ENITEC — ESGO European Network for Individualised Treatment of Endometrial Cancer

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Targeted therapies in uterine sarcomas and carcinosarcomas- the summary of ENITEC (European Network of Individualised Treatment in Endometrial Cancer) collaboration project.

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Introduction

The results of systemic therapy among the most of patients suffering from uterine sarcomas and carcinosarcomas remains unsatisfactory. Strong need of further research on multi-drug regimens is widely postulated. To investigate this problem the collaboration in ENITEC group was raised.

Material and methods

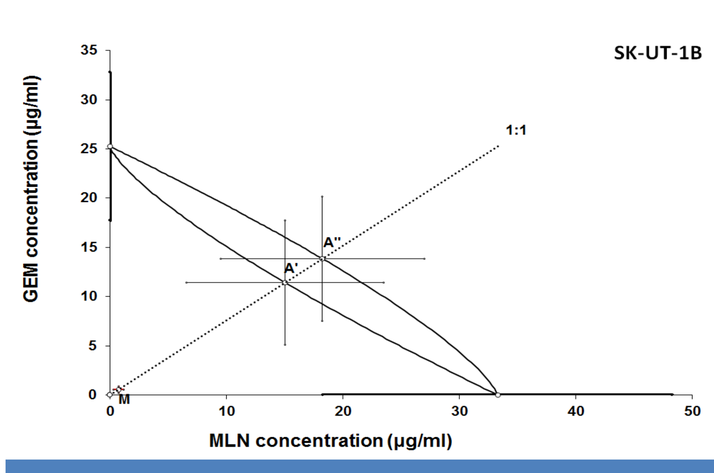
Two uterine sarcomas (MES-SA, ESS-1), two carcinosarcoma (SK-UT-1, SKUT-1B) cell lines and control line HSF (Human Skin Fibroblasts) were cultured. Cells were incubated in presence of gemcitabine, mTOR inhibitors (rapamycin, MLN0128) and natural compound (fucoidan). Cell viability was assessed with MTT test. The combinations of investigated drugs activities were assessed using isobolography. Additionally, apoptosis and cell cycle were assessed.

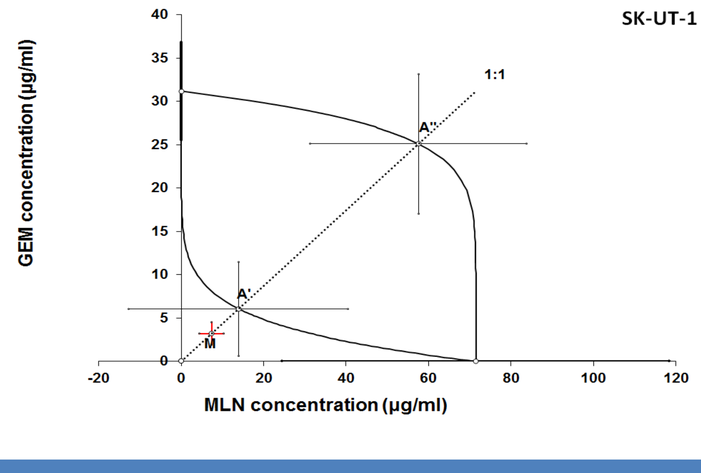
Results

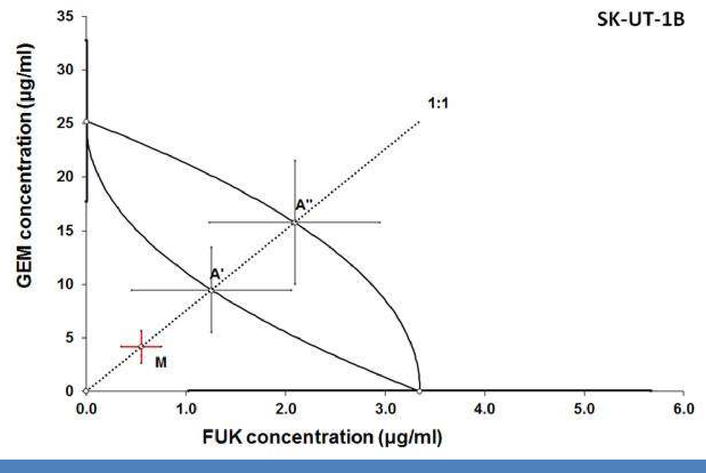
Gemcitabine decreases cell viability among all tested cell lines with strongest effect in SK-UT-1, SK-UT-1B, and ESS-1. Rapamycin affects cell viability in ESS-1 and MES-SA but not carcinosarcoma and HSF cell lines. MLN0128 influenced cell viability among all tested lines but in ESS-1 and MES-SA in significantly lower concentration comparing to the others. Fucoidan significantly decreases cell viability in SK-UT-1, SK-UT-1B, and ESS-1 cell lines, but not in MES-SA. Fucoidan was not substantially affecting proliferation among normal cells. The IC50 values for tested agents in uterine sarcoma and carcinosarcoma cell lines are presented in table.

Cell lines	Rapamycin	INK 128	Fucoidan	Gemcitabine
	IC_{50} (ng/ml)	IC_{50} (ng/ml)	IC_{50} (mg/ml)	IC_{50} (ng/ml)
SK-UT-1	NA	214.2	0.966	31.173
SK-UT-1B	NA	33.260	3.348	25.243
ESS-1	971.505	15.808	0.848	13,875
MES-SA	1.602	2.789	NA	72,482

The isobolographic analysis revealed synergistic effect of following combinations: gemcitabine + fucoidan and gemcitabine + MLN0128 in SK-UT-1B. Antagonism of gemcitabine + MLN0128 was noticed in MES-SA cell line. The effects of other combinations of tested drugs were additive. Supra-additive and antagonistic interactions among tested agents are presentad on isobolograms below.







Conclusions

- Fucoidan showed high activity against carcinosarcoma cell lines- due to its similarity to endometrial cancer further experiments with this substance are justified.
- MES-SA and ESS-1 lines are significantly more sensitive to mTORi comparing to others cell lines.
- Antagonistic effect between gemcitabine and MLN0128 in MES-SA might be avoided in designing future clinical trials- it's mechanism should be clarified.
- Synergism observed between gemcitabine and novel agents (fucoidan and MLN0128) in carcinosarcoma cell line might be used in planning future therapies

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