A multicenter phase II study of the efficacy and safety of Quisinostat (an HDAC inhibitor) in combination with Paclitaxel and Carboplatin chemotherapy (CT) in patients (pts) with recurrent platinum resistant high grade serous epithelial ovarian, primarily peritoneal or fallopian tube carcinoma cancer (OC)

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BACKGROUND

Quisinostat is histone deacetylase inhibitor (HDAC) with the chemical name N-hydroxy-2-[4-[[[(1-methyl-1H-indol-3-yl)methyl]amino]methyl]-1-piperidinyl]-5-pyrimidinecarboxamide monohydrochloride that belongs to the class of aromatic hydroxamic acids.

Combinations of HDAC inhibitors with other types of antineoplastic drugs which have already been approved or studied by now show promising results when studied in tumor cell cultures. It was proven that Quisinostat increases HDAC1-inhibited E-cadherin expression (at the low concentrations of 30 nM) which increases sensitivity to the epidermal growth factor inhibitors in case of NSCLC models and stops proliferation of paclitaxel-resistant cells.

The mechanism of action of Quisinostat includes protein acetylation, leading to re-activation of tumor suppressor genes and restoration of tumor sensitivity to chemotherapy. In phase Ib study Quisinostat in combination with paclitaxel and carboplatin showed promising activity in pts with recurrent platinum resistant OC.

The primary endpoint of a Phase II study of Quisinostat in combination with paclitaxel and carboplatin in patients with recurrent platinum resistant OC (NCT02948075) has been met. Here we present the results obtained up to date.

METHODS

Study population

The study population consists of female patients with histologically confirmed diagnosis of serous epithelial ovarian, primary peritoneal or fallopian tube carcinoma who are currently showing objective progression not less than 1 month and not more than 6 months after termination of the first line platinum and Paclitaxel based chemotherapy and for whom a second line of the chemotherapy is indicated.

Inclusion criteria

The main inclusion criteria were:

1. Signed patient's information sheet and informed consent form to participate in the study.
2. Females aged ≥ 18 years.
3. Patients must have an ECOG status of 0 or 1.
4. Patients must have received only 1 prior line of platinum and Paclitaxel based chemotherapy
5. Tumor progression observed not less than 1 month and no more than 6 months after completion of the planned number of cycles of first line platinum/Paclitaxel based chemotherapy (Carboplatin in the dose AUC5-6 or Cisplatin in the dose ≥ 75 mg/m^2, in combination with paclitaxel for 6 q3-4 wk cycles) and indications for undergoing the second line chemotherapy.
6. The patients must have at least one measurable lesion according to RECIST 1.1 criteria.
7. Tissue block from archived material at diagnosis must be available and be submitted for predictive biomarker analysis tumor progression observed not less than 1 month and no more than 6 months after completion of the planned number of cycles of 1st line platinum/paclitaxel based CT.

Investigational products, doses and method of administration

Quisinostat was administered orally in the morning at dose 12 mg p.o. each 3 week cycle on Days 1, 3, 5, 7, 9, 11 with paclitaxel (175 mg/m^2) and carboplatin (AUC5) on Day 7 of each cycle, for the 2nd line. Patients received up to 6 cycles.

Statistical methods:

The primary efficacy endpoint is the objective response rate (ORR) verified by ICR. The secondary endpoints include safety, progression free survival (PFS) and overall survival. The study design implies the use of the two-stage Simon model: 29 patients who underwent Quisinostat treatment would provide 80% power for hypothesis testing in order to obtain preliminary efficacy assessment of the Investigational product and reach a decision on the merits of its future examination (α = 0,05). Taking into consideration the fact that the study is comprised of the patients who are resistant to platinum-based drugs of the first line chemotherapy, these patients take these drugs once again, and it was expected that the frequency of the objective response would not exceed 10% without Quisinostat (p_0 = 0,1). Due to Quisinostat administration, which is supposed to be associated with the restoring of tumor sensitivity to platinum-based drugs, the frequency of the objective response was expected to be 30% (p_1 = 0,3). The obtained results exceeded this value which is reflected further.

RESULTS

31 pts were enrolled (30 pts evaluated). Median age was 57 years. Twenty-one pts (67.7%) received all 6 cycles of therapy. The characteristics of eligible patients according to the histological type of tumor are presented in Table 1.

