In vitro chemosensitivity of patient-derived ovarian cancer samples is not correlated with homologous recombination deficiency, platinum sensitivity, or cancer stem cell frequency

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Topic: Ovarian

Objectives

Homologous recombination deficiency (HRD) is a biomarker of response to poly-ADP ribose inhibitor (PARPi) treatment in epithelial ovarian cancer (EOC). Clinical studies have demonstrated high correlation between platinum sensitivity and response to PARPi. Chemoresistance and cancer recurrence are driven, in part, by the population of cancer stem-like cells (CSCs) that persist despite primary treatment. We hypothesized that in vitro response to cisplatin and olaparib are correlated with one another and with HRD status, clinical platinum response, and CSC frequency. Published cisplatin IC50 for EOC is between 3-14uM, and olaparib IC50 is 0.3nM-21uM.

Methods

Chemosensitivity was characterized via MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cell viability assay. CSC frequency was determined via flow cytometry. Experiments were performed in triplicate. Clinical information on genetic status and platinum sensitivity were extracted from the electronic medical records. We identified 15 cell types for study, 12 derived from patient (PD) samples collected via institutional biobank and 3 immortalized cell lines commonly studied in ovarian cancer.

Results

10/15 PD cell types were derived from patients with platinum sensitive EOC; of the remaining 5, 3 were platinum resistant, one platinum refractory, and one is currently undergoing primary adjuvant chemotherapy. 5 cell types are proficient in homologous recombination (HRP), while 9 are HRD. Cisplatin IC50s for HRP cell types were 3.65-28.77 uM and 0.93-27.28 uM for HRD cells (table). Olaparib IC50s were 5.11-10.37 uM (HRP) and 3.77-15.41 uM (HRD) (table). Frequency of CSCs ranged from 0.165 to 6.69% (table).

Conclusions

In a sample of 15 patient-derived cell types, chemosensitivity to cisplatin and olaparib varied significantly. In contrast to clinical studies, HRD status did not reliably predict in vitro chemosensitivity to either cisplatin or olaparib. Furthermore, chemosensitivity to cisplatin and olaparib were not consistently correlated with one another. This suggests that platinum response may not be an adequate surrogate to predict PARPi response. CSC population did not correlate with chemosensitivity in 3 cell types. Characterization of CSC populations in the remaining cell types is ongoing.

Abstract Table or Graph

Table 1: Summary of characteristics of 15 epithelial ovarian cancer cell samples, including homologous recombination status, platinum sensitivity, IC50 to cisplatin and olaparib, as well as cancer stem-like cell population frequency.

Cell Sample	Homologous Recombination Status	Platinum Response	Cisplatin IC50 (uM)	Olaparib IC50 (uM)	Cancer Stem-like Cell Population Frequency (ECAD/NCAD/CD44/ CD117/CD133 positive)
PD1	proficient	Platinum Resistant	28.77	10.37	1.33%
PD2	proficient	Platinum Sensitive	9.65	5.23	-
PD3	deficient	Platinum Sensitive	11.34	15.41	-
PD5	deficient (BRCA1 germline)	Platinum Sensitive	1.84	7.51	6.69%
PD8	deficient (BRCA1 somatic)	Platinum Sensitive	2.89	3.77	0.165%
PD9	proficient	Platinum Sensitive	5.61	5.78	-
PD13	deficient	Platinum Sensitive	16.23	6.3	-
PD14	deficient	Platinum Refractory	5.61	10.01	-
PD18	deficient (BRCA2 germline)	Platinum Sensitive	3.25	12	-
PD19	deficient (BRCA1 somatic)	Platinum Sensitive	19.1	6.41	-
PD21	deficient (BRCA1 somatic)	Platinum Sensitive	27.28	-	-
PD22	unknown	undergoing primary adjuvant chemotherapy	6.94	26.62	-
OVCAR8	proficient	Platinum Resistant	3.88	5.11	-
PEO1	deficient (BRCA2 germline)	Platinum Sensitive	0.93	4.3	-
PEO4	proficient	Platinum Resistant	3.65	6.16	-