Results

Figure 2. The combination of ivospemin and either gemcitabine, topotecan or doxorubicin increases toxicity in ovarian cancer cell lines. A. A2780 ovarian cancer cells were treated with ivospeminalone (A) or in combination with gemcitabine (50μM), topotecan (50μM), or doxorubicin (0.5μM), (ivospemin) with doxorubicin having the greatest combined toxicity with ivospemin. Both taxanes (2μM), paclitaxel and doxorubicin, had no added benefit compared to ivospemin treatment alone regardless of cisplatin sensitivity (A/B). IWI murine ovarian cancer cells (C) also exhibited increased cell viability when cotreated with SBP-101 and either gemcitabine, topotecan or doxorubicin.

Figure 3. Ivospemin (SBP-101) increases survival and decreases tumor burden in doxorubicin-treated mice in the VDID8 C57Bl/6 mouse model of ovarian cancer. Mice were injected with 350,000 VEGF+, Defensin+ ID8 ovarian cancer cells on day 0. Treatment with all four drugs began on day 3 at the following doses: ivospemin (24 μg/kg qw, alternating weeks); gemcitabine (30 μg/kg qw); topotecan (1 μg/kg qw); doxorubicin (1 μg/kg qw) (A). All doses are clinically relevant. SBP-101 and doxorubicin were the only single agents with a statistically significant survival advantage over control mice. While doxorubicin treatment more than doubled the median lifespan of mock mice, the addition of SBP-101 still resulted in a 35% increase in median lifespan. The combination of ivospemin and doxorubicin significantly increases overall survival in an immunosuppressive murine ovarian cancer model even at sub-clinical doxorubicin dosing levels. There is a significant unmet need in the treatment of women with platinum-resistant ovarian cancer, and the results presented here suggest that the combination of ivospemin and doxorubicin may be useful in the treatment of these patients. Future studies will evaluate other molecular pathways influenced by the combination treatment to help determine other potential combinatorial strategies. Additionally, combining DFM0 with ivospemin in vitro results in a cooperative antiproliferative response. DFM0 is notably well-tolerated and can influence immune cells to promote a more immune-friendly tumor microenvironment. Future experiments will evaluate the effect of adding DFM0 to ivospemin treatment as well as the influence on immune cells within the tumor microenvironment.

Conclusions

Ivospemin (SBP-101), an analogue of the naturally occurring polyamine spermine, suppresses the growth of ovarian cancer both in vitro and in vivo through modulation of polyamine metabolism. The addition of ivospemin to chemotherapeutics gemcitabine, topotecan, and doxorubicin increases the toxicity of each drug in an independent manner regardless of the tumor cell’s cisplatin sensitivity. The combination of ivospemin and doxorubicin significantly increases overall survival in an immunosuppressive murine ovarian cancer model even at sub-clinical doxorubicin dosing levels. There is a significant unmet need in the treatment of women with platinum-resistant ovarian cancer, and the results presented here suggest that the combination of ivospemin and doxorubicin may be useful in the treatment of these patients. Future studies will evaluate other molecular pathways influenced by the combination treatment to help determine other potential combinatorial strategies. Additionally, combining DFM0 with ivospemin in vitro results in a cooperative antiproliferative response. DFM0 is notably well-tolerated and can influence immune cells to promote a more immune-friendly tumor microenvironment. Future experiments will evaluate the effect of adding DFM0 to ivospemin treatment as well as the influence on immune cells within the tumor microenvironment.

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Abstract #4944

Spermine can be directly catabolized to spermidine by spermidine oxidase (SMOX) with the production of hydrogen peroxide and 3-acetylaminopropnaal (3-AAP) as byproducts. The combination of ivospemin and either gemcitabine, topotecan or doxorubicin increases toxicity in ovarian cancer cell lines. In both cisplatin-sensitive (A) and cisplatin-resistant (B) human ovarian cancer cell lines, treatment with gemcitabine (50μM), topotecan (50μM), and doxorubicin (0.5μM) increased the toxicity of SBP-101(1μM) (ivospemin) with doxorubicin having the greatest combined toxicity with ivospemin. Both taxanes (2μM), paclitaxel and doxorubicin, had no added benefit compared to ivospemin treatment alone regardless of cisplatin sensitivity (A/B). IMI murine ovarian cancer cells (C) also exhibited increased cell viability when cotreated with SBP-101 and either gemcitabine, topotecan or doxorubicin.

