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219 EFFECT OF OLAPARIB TREATMENT ON CELL CYCLE, SENEESCENCE AND CELL DEATH IN OVARIAN CANCER CELLS

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Objectives High-grade serous ovarian cancer (HGSOC) is the most frequent and deadly histological type of ovarian cancer. Targeted treatment approaches, such as PARP inhibitors, have brought significant improvement in management of this disease. Here we analyzed molecular mechanisms of olaparib influence on ovarian cancer cells.

Methods We used our newly established HGSOC cell line OVPA8 (ECACC #1906260¹) and three other lines (A2780, SKOV3, KURAMOCHI). BRCA1/2 mutations were analyzed by Sanger sequencing and NGS. Cells were treated by olaparib (AZD2281). Metabolic activity and viability were assessed using AlamarBlue and crystal violet assay, respectively. Half maximal inhibitory concentrations (IC50) were determined using GraphPadPrism software. Cell death and cell-cycle distribution were analyzed by flow cytometry.

Results NGS analysis revealed BRCA1 pathological mutation c.3700_3704delGTAAA (p.Val1234Glnf) and loss of heterozygosity in BRCA2 in OVPA8. BRCA2 pathological mutation c.6952C>T (p.Arg2318Ter) was described in KURAMOCHI, BRCA2 mutations of unknown significance in A2780 (c. T8195G, p.L2732X) and SKOV3 (c.7364A>G, p.H2455R).² The IC50 values were 3.99µM, 5.13µM, 6.77µM and 25.6µM for OVPA8, A2780, KURAMOCHI and SKOV3, respectively. Olaparib treatment resulted in G2/M arrest in all cell lines, increased senescence and cell death (except SKOV3).

Conclusions All analyzed cell lines, except SKOV3, had low olaparib IC50 values. The same correlation was found for the level of cell death and senescence what may be related to the functional status of BRCA1/2. Cell cycle G2/M phase arrest was observed in all ovarian cancer cell lines.

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220 FUNCTIONAL ANALYSIS OF ZFH4 AS A NOVEL THERAPEUTIC TARGET IN OVARIAN CANCER

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Introduction Ovarian cancer is one of the most lethal gynecologic malignancies. Many patients are diagnosed in advanced stages of disease where the prognosis is poor due to the inevitable acquired resistance to platinum agents. Thus, novel therapeutic strategies effective for platinum-resistant cases are required. Zinc Finger Homeobox 4 (ZFHX4) has been known as one of the major transcription regulators in nerve and muscle differentiation. Recent researches including our genome-wide exploration indicate ZFHX4 is also involved in carcinogenesis and cancer progression. The objective of this study was to investigate the potential of ZFHX4 as a novel therapeutic target in ovarian cancer.

Methods Correlations between ZFHX4 mRNA expression and overall survival in 61 ovarian cancer cases treated at our institute and in the cases registered in TCGA database respectively were assessed by log-rank test. RNAi knockdown was introduced to several ovarian cancer cells to investigate the influence of ZFHX4 on cancer cell proliferation, migration and platinum sensitivity.

[Results] Both in our clinical dataset and TCGA data, the overall survival was significantly poor in the group in which ZFHX4 is highly expressed. In cell model assay, ZFHX4 knockdown significantly suppressed ovarian cancer cell proliferation. Decreased motility was observed in the cells treated with siRNA targeting ZFHX4 by scratch assay. Furthermore, ZFHX4 knockdown increased cisplatin sensitivity.

Conclusions Altogether, our results suggest ZFHX4 functions to promote cancer cell proliferation, migration and platinum-resistance. Interruption of ZFHX4 function independently or in combination with platinum agents has a potential to bring benefit for the treatment of ovarian cancer.

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221 PARAAORTIC LYMPHADENECTOMY IN CERVICAL CANCER STAGE IIIC1R INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS 2018: EXPERIENCE AT THE INSTITUTO NACIONAL DE CANCEROLOGÍA

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Introduction The objective of this study is to describe surgical and oncological outcomes of patients with cervical cancer stage IIIC1r FIGO 2018, underwent to staging paraaortic lymphadenectomy at the Instituto Nacional de Cancerología. Bogotá-Colombia, between January 2016 to March 2019.

Methods Retrospective study. Data collected included clinical characteristics, histopathological, surgical results. Furthermore, overall survival and disease-free survival were described in the population. A univariate descriptive analysis was performed. Survival curves were estimated with the Kaplan-Meier method. Statistical software R -Project version 3.6.2 was used.