Table 1. Demographic data.

Factors	N(%)
Median age	57 years
Race:	
Caucasian	31 (100%)
Stage of Disease at Initial Diagnosis:	
Stage II	2 (6.4%)
Stage III	18 (58%)
Stage IV	11 (35.6%)
Histology:	
Papillary/Serous	28 (90.4%)
Clear cell adenocarcinoma	2 (6.4%)
Endometrioid adenocarcinoma	1 (3.2%)
1st line of chemotherapy:	
Paclitaxel + carboplatin	28 (90.3%)
Paclitaxel + cisplatin	3 (9.7%)
Completion of study treatment :	
Completed	18 (58%)
Continue treatment	3 (9.7%)
Treatment terminated due to progression	3 (9.7%)
Withdrawn due to AE	3 (9.7%)
Withdrawn due to another reasons	4 (12.9%)

Analysis of primary efficacy endpoint

ORR was 51.6% (16 pts) (table 2). Median duration of response was 5 months (4.2-5.7). Median PFS - 7 months (95%CI 4.8-9.2) (Fig. 1).

Tab. 2. Best response.

Best response	N (%)
Complete response	1 (3.2%)
Partial response	15 (48.4%)
Stable disease	13 (42%)
Disease control	29 (93.6%)
Disease progression	2 (6.4%)

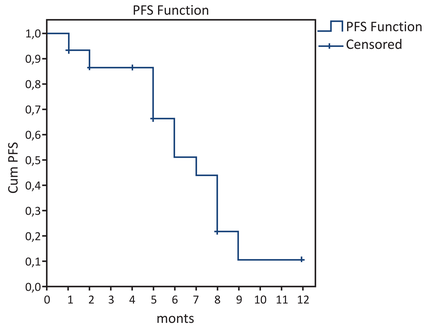
Toxicity

SAE were observed in 16,1% of pts, AEs of grade 3 or 4 – in 71% and 48.4% pts temporarily discontinued therapy due to AE. Dose reduction of CT due to AE was performed in 22.6% pts. The most common adverse events were neutropenia – 67,7%, nausea – 61.3%, weakness – 29%, thrombocytopenia – 22.6%, neuropathy – 19.4%, vomiting – 19.4% (table 3).

Tab. 3. Toxicity.

Toxicity	N(%)	
All kinds of toxicity	29 (93.5%)	
	Grade 1/2	Grade 3/4
neutropenia	9 (29,0%)	23 (74,2%)
nausea	21 (67,7%)	0
weakness	13 (41,9%)	0
thrombocytopenia	9 (29,0%)	2 (6,5%)
vomiting	6 (19,4%)	0
Drug temporarily discontinuation:		
Qusinostat	13 (42%)	
Paclitaxel	15 (48.4%)	
Capboplatin	15 (48.4%)	
Dose reduction:		
Qusinostat	0	
Paclitaxel	11 (35.4%)	
Capboplatin	11 (35.4%)	

Fig 1. Progression Free Survival.



DISCUSSION

Platinum agents remain the most active treatment in patients with advanced ovarian cancer. However PD is observed sooner or later. Quisinostat in combination with the background chemotherapy showed promising efficacy results. In our study all patients with ovarian cancer had previously been treated with paclitaxel and platinum-containing chemotherapy. Among platinum-resistant pts response rate was 51,6% which is much higher than in published studies results. Platinum-based chemotherapy have modest efficacy in platinum-resistant and partially platinum-sensitive recurrent ovarian cancer. Response rate is reported to be 10-17%. The administration of non-platinum drugs: liposomal doxorubicin, paclitaxel, topotecan, gemcitabine is accompanied by an objective effect of 10-15% of patients, a median PFS - of 3-4 months, and OS - of about 12 months. The results of the current study support the experimental data which demonstrated capability of Quisinostat to overcome inherited or acquired resistance of tumor cells to platinum drugs.

CONCLUSIONS

Quisinostat in combination with paclitaxel and carboplatin showed high efficacy and good tolerability in patients with recurrent platinum resistant ovarian cancer. Further biomarker analysis is warranted.

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