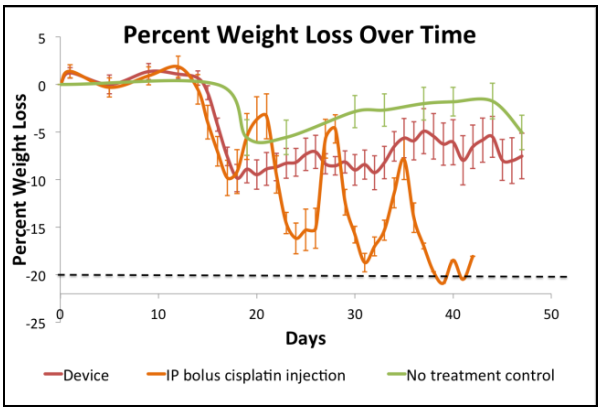

Figure 2. Animal weight during treatment administration

treatment. Histological analysis revealed protein casts in the kidneys and bone marrow depletion in the IP bolus treated animals, indicative of the dose-limiting nephrotoxicity and leukopenia characteristic of cisplatin.

Conclusions:

The device provides a viable improvement over the current standard of IP chemotherapeutic treatment for ovarian cancer. Preliminary experiments show that the device has a better toxicity profile than IP bolus treatment while being efficacious in limiting ovarian tumor growth. The optimized device is envisioned to be implanted laparoscopically during the tumor debulking surgery, blending seamlessly with the current standard of care. The device platform could also deliver other agents such as nanoparticles, and thus has a wide spectrum of drug delivery applications.