

Perioperative blood transfusion in ovarian cancer patients with post neoadjuvant chemotherapy and interval cytoreduction surgery

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ABSTRACT

Introduction: The adoption of Neoadjuvant Chemotherapy (NACT) preceding Interval Cytoreductive Surgery (ICS) has become increasingly favoured in the management of ovarian cancer. Nevertheless, in the context of NACT, more than 50% of patients experience grade 3-4 anaemia as a result of myelosuppressive chemotherapy, thereby elevating the perioperative risk for blood transfusion. The main goal was to assess the incidence of Perioperative Blood Transfusion (PBT) in ovarian cancer patients undergoing ICS following NACT. The secondary objective involved examining the impact of perioperative blood transfusion on Disease-Free Survival (DFS) in these individuals.

Methods: Retrospective study, clinical and transfusion details on ovarian cancer patients who underwent NACT followed by ICS was captured. The outcome of interest was administration of RBC transfusions to the patients during the perioperative period. DFS was expressed in Kaplan Meier plot and compared based on PBT risk using log rank test.

Results: A total of 69 patients were included in analysis, with median age of 52 (32 to 68) years. Baseline Haemoglobin (Hb) and preoperative Hb was 11.6 g/dL and 10.7 g/dL. CA 125 at baseline and before surgery was 1545 and 52 units/mL. Median surgery duration was 3.5 hours and blood loss were 500 (100 ml to 2500 ml). 37 (54%) patients received PBT with units ranging from 0 to 5 RBC units. The DFS in patients with PBT was lower than patients without transfusion, but without statistical significance (16 vs. 21 months, $p=0.618$).

Conclusion: PBT was observed in 54% of ca ovary patients who underwent NACT and ICS. Patients exposed to PBT experienced a decrease in DFS compared to those without PBT, although this difference was not statistically significant.

Keywords: perioperative blood transfusion, interval cytoreduction, ca ovary, rbc transfusion

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INTRODUCTION

Perioperative Blood Transfusions (PBT) are not uncommon in cancer patients. PBT was performed to ensure optimal tissue oxygenation in patients undergoing surgery [1]. The European Cancer Anaemia Survey (ECAS) observed that 48% of gynaecologic cancer patients had anaemia upon enrolment. This anaemia stemmed from various factors such as marrow dysfunction (resulting from chemotherapy, radiation, or metastasis), blood loss (associated with surgery or tumour-related factors), and renal dysfunction (attributed to platinum-based chemotherapy) [2].

The adoption of Neoadjuvant Chemotherapy (NACT) preceding Interval Cytoreductive Surgery (ICS) has become increasingly favoured over traditional treatment approaches [3, 4]. Nevertheless, the utilization of myelosuppressive chemotherapy in NACT has led to a notable incidence of grade 3-4 anaemia, affecting over 50% of patients [5]. Consequently, there is an elevated risk of requiring blood transfusions during ICS for patients undergoing NACT [6].

Numerous studies have verified the immune-modulating impact of blood transfusions, correlating with heightened risks of postoperative infections and cancer recurrence [2, 6]. De Oliveira et al. identified a connection between the risk of recurrence and allogeneic blood transfusion in patients with epithelial ovarian cancer undergoing optimal cytoreductive surgery [7].

Blood transfusions are typically administered when the Haemoglobin (Hb) level falls to 8 g/dL or below in surgical contexts [2]. Given that these patients undergo extensive debulking surgeries following NACT, they are rendered more vulnerable to requiring blood transfusions during the perioperative period as well. The main goal was to assess the incidence of Perioperative Blood Transfusion (PBT) in ovarian cancer patients undergoing ICS following NACT. The secondary objective involved examining the impact of PBT on Disease-Free Survival (DFS) in these individuals.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at a tertiary cancer centre in South India. It included all ovarian cancer patients who underwent NACT followed by ICS at the institution between January 2014 and December 2019. Patients were excluded if they underwent prior surgical therapy for the

disease or treated for non-epithelial ovarian tumours. The goal of the treating surgeons was to achieve complete excision of the tumour burden (R₀ resection). However, the extent of surgery was adjusted based on factors such as the patient's condition, tumour location, and stage.

The primary outcome of interest was PBT with Red Blood Cell (RBC) units during the surgery. PBT was defined as RBC transfusion during the intraoperative period and day of surgery, as the decision and timing of RBC transfusion depended on the treating physician. Additionally, RBC transfusion during the entire hospital admission was documented by reviewing hospital records. The standard transfusion threshold was to maintain Haemoglobin (Hb) levels above 8 g/dL in the perioperative period. Patients were grouped based on their PBT status.