Results 40 patients were included in the analysis. The mean age was 43 years (29–66). Surgical approach was extraperitoneal in 31 (77.5%) and transperitoneal in 9 (22.5%) of the cases. The mean operating time was 147.5 minutes (120.2–186.2). Surgical bleeding had a median of 30 ml (10–50). There were no intraoperative complications or death associated with the procedure. The median paraaortic lymph node count was 8.5 nodes (5.75–15). Six (15%) patients had para-aortic compromise and all received extended field radiotherapy. At follow-up, 5% of patients presented recurrent disease (n= 1 lung and n= 1 supraclavicular lymph node). The overall survival (OS) was 88.7% and the disease-free survival (DFS) was 74.3% in the population.

Conclusion Paraaortic lymphadenectomy in stage IIIC1r cervical cancer in our study detected 15% of patients with lymph node involvement, without associated morbidity. It was not possible to evaluate the oncological impact of this procedure in the study population.

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HIGH INCIDENCE OF VENOUS THROMBOEMBOLISM IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY FOR ADVANCED STAGE OVARIAN CANCER

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Objectives There is paucity of data on venous thromboembolism (VTE) in patients receiving neoadjuvant chemotherapy (NACT) for ovarian cancer. We explored the incidence and predictors of VTE in this patient population.

Methods We performed a retrospective review of women with primary ovarian, fallopian tube or peritoneal cancer who received NACT from January 2012 to October 2018. Patients with a history of VTE prior to cancer diagnosis were excluded. The primary outcome was incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE) after cancer diagnosis and before interval debulking surgery. We explored demographic and clinical variables associated with VTE.

Results VTE was diagnosed in 25 (28%) of 90 patients and 16 (64%) had PE. 67% of patients had VTE during NACT and 8 patients after their cancer diagnosis, before initiation of NACT. The majority of patients had stage III disease and serous adenocarcinoma. African Americans were 3 times more likely than other races to experience VTE (OR 3.22; CI 0.997–10.42; P = 0.051). Significantly more patients without VTE had debulking surgery (88% vs 60%, P = 0.005). The risk of DVT increased by 8.7% per year of age (OR 1.087; 95% CI 1.01–1.17). Obesity, smoking status, medical comorbidities, disease stage, histology, invasive diagnostic surgery, and length of NACT were not predictors of VTE.

Conclusions The incidence of VTE during neoadjuvant chemotherapy is high. Older age and African American race may be potential risk factors for VTE. This information will help mitigate disparities in the treatment of advanced stage ovarian cancer.

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A THREE PROTEIN SIGNATURE FAILS TO EXTERNALLY VALIDATE AS A BIOMARKER TO PREDICT SURGICAL OUTCOME IN HIGH GRADE SEROUS OVARIAN CANCER

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Introduction Complete cytoreduction is associated with improved survival in patients with advanced High Grade Serous Ovarian Cancer (HGSO). To aid clinical decision making, many surgical outcome prediction tools have been proposed, but none have been sufficiently validated to warrant routine clinical usage. Here we attempted to externally validate a promising three protein signature, which had shown strong association with suboptimal surgical debulking (AUC 0.89, accuracy 92.8%).

Methods 241 HGSO tumour samples were collected from patients who participated in a large multicentre trial (ICON5). Samples were collected at the time of initial surgery and before randomisation. Surgical outcome data were collated from the study records. Immunohistochemical scores were generated by two independent observers for the three proteins in the original signature (POSTN, CXCL14 and pSmad2/3). Predictive values were generated for individual and combination protein signatures and as part of a multivariable model using logistic regression.

Results When assessed individually, none of the proteins showed any predictive affinity for suboptimal surgical outcome in our cohort (AUC POSTN 0.55, pSmad 2/3 0.53, CXCL 14 0.62). The combined signature again showed poor predictive ability, AUC 0.58, as did the multivariable model, AUC 0.63.

Conclusion Despite showing original promise, when this protein signature is applied to a large external cohort, it is unable to accurately predictive surgical outcomes. This could be attributed to overfitting of the original model, or differences in surgical practice in our cohort.

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ADJUVANT CHEMOTHERAPY IN SURGICAL STAGE I OR II ENDOMETRIOID ENDOMETRIAL CANCER WITH MYOMETRIAL INVASION >50%: A MULTICENTER RETROSPECTIVE STUDY WITH LONG-TERM FOLLOW-UP

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