Ovarian cancers have extremely immunosuppressive tumor microenvironments (TME) and metabolic reprogramming of the TME to reduce immunosuppressive phenotypes is a promising approach for treatment. Sustained elevation of polyamine levels supports an immunosuppressive TME, and evidence suggests that pharmacologic depletion of polyamines may reduce immunosuppressive phenotypes. DFMO treatment in the immunosuppressive VDID8 model influences the immune cells of the TME, and we therefore are investigating the combination of ivospemin and DFMO in ovarian cancer. In addition to the cooperativity of ivospemin and chemotherapeutic agents, we have observed a cooperative antiproliferative response in ovarian cancer cells following DFMO and ivospemin cotreatment. Together, these studies suggest the potential of polyamine modulation by ivospemin and DFMO in combination with standard of care chemotherapy. Future studies will determine influences on the immune microenvironment and will evaluate cooperativity between ivospemin, DFMO, and chemotherapy.

Figure 4. Subclinical dosing of doxorubicin in combination with ivospemin is sufficient to increase survival of VDID8-injected C57Bl/6 female mice. SBP-101 treatment was completed 2qw of alternating weeks at a dose of 24 mg/kg for a total of 8 treatments (4 treatment weeks). Doxorubicin treatment was completed 2qw every week for 4 weeks (8 total treatments) at a dose of 0.5 mg/kg. The doxorubicin dosing in this experiment represents a 66% reduction in total doxorubicin exposure compared to Figure 3. Even with the sub-clinical dose of doxorubicin (66% reduction in total doxorubicin exposure), the addition of SBP-101 resulted in a 20% increase in median lifespan.

Figure 5. The addition of the ODC inhibitor, difluoromethylornithine (DFMO), to SBP-101 results in a cooperative antiproliferative response in A2780 ovarian cancer cells. Cells were treated with DFMO for 48 hours prior to SBP-101 addition. The 66% CI for IC50 values for treatment are (7 – 11 μM) for DFMO alone, (0.15 – 13 μM) for DFMO + 0.5μM SBP-101, and (11 – 14 μM) for DFMO + 1μM SBP-101. The combination of ivospemin and DFMO significantly increases overall survival in an immunosuppressive murine ovarian cancer model even at sub-clinical doxorubicin dosing levels. There is a significant unmet need in the treatment of women with platinum-resistant ovarian cancer, and the results presented here suggest that the combination of ivospemin and doxorubicin may be useful in the treatment of these patients. Future studies will evaluate other molecular pathways influenced by the combination treatment to help determine other potential combinatorial strategies. Additionally, combining DFM0 with ivospemin in vitro results in a cooperative antiproliferative response. DFM0 is notably well-tolerated and can influence immune cells to promote a more immune-friendly tumor microenvironment. Future experiments will evaluate the effect of adding DFM0 to ivospemin treatment as well as the influence on immune cells within the tumor microenvironment.

Polyamine Metabolism

SPM can be directly catabolized to SPD by spermidine oxidase (SMOX) with the production of 3-aminopropanial (3-AP) and hydrogen peroxide as byproducts. Both SPM and SPD can be back-converted to their precursors by SSAT utilizing an acetylated intermediate with hydrogen peroxide and 3-acetaminopropanial (3-AP) as byproducts.

SPM can be directly catabolized to SPD by spermidine oxidase (SMOX) with the production of hydrogen peroxide and 3-acetylaminopropnaal (3-AAP) as byproducts. The addition of ivospemin and either gemcitabine, topotecan or doxorubicin increases toxicity in ovarian cancer cell lines. In both cisplatin-sensitive (A) and cisplatin-resistant (B) human ovarian cancer cell lines, treatment with gemcitabine (50μM), topotecan (50μM), and doxorubicin (0.5μM) increased the toxicity of SBP-101(1μM) (ivospemin) with doxorubicin having the greatest combined toxicity with ivospemin. Both taxanes (2μM), paclitaxel and doxorubicin, had no added benefit compared to ivospemin treatment alone regardless of cisplatin sensitivity (A/B). IMI murine ovarian cancer cells (C) also exhibited increased cell viability when cotreated with SBP-101 and either gemcitabine, topotecan or doxorubicin.