Data collection involved extracting demographic and clinical parameters from medical records, including age, BMI, diagnosis, disease stage, CA125 levels, comorbidities, baseline investigations before surgery, duration of surgery, extent of resection, intraoperative blood loss and type of chemotherapy received. Survival outcomes were assessed in terms of DFS measured as the time interval between surgery and recurrence.

Statistical analysis

The patient and procedural data collected were documented in study proforma. Categorical variables were expressed in frequencies and continuous variables by mean (SD), median (Range). Chi square test/Fischer exact test was used to study the association between the categorical variables. Similarly, Mann Whitney U test was used to study association in continuous variables. DFS was expressed in Kaplan Meier plot and log rank test.

RESULTS

A total of 69 patients were analysed, with a median age of 52 years (Range: 32 years to 68 years). The baseline Hb level was 11.6 g/dL, while the preoperative Hb level was 10.7 g/dL (Table 1). Before commencing any treatment, the prevalence of anaemia (Hb<12 g/dL) was observed in 40 patients (58%), whereas following NACT, the prevalence of anaemia rose to 57 patients (83%) in the study cohort. CA 125 levels at baseline and preoperative periods were

recorded as 1545 and 52 units/mL, respectively. Majority of patients were in clinical stage 3 (61%) and rest stage 4.

The median follow-up time was 23 months (range 0 to 85). Most (75%) patients received chemotherapy regimen as Paclitaxel and Carboplatin, while others received Cyclophosphamide, Adriamycin and cis- dichlorodiammine-Platinum (CAP) regimen. The median duration of surgery was 3.5 hours, with a blood loss ranging from 100 ml to 2500 ml.

Table 2 examines RBC transfusions in ovarian cancer patients during their hospitalization for surgery. Among the 69 patients, six received RBC transfusions during the preoperative period with 5 patients receiving single unit and one patient receiving two unit's transfusion. During the perioperative period, RBC transfusions were administered to 37 patients (54%) with the number of RBC units transfused varying from 0 to 5. The preoperative Hb levels patients with and without PBT were similar (10.6 vs. 10.9 g/dL; p=0.291). The PBT was not strongly associated when patients were grouped with preoperative Hb<10g, (30.6% vs. 27.6%; p=0.794; OR=0.866; CI=0.29-2.54). Additionally, 26 patients (38%) received RBC transfusions during the postoperative period. Altogether, 53 patients (77%) received RBC transfusions at some point during their hospitalization. Plasma and platelet transfusions were required only in 11 (16%) patients during the perioperative period.

Optimal cytoreduction, defined as less than 1.0 cm residual disease, was achieved in 61 (94%) patients. The extended resection was required in 35 (54%) patients. Complex and extensive resections that included appendectomy, pelvic peritonectomy, total peritonectomy with cholecystectomy, and other operative details are shown in table 3. Univariate analysis showed no difference in PBT risk with respect to major resections. Recurrence was reported in 36 patients (52%) following ICS. There was no relationship between perioperative RBC transfusion and recurrence in these patients (Table 4).

Upon stratifying patients based on PBT, DFS was lower in patients with PBT during ICS, however the difference was not statistically significant (16 months vs. 21 months, p=0.618) (Figure 1).

Tab. 1. Clinical characteristics of Ca Ovary patients underwent Interval cytoreduction surgery (n=69)

		Median	Range
Age	Years	52	32-68
BMI	-	24	18-36.1
Baseline CA125	Units/mL	1545	13.1-36098
Baseline Hb	g/dL	11.6	8.4-13.8
Preoperative Hb	g/dL	10.7	8.3-13.8
Preoperative Platelets	× 10 ³ /ul	294	109-652
Preoperative PT	sec	13.8	10-18.9
Surgery Duration	Hours	3.5	1.25-8.5
Blood Loss	mL	500	100-2500

BMI – Body mass index; Hb – Haemoglobin; PT – Prothrombin time

Tab. 2. RBC Transfusions in Ca Ovary patients who underwent interval cytoreduction surgery (n=69)

RBC Transfusions	N (%)	RBC Units Transfused	
		Mean (SD)	Median (Range)
Preoperative	6 (9)	0.1 (0.35)	0 (0-2)
Perioperative	37 (54)	1.0 (1.25)	1 (0-5)
Postoperative	26 (38)	0.45 (0.65)	0 (0-2)
During admission	53 (77)	1.57 (1.4)	1 (0-6)

