TRIPLE ARM PROSPECTIVE NON-RANDOMIZED OBSERVATIONAL STUDY ANALYSING DELAY IN TIME TO ADJUVANT CHEMOTHERAPY AND ITS IMPACT ON OUTCOME IN COMPLETELY RESECTED ADVANCED EPITHELIAL OVARIAN MALIGNANCIES

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Introduction:

- Adjuvant chemotherapy plays important role in the survival outcome of majority of solid tumors.
- Delaying adjuvant chemotherapy has been proven to worsen outcomes of many cancers, including colon [1] and breast cancer [2], but unclear in EOC [3].
- Surgical resection leads to accelerated metastatic tumor growth due to shuttling of cells in G0 phase into the cell cycle [4].
- The interval between resection and chemotherapy provides opportunity for micrometastases to proliferate.
- But the impact of time to start adjuvant chemotherapy in EOC is unclear, even though multiple large retrospective data or meta-analysis exists in the literature [5,6].
- The impact of same after HIPEC has not been published so far.

AIMS & OBJECTIVES:

1. To define the association of type of surgery and the time to adjuvant chemotherapy
2. Impact of delay in starting adjuvant chemotherapy on survival outcome

MATERIALS & METHODS:

- Prospective study
- Manipal Comprehensive Cancer Centre, Bangalore, India.

INCLUSION CRITERIA: Patients with

1. Advanced epithelial ovarian carcinoma : Stage IIIC
2. Able to achieve CC score 0
3. Good performance status (ECOG 0 or 1)

EXCLUSION CRITERIA:

1. Recurrent disease
2. Non epithelial ovarian primary

METHODOLOGY:

- Optimal cytoreduction done with standard steps of CRS.
- In patients who were planned for intraperitoneal chemotherapy (IP), port was inserted at the end of the procedure.
- For patient who were planned for HIPEC, HIPEC was done by semi open technique at the end of CRS and was based on the institutional protocol (Inj cisplatin 100mg/m² over 90min at 41.5°C).
- Patients received adjuvant chemotherapy on day-care basis after the recovery and IP chemotherapy for IP port group.
- Time to start adjuvant chemotherapy (from the day of surgery) was calculated for all 3 groups: 42 days was taken as cut off to define “Delay” [7].
- Time to recurrence (DFS) and overall survival were calculated & analysed.

Time to adjuvant chemotherapy	No of patients	Median DFS (months)	p	Median OS (months)	p
Whole COHORT					
<42days	106	37	0.06	88	0.49
>42days	58	28		71	
CRS alone					
<42days	34	30	0.02	70	0.1
>42days	12	17		50	
CRS+IP group					
<42days	35	36	0.78	88	-
>42days	8	30		NA	
CRS+HIPEC					
<42days	37	35.5	0.17	NA	-
>42days	38	32		52	

CRS ALONE GROUP: Delay in chemotherapy vs Survival outcome

Time to adjuvant chemotherapy (days)	NON HIPEC GROUP Median DFS (months)	p	HIPEC GROUP Median DFS (months)	P
<42	32	0.08	35.5	0.17
>42	20		32	

CRS-IP GROUP

HIPEC GROUP

NON-HIPEC GROUP

RESULTS:

Manipal Comprehensive Cancer Experience
>1300 CRS for Ca Ovary cancer

Type Of Surgery	Median Time to Adjuvant chemotherapy (in Days)	Median DFS (Months)
CRS	32	28
CRS+IP	34	36
CRS+HIPEC	41	33
TOTAL	35	34

DISCUSSION:

30% of patients had delay in starting adjuvant chemotherapy: 20% in the NON-HIPEC group & 45% in HIPEC group.

Reasons for treatment delays in HIPEC group : electrolyte imbalance, hematologic toxicities,

In the NON-HIPEC group (i.e CRS group and CRS+IP), delay in adjuvant chemotherapy had an impact on DFS (20months vs 32months, p=0.08), Difference in DFS was not significant in the HIPEC group.

In HIPEC group, delay did not have significant impact on survival outcome: single dose of HIPEC administered at the time of surgery itself acts as adjuvant consolidation therapy.

CONCLUSION:

- First study available, which has taken all 3 modalities of treatment of Stage IIIC carcinoma ovary & addressed the effect of delay in adjuvant chemotherapy over survival outcome.
- Delay in starting adjuvant chemotherapy adversely affects DFS without significant impact on OS especially in patients undergoing optimal CRS alone.
- Intra-peritoneal chemotherapy after optimal CRS can improve DFS
- In patients receiving HIPEC, impact of delay in adjuvant chemotherapy on survival is not significant impact: as HIPEC itself can act as an adjuvant chemotherapy
- Well designed randomized studies are required to validate this results with long term follow up.

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