Comprehensive cytokine and chemokine evaluation in plasma samples of primary, non-metastatic high grade serous ovarian cancer patients to estimate outcome and platinum resistance

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BACKGROUND

- Ovarian cancer (OC) still has the highest mortality rate of all gynecological malignancies, diagnosed mostly at advanced stages, resulting in a generally poor outcome.
- Radical tumor debulking, followed by platinum-based chemotherapy with/without bevacizumab and with/without PARP inhibitors is the standard of care in advanced OC.
- However, the majority of patients will ultimately relapse due to the development of platinum resistance. Immunologic processes play an important role in tumorigenesis and therapy response.

- **Here, we determined cytokine and chemokine levels in blood samples of primary, non-metastatic, high grade serous (HGS) OC patients before and after therapy to estimate their value with regard to progression-free survival (PFS), overall survival (OS) and platinum resistance.**

METHODS

- Plasma samples of 29 HGSOC patients were collected both prior (n=29) and following platinum-based chemotherapy (n=20) with/without bevacizumab.
- Blood samples were processed and plasma was isolated and stored under liquid nitrogen.
- Patients were monitored for disease progression and overall survival.
- Cytokine and chemokine levels in the plasma samples were quantified using the Olink Target 48 Cytokine panel (LuminoDX, San Diego, USA), which includes 45 immune-related proteins and requires only 1 µL of sample.
- The correlation between cytokine levels and PFS as well as OS was assessed using the Cox proportional hazards model and Log-rank test, and platinum resistance was evaluated using the student's t-test.

29 primary, non-metastatic HGSOC patients enrolled

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Exclusion criteria:
- Non-serous histology
- Metastatic disease
- Insufficient sample quality
- Missing follow-up data

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Final cohort:
29 patients included
Baseline samples: n=29
Post-therapy samples: n=20

Figure 1. Patient cohort and exclusion criteria

PATIENTS

- At the time of analysis, **51.7% (n = 15) of patients were deceased**
- The **median age at diagnosis** was 65 years (SD 9.9).
- The majority of patients presented with **FIGO stage IIIc (51.7%)**, followed by **stage IV (24.1%)**.
- Most patients had **nodal involvement (41.4% N1);** 31.0% were N0.
- **Metastatic disease** was present in **27.6%** of patients.
- **Complete resection (R0) was achieved in 65.5%;** residual disease remained in the rest.
- **BRCA status** was **negative in 58.6%** of patients, positive in 10.3%, and unknown in 31.0%.
- **93.1%** of patients received **carboplatin and paclitaxel** as first-line chemotherapy.
- **Bevacizumab** was administered to **55.2%** of patients, while 34.5% did not receive it.
- **PARP inhibitors** were used in **34.5%** of patients.
- **Disease progression** was observed in **55.2%** of patients.
- **Platinum resistance** occurred in **10.3%** of patients.

Table 1. Patient characteristics

	Median	Standard deviation (SD)
Age (years)	65	9.9
	n	**Percentage (%)**
FIGO Stage (2009)		
Ia	2	6.9
Ib	0	0
Ic	1	3.4
IIa	0	0
IIb	1	3.4
IIIa	1	3.4
IIIb	2	6.9
IIIc	15	51.7
IVa	3	10.3
IVb	4	13.8
N		
N0	9	31.0
N1	12	41.4
Nx	8	27.6
M0	21	72.4
M1	8	27.6
Postoperative tumor residual		
R0	19	65.5
R1 (< 1 cm)	6	20.7
R2 (> 1cm)	3	10.3
RX	1	3.4

	n	Percentage (%)
BRCA status		
postitive	3	10.3
negative	17	58.6
unknown	9	31.0
Adjuvant therapy		
Carboplatin/Paclitaxel	27	93.1
unknown	2	6.9
Bevacizumab	1	3.4
used	16	55.2
not used	10	34.5
unknown	3	10.3
PARP-Inhibitor		
Used	10	34.5
Not used	16	55.2
Disease progression		
Yes	16	55.2
No	7	24.1
Unknown	6	20.7
Platinum resistance		
Yes	3	10.3
No	18	62.1
Unknown	8	27.6