Tab. 3. Details of perioperative RBC transfusion with clinical and operative details of interval cytoreduction in Ca Ovary patients (n=69)

		N	Perioperative RBC Transfusions		p-value
			Yes =37	No =32	
			n (%)	n (%)	
Age	Median (Range)	-	53 (35-68)	48 (32-68)	0.249
BMI	Median (Range)	-	22.9 (18-29.5)	24.6(18-36.1)	0.211
Baseline Hb	Median (Range)	-	11.6 (8.4-13.8)	10.9 (8.8-13.5)	0.402
Preoperative Hb	Median (Range)	-	10.6(8.3-13.8)	10.9(8.8-13.5)	0.291
Preoperative CA 125	Median (Range)	-	55 (0-1393)	37 (3.7-1500)	0.606
Clinical Stage	Stage 3	38	21 (60)	17 (63)	0.511
	Stage 4	24	14 (40)	10 (37)	
Chemo Regimen	P+C	43	24	19	0.54
	CAP	14	6	8	
Cytoreduction	Optimal	61	32 (94)	29 (93)	0.51
	Suboptimal	3	1 (3)	2 (7)	
	Residual disease	1	1 (3)	0	
Blood Loss	Median (Range)	-	800 (180-2500)	300 (100-1000)	<0.001
Duration of Surgery	Median (Range)	-	4.0 (1.5-8.5)	3.0 (1.3-7.5)	0.001
Hospital Stay	Median (Range)	-	20 (8-36)	16 (8-32)	0.031
Extended Resection	Yes	35	21 (60)	14 (47)	0.282
	No	30	14 (40)	16 (53)	
Surgery Resections	Appendicectomy	6	3 (4.5)	3 (4.5)	1
	Peritonectomy + cholecystectomy	7	5 (7.6)	2 (3)	0.433
	Pelvic peritonectomy	7	5(7.6)	2 (3)	0.433
	Gut resection	19	11 (17)	8 (12)	0.786
	Bladder stripping	5	3 (4.5)	2 (3)	1
	Diaphragmatic resection	9	6 (9.1)	3 (4.5)	0.484
	Splenectomy	4	1 (1.5)	3 (4.6)	0.328

Tab. 4. Patient's Perioperative RBC transfusion during interval cytoreduction surgery and Recurrence in Ca ovary patients(n=69)

		Peri-operative		p-value
		RBC transfusions		
		Yes	No	
Recurrence	Yes	20 (56%)	16 (44%)	0.737
	No	17 (51%)	16 (49%)	

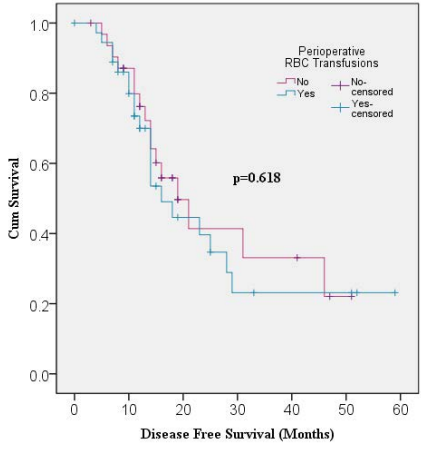


Fig. 1. Logrank Test comparing perioperative RBC transfusion with Disease Free Survival in patients underwent interval cytoreduction surgery for Ca Ovary

DISCUSSION

Blood transfusions are frequently administered to patients with gynaecologic malignancies, yet there remains a paucity of research and data to inform transfusion practices in carcinoma ovary patients. The association between transfusion, prognosis, and recurrence is intriguing but complex in any setting, and should caution surgical decision-making. Compelling evidence has emerged challenging the liberal administration of blood transfusions in colorectal surgery and critically ill patients. Nevertheless, uncertainties persist regarding the relevance of these findings to gynaecologic cancer patients [2].

The ICS in patients who underwent post NACT showed 54% patients requiring RBC transfusion in the perioperative period i.e. on the day of surgery. Up to 77% of patients exhibited the highest probability of requiring RBC transfusion during their hospital admission. Mccool and colleagues noted that 77% of patients who underwent ICS following NACT were subjected to allogeneic perioperative RBC transfusion. They defined RBC transfusion during the index hospitalization for ICS as within the perioperative period [6]. Both the studies observed similar RBC transfusion pattern during the hospital admission for ICS. While Münstedt et al. in 2003 had reported 35% patients receiving at least one transfusion with primary debulking laparotomy combined with tumour reductive surgery in ovarian cancer [8]. Moreover, owing to the nature of ovarian cancer treatment, frequently involving extensive debulking surgeries, individuals with ovarian cancer are especially prone to developing anaemia [2].

