Form 3

Abstract of Thesis

Name (Li Yanyi)	
Title	Finding potential synergistic drugs to reduce chemo-resistance for the treatment of highly malignant tumors in female (女性の高悪性度腫瘍に対する化学療法抵抗性を軽減するための相乗効果のある薬剤の探索研究)

Abstract of Thesis

[Purpose] Ovarian cancer is the most lethal gynecological malignancy in female, with the incidence rate of 6.6 per 100 thousand, leading to more than 200 thousand deaths in 2020 worldwide. Surgery and chemotherapy are the primary treatments for it, however, the 5-year survival rate is consistently below 40% in China mainly due to chemo-resistance and recurrence. Choriocarcinoma (CC) is characterized by rapid growth, high invasion, and high metastatic potential which mainly dependents on chemotherapy, unfortunately, about 10-20% of patients with CC are resistant to chemotherapy or present with high rates of recurrence. Drug combination is a common method to alleviate chemo-resistance, however, it usually takes many years for new drugs/reagent to put into clinical use, many patients died while waiting. Another efficient approach is combining drugs that are already been used in clinical practice, and alleviate chemo-resistance effectively and timely, thus the study focus on finding potential synergistic clinical drugs to reduce chemo-resistance for the treatment of highly malignant tumors in female.

[Methods/Results] Study1 Evaluating the effect of Talazoparib (BMN673) ,a novel PARP inhibitor, combined with cisplatin on the proliferation and apoptosis of ovarian cancer cells by CCK-8, Colony formation, cell cycle, Apoptosis analysis in vitro, on xenograft tumors of ovarian cancer cell origin in vivo. The study found that BMN673 had a dose-dependent synergistic effect with cisplatin, viability and proliferation of the combined treatment group was significantly reduced compared with the BMN673 or DDP alone group, while increased number of apoptotic and pro-apoptotic cells positive cells in the combination group was observed compared with the BMN673 or DDP alone. The combination of cisplatin and BMN673 significantly inhibited the growth, size and weight of transplanted tumors($p < 0.05$), the number of TUNEL positive cells the increased while Ki67 positive cells decreased in the combination group compared with cisplatin or BMN673 alone($p < 0.05$).

Study2 CKK-8, colony formation, transwell and flow cytometry were used to detect the effect of insulin on 5-FU resistance in CC cells JEG-3 and JARS, xenograft mice were used to evaluate the effect of insulin on 5-FU resistance in vivo. Results showed that insulin combined with 5-FU suppressed cell viability in JEG-3 and JAR compared with 5-FU alone in 72 h. What's more, insulin combined with 5-FU promoted cell apoptosis, inhibited cell proliferation, migration, and phosphorylation of survivin at residue threonine 34 (Thr34) and drug resistance-related proteins, P-GP and MRP1 levels ($p < 0.05$). In vivo experiment showed that insulin combined with 5-FU suppressed tumor volume by 35% compared with 5-FU alone and 73% compared with control in CC xenograft mice.

[Conclusion] The results favored the strategies of co-administration of Talazoparib with cisplatin for ovarian cancer therapy and insulin with 5-FU in choriocarcinoma treatment in cells and animal experiments, provided the basis for further clinical trial & application and expected to improve the treatment and survival time in the female population who were resistant to chemotherapy.

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論文審査の結果の要旨及び担当者

氏　名　（　Li Yanyi　）		
	（職）	氏　名
論文審査担当者	主 査　教 授	遠藤 誠之
	副 査　教 授	渡邊 浩子
	副 査　教 授	鎌田 佳宏
	副 査　特任教授（常勤）	大野　ゆう子

論文審査の結果の要旨

Ovarian cancer is the most lethal gynecological malignancy in female, the 5-year survival rate is consistently low, choriocarcinoma is characterized by rapid growth, high invasion, and high metastatic potential which mainly dependents on chemotherapy, unfortunately, chemotherapy resistance is not uncommon in the two gynecological malignancy tumors.

The purpose of the study is finding potential synergistic clinical drugs to reduce chemotherapy resistance in ovarian cancer and choriocarcinoma. It could reduce costs and shorten development cycle by combining the clinical drugs than developing new drugs, thus the objective of this study has clinical significance.

Study1 Evaluating the effect of Talazoparib (BMN673) ,a novel PARP inhibitor, combined with cisplatin (DDP) on the proliferation and apoptosis of ovarian cancer cells and on xenograft tumors of ovarian cancer cell origin in vivo. The study found that BMN673 had a synergistic effect with cisplatin, viability and proliferation of the combined treatment group was significantly reduced compared with the BMN673 or DDP alone group, while increased number of apoptotic positive cells in the combination group was observed compared with the BMN673 or DDP alone. The combination of cisplatin and BMN673 significantly inhibited the volume and weight of transplanted tumors($p < 0.05$) in vivo.

Study2 Evaluating the effect of insulin on 5-FU resistance. Results showed that insulin combined with 5-FU suppressed cell viability in JEG-3 and JAR compared with 5-FU alone in 72h. What’s more, insulin combined with 5-FU promoted cell apoptosis, inhibited cell proliferation, migration, and phosphorylation of survivin at residue threonine 34 (Thr34) and drug resistance-related proteins, P-GP and MRP1 levels ($p < 0.05$). In vivo experiment showed that insulin combined with 5-FU suppressed tumor volume by 35% compared with 5-FU alone and 73% compared with control in CC xenograft mice.

The research methods, both cell experiments in vitro and xenograft tumor in vivo, are appropriate, and the results are convincing.

The study favors the strategies of co-administration of Talazoparib with cisplatin for ovarian cancer therapy and insulin with 5-FU in choriocarcinoma treatment, providing the basis for further clinical trial and application in the female population who are resistant to chemotherapy.

Therefore, this study meets the requirements of doctoral dissertation.