RESULTS

Table 2. Cytokines that are significantly correlated with Overall Survival

	Baseline vs. Longitudinal Changes	Overall Survival
CCL4	Higher Baseline Level	Correlated to Better Survival
IL17C	Longitudinal Increased Level	Correlated to Poor Survival
TNF	Longitudinal Increased Level	Correlated to Poor Survival
CCL2	Longitudinal Increased Level	Correlated to Poor Survival

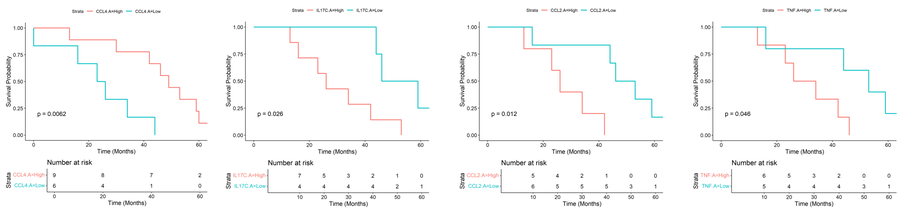
Statistical significance: Cox proportional hazards model p<0.05

Table 3. Cytokines that are significantly correlated with Progression Free Survival

	Baseline vs. Longitudinal Changes	Progression Free Survival
IL27	Higher Baseline Level	Correlated to Poor Survival
IL1B	Higher Baseline Level	Correlated to Poor Survival
VEGFA	Higher Baseline Level	Correlated to Poor Survival
IL6	Higher Baseline Level	Correlated to Poor Survival
IL13	Longitudinal Increased Level	Correlated to Poor Survival

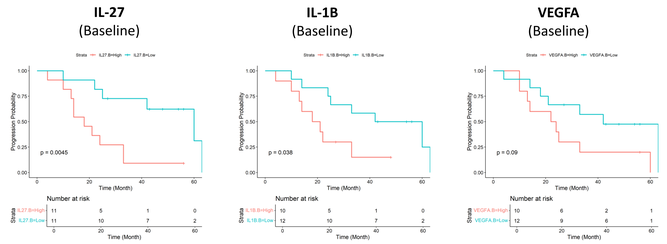
Statistical significance: Cox proportional hazards model p<0.05

Figure 2. Kaplan–Meier Estimate for Overall Survival Analysis



Note: The median value of gene expression was used as an arbitrary cutoff to define "high" vs. "low" groups.

Figure 3. Kaplan–Meier Estimate for Progression Free Survival Analysis



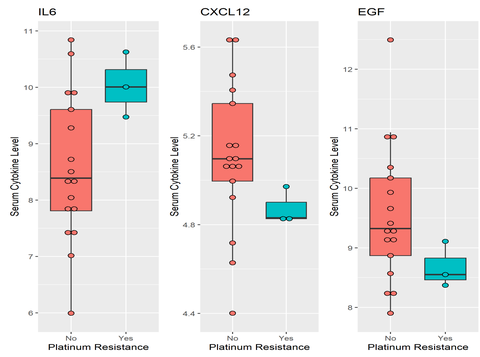
Note: The median value of gene expression was used as an arbitrary cutoff to define "high" vs. "low" groups.

Table 4. Cytokines that are significantly correlated with platinum resistance

Gene Symbol	Difference (Resi – nonResi)	P
IL6	1.47	0.016
CXCL12	-0.23	0.026
EGF	-0.88	0.034

Statistical significance: Student t-test p<0.05

Figure 4. Boxplots for Platinum Resistance and Non-resistance Patients



DISCUSSION AND CONCLUSION

- **Serum cytokine levels in ovarian cancer patients demonstrated prognostic value for both OS and PFS.**
  - **CCL4:**
    - Higher baseline CCL4 expression was associated with **prolonged OS** (p<0.05). A longitudinal increase in CCL4 levels was also trending to **improved OS**.
  - **IL17C:**
    - A longitudinal increase in IL17C was associated with **worse OS** (p<0.05). The elevated baseline IL17C expression was also trending with **poor OS and shorter PFS**.
  - **IL-6:** The elevated baseline IL-6 expression was correlated with potential **platinum resistance** (p<0.05).

Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 22-26, 2025, Boston, USA

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