Hensley and colleagues observed that a pretreatment haemoglobin (Hb) level lower than 10 g/dL ($p < 0.01$, OR=3.78, CI=1.52-9.44) emerged as a notable predictor for requiring transfusions among patients receiving carboplatin-paclitaxel therapy [9]. However, in the present study, preoperative Hb < 10g did not consistently predict PBT ($p = 0.794$; OR=0.866; CI=0.29-2.54). Among the patients with PBT, preoperative haemoglobin concentration was observed to be lower (10.6 *vs.* 10.9g/dL; $p = 0.291$) and also observed to have higher volume of blood loss (800 mL *vs.* 300 mL; $p < 0.001$), prolonged duration of surgery (4 hr *vs.* 3 hr; $p = 0.001$) and prolonged length of stay (20 days *vs.* 16 days; $p = 0.031$) in group exposed to PBT. Also, the incidence of Hb levels below 12 g/dL increased from 40 patients (58%) before NACT to 57 patients (83%) after chemotherapy.

A total of 35 patients underwent extended resections and among 69 patients with advanced ovarian cancer, including 19 underwent gut resection, 9 underwent diaphragmatic resection, 7 underwent total peritonectomy and bladder stripping in 5 patients. The extent of resection did not influence PBT in this study (Table 3). Previous study found that transfusion correlated with a 2.68-fold increase in the odds of composite morbidity (OR= 2.68; CI= 2.10–3.42), surgical site infections (OR=1.80; CI=1.38–2.34) and mortality (OR= 3.38; CI= 1.80–6.35) following adjustments for clinical and operative factors such as presence of ascites, procedure complexity, operative time etc [8].

Previous studies from Münstedt et al. in 2003 and Cybulska et al. in 2017 have demonstrated a correlation between survival rates

and anaemia in ovarian cancer patients, with extended survival rates (52.3% *vs.* 38.5%) observed in patients with Hb levels exceeding 12g/dL both before and during chemotherapy [2, 10]. There was no difference in DFS in patients with and without PBT (16 months *vs.* 21 months, $p = 0.618$) in patients with ca ovary in the present study. Our findings align with prior research conducted by Mccool and colleagues that perioperative transfusion was not linked to a notable disparity in progression-free survival (7.6 months *vs.* 9.4 months, $p = 0.4617$). Likewise, no discernible difference was observed between the groups in terms of overall survival (23.6 months in the transfused group *vs.* 22.5 months in the non-transfused group; $p = 0.1723$) [6].

Our study has several limitations. Firstly, its retrospective design may inherently lack important clinical variables necessary to demonstrate the impact of perioperative differences on outcomes in study patients. Given the dearth of evidence-based data in gynaecologic oncology and to our knowledge, this study represents the first investigation into perioperative outcomes concerning RBC transfusions in gynaecologic oncology patients from Indian demographics.

Two prospective studies have illustrated that intravenous (IV) iron represents a well-tolerated primary preventive measure against blood transfusions in ovarian cancer patients undergoing platinum/taxeme chemotherapy. Participants who were allocated to receive IV iron alongside each chemotherapy cycle exhibited elevated nadir Haemoglobin (Hb) levels, occurring later in the treatment regimen, and required fewer Red Blood Cell (RBC) transfusions overall throughout the study duration [2, 11, 12]. It is imperative for each hospital to develop a Patient Blood Management (PBM) program that delineates precise transfusion criteria, taking into account individual patient clinical risk factors, symptoms, and tolerance to anaemia. PBM efforts should give precedence to managing perioperative anaemia and coagulopathy, integrating blood conservation techniques, advocating for patient-centred transfusion approaches, and integrating metrics for assessing patient outcomes [2]. Understanding blood transfusion practices in gynaecologic oncology may lead to more efficient use of blood bank resources and improved short-term and long-term clinical outcomes for patients.

CONCLUSION

In conclusion, the present study observed a notable prevalence of PBT among carcinoma ovary patients undergoing ICS after NACT. Patients exposed to PBT exhibited a reduced DFS in contrast to those without PBT although this difference was not statistically significant. Future investigations focussing on addressing preoperative anaemia during NACT could potentially aid in lowering blood product usage within this patient group.

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