Immune status as predictor for response to chemotherapy and time to recurrence in ovarian cancer

Taylor Badger[1], Kathleen Groesch[2,3], Teresa Wilson[2,3], Paula Diaz-Sylvester[2,3], Kristin Delfino[2], Laurent Brard[3,4], Andrea Braundmeier-Fleming[1,3,4]

[1]Department of Medical Microbiology, Immunology and Cell Biology, SIU School of Medicine; [2]Center for Clinical Research, SIU School of Medicine; [3]Department of Obstetrics & Gynecology, SIU School of Medicine; [4]Simmons Cancer Institute, SIU School of Medicine

SIU MEDICINE

Abstract

- 85% of ovarian cancer (OC) patients recur after first-line chemotherapy
- Analysis of T-cell populations in peripheral blood provides insights into patients' immune status
- OC causes peripheral inflammation (higher ratio of Th17:Tregs)
- Positive correlation between Th17:Treg ratio and time to recurrence suggests greater inflammation is associated with a longer interval until recurrence

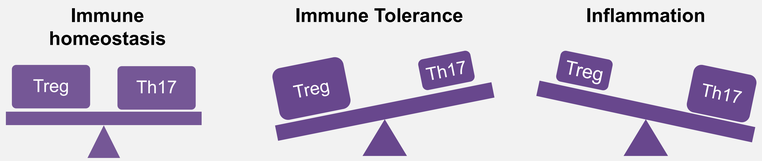
Hypothesis

Patient immune status (ratio of Th17:Tregs) will predict chemotherapy responsiveness and the time to recurrence in patients with OC.

Cancer → **Inflammation** → **Chemotherapy response**

Introduction

- Epithelial ovarian cancer (OC) is the most deadly cancer of the female reproductive system
- 5-year relative survival rate is 49.1% with a high rate of disease recurrence
- ~85% of patients who reach full remission after first-line chemotherapy will recur
- There is a known link between peripheral inflammation and pathological states (i.e., OC)
- T lymphocyte populations can give insight into immune status
- Th17 cells (a type of T helper cell) are pro-inflammatory cells
- T regulatory cells (Tregs) are tolerant T cells that inhibit effector T-cell activation
- A higher ratio of Th17:Tregs indicates higher degree of inflammation



Materials and Methods

Patient recruitment: Participants with an adnexal mass suspicious for OC who presented to SIU School of Medicine, Department of Ob/Gyn, Division of Gynecologic Oncology were approached to determine eligibility. Following consent, samples were collected on the day of surgery (DOS) and at a postoperative appointment ~ 6-10 weeks after surgery.

Response to chemotherapy	Definition	# of study patients (n=9)
Refractory	Recurrence/progression during chemo or within one month of chemo completion	n=0
Resistant	Recurrence between 1 and 6 months after chemo completion	n=1
Sensitive	Recurrence AFTER 6 months of chemo completion or no recurrence at all	n=8 (n=3, no recurrence)

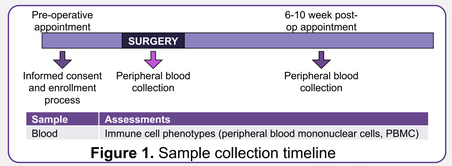
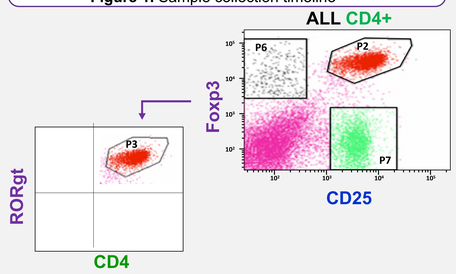


Figure 1. Sample collection timeline

Target Immune Cells	Markers	Gate
Natural Tregs (nTregs)	$CD4^+CD25^+Foxp3^+$	P2
Inducible Tregs (iTregs)	Th3-$CD4^+CD25^-Foxp3^+$ Tr1-$CD4^+CD25^+Foxp3^-$	P6 P7
Th17	$CD4^+$ $RORgt^+$	P3



