THE EFFECT OF MILD HYPERTHERMIA ON PRECLINICAL SYNERGISTIC MECHANISMS OF OVARIAN CANCER

However, antitumor immune responses are often invalidated by immune evasion mechanisms such as the overexpression of heat shock protein 70 molecular chaperones (mortalin, Grp78 and hsc70) with their client oncoproteins. We sought to evaluate efficacy, toxicity and mechanisms of SHetA2 in combination with other drugs.

Single and combined drug effects were compared in cell culture and murine xenograft models of human gynecologic cancer cell lines. Mechanisms were evaluated by immunohistochemistry of tumors, immunofluorescent and electron microscopic cell imaging, Seahorse assays, and co-immunoprecipitation, western blot, and mass spectrometry of protein extracts.

Results SHetA2 interacted synergistically with a p53 reactivator, paclitaxel, and cyclin dependent kinase 4 or 6 inhibitors (CDK4/6i’s) in cell culture. Synergy with paclitaxel was verified in two endometrial cancer xenograft models and additive interaction was observed for all other combinations in endometrial, cervical or ovarian xenograft models of treatment or maintenance therapy. Mechanisms of drug synergies involved SHetA2-induced mitochondrial damage, mitophagy and cell cycle arrest mediated by release of client proteins (p53, cyclin D1, CDK4/6, apoptosis inducing factor/AIF, metabolic enzymes) from HSP70 protection, and complemented by effects of the other drugs on these client proteins and their pathways.

Conclusions SHetA2 activity against gynecologic cancers can be enhanced by paclitaxel, p53 reactivators, and CDK4/6i’s, which have complementary mechanisms against HSP70 client proteins. These studies support development of SHetA2 as a synergistic complement to existing therapies in gynecologic cancers.

Objective Cytoreductive surgery with HIPEC has shown promising results in interval setting in advanced epithelial ovarian cancer. Its role in upfront setting has not yet been established.

Methods All eligible patients underwent CRS HIPEC as per institution protocol. Relevant data was entered prospectively in institutional HIPEC registry and analysed retrospectively for study period from February 2014 – February 2019.

Results Out of 190 patients, 80 underwent CRS HIPEC in upfront setting and 110 in interval setting. Median age was 54±7.45 years, upfront group had higher PCI (14.1±8.75 vs. 9.6±5.2. 2), and required longer duration of surgery (10.6±1.73 vs. 8.4±1.71 hrs) had more blood loss (1025 ±668.76 vs.680±302.23 ml). Upfront group required more diaphragmatic resections, bowel resections and multivisceral resections. The overall G3-G4 morbidity was comparable (25.4%vs. 27.3%), upfront group had more surgical morbidity (20%vs.9.1%) whereas interval group had more medical morbidity i.e. electrolyte imbalance and haematological. After a median follow up of 43 months, median DFS was 33 months in upfront vs. 30 months in interval group, p=0.75, median OS was 46 months interval group and was not yet achieved in upfront group.(p=0.13). 4 year OS was 85%vs 60%. Performance status (P =0.025 C.I 1.190–12.80) was the only factor predicting morbidity on multi-variate analysis.

Conclusions In patients of advanced EOC upfront CRS HIPEC showed promising outcomes and better survival with similar morbidity and mortality. Upfront group had more surgical morbidity whereas interval group had more medical morbidity. Mutli-institutional randomised studies are needed to define patient selection and study morbidity patterns.

E-poster viewing: Basic/translational science

EP002/#550 PRECLINICAL SYNERGISTIC MECHANISMS OF INVESTIGATIONAL NEW DRUG, SHET2A

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Objective The investigational new drug, SHetA2 (NSC 726189) is being evaluated in a Phase 1 clinical trial in advanced and recurrent ovarian, cervical and endometrial cancers (clinicaltrials.gov: NCT04928308). SHetA2 selectively kills cancer cells without harming healthy cells by disrupting complexes of heat shock protein 70 molecular chaperones (mortalin, Grp78 and hsc70) with their client oncoproteins. We sought to evaluate efficacy, toxicity and mechanisms of SHetA2 in combination with other drugs.

Methods Single and combined drug effects were compared in cell culture and murine xenograft models of human gynecologic cancer cell lines. Mechanisms were evaluated by immunohistochemistry of tumors, immunofluorescent and electron microscopic cell imaging, Seahorse assays, and co-immunoprecipitation, western blot, and mass spectrometry of protein extracts.

Results SHetA2 interacted synergistically with a p53 reactivator, paclitaxel, and cyclin dependent kinase 4 or 6 inhibitors (CDK4/6i’s) in cell culture. Synergy with paclitaxel was verified in two endometrial cancer xenograft models and additive interaction was observed for all other combinations in endometrial, cervical or ovarian xenograft models of treatment or maintenance therapy. Mechanisms of drug synergies involved SHetA2-induced mitochondrial damage, mitophagy and cell cycle arrest mediated by release of client proteins (p53, cyclin D1, CDK4/6, apoptosis inducing factor/AIF, metabolic enzymes) from HSP70 protection, and complemented by effects of the other drugs on these client proteins and their pathways.

Conclusions SHetA2 activity against gynecologic cancers can be enhanced by paclitaxel, p53 reactivators, and CDK4/6i’s, which have complementary mechanisms against HSP70 client proteins. These studies support development of SHetA2 as a synergistic complement to existing therapies in gynecologic cancers.