Results

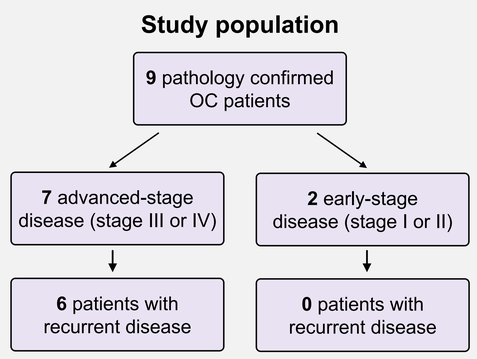
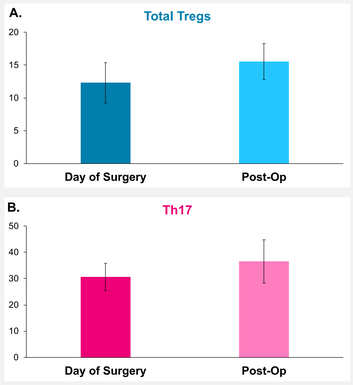


Figure 2. Flow chart of current patient enrollment



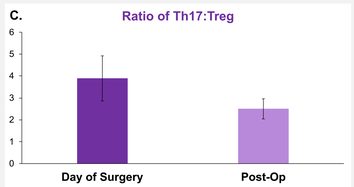
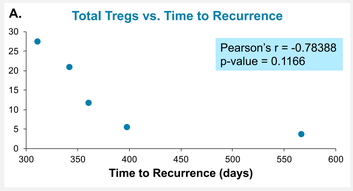
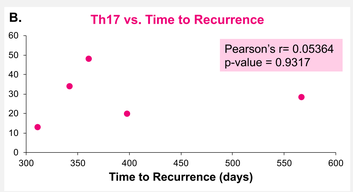


Figure 3. T lymphocyte population in 8 ovarian cancer patients on day of surgery (DOS) and at 6-10 weeks post-op. Quantification of ***(A)*** Total Tregs ***(B)*** Th17 cells ***(C)*** ratio of Th17:Treg cells.





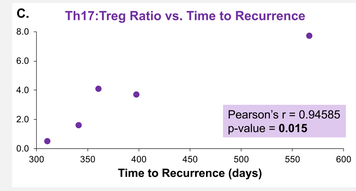


Figure 4. Pearson's Correlation was performed comparing immune phenotypes associated with time to recurrence for 5 chemo sensitive patients. ***(A)*** Total Tregs were not associated with time to recurrence. ***(B)*** Th17 cells were not associated with time to recurrence. ***(C)*** Th17:Treg ratio shows a **significant** positive correlation with time to recurrence.

Results and Conclusions

Immune phenotype in OC patients from DOS to Post-Op

1. Average ratio of Th17:Treg cells decreased from DOS to the post-operative (post-op) timepoint
2. Average Th17 cells increased from DOS to post-op, indicating more inflammation at post-op
3. Average Treg cells also increased from DOS to post-op, to a lesser degree than Th17 cells

Correlation between immune phenotypes and time to recurrence

1. Positive correlation in chemo-sensitive patients who had recurrent disease → higher level of systemic inflammation (**IMMUNE ACTIVATION TO DISEASE**) → greater delay in time to recurrence
2. Immune tolerance, lower Th17:Treg ratio, is associated with recurrence of disease
3. Nonsignificant negative relationship between total Tregs and time to recurrence

Future Directions

- Larger sample size may show a significant relationship between total Tregs and time to recurrence
- Larger sample size may enable a more powerful assessment of how immune phenotypes may correlate with patients' responsiveness to chemotherapy
- Future developments may allow providers to tailor chemotherapy for patients to predict the best possible response to chemotherapy based on immune phenotype

Sources of Funding

- Simmons Cancer Institute, SIU School of Medicine, Springfield, IL
- Department of Obstetrics and Gynecology, SIU School of Medicine, IL
- Department of Medical Microbiology, Immunology, and Cell Biology, SIU School of Medicine, Springfield, IL
- Supported in part by an Alpha Omega Alpha Carolyn L. Kuckein Student Research Fellowship