ORIGINAL ARTICLE

Predictive Factors Involved in Determining response to Neoadjuvant Chemotherapy in High Grade Serous ovarian cancer and impact of response on 5 years disease free survival and overall survival

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ABSTRACT

Aim: To evaluate all the known factors that may play a role in predicting response to chemotherapy and to see impact of response on five years' disease free survival (DFS) and overall survival (OS).

Methods: Data of 156 patients was reviewed retrospectively from January 2012 to December 2012 at Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore, Pakistan. All received neoadjant chemotherapy (NAC)and had no distant metastasis. The response was measured in term of percentage ureduction from 1st radiological size on presentation to final size on histopathology (on resected specimen). Four groups were identified, complete responder (CR) (100% reduction),Responders (R) (>50% reduction),Partial responder (PR) (<50% reduction) and Non-responder (NR)..

Results: Median age of patients was 45 years (25-64 years). 67% of patient underwent debulking surgery on ovarian protocol without pelvic node dissection. Mortality for whole group was 22%, and recurrence was shown in 34%(Majority 26% were distant). Out of 156 patients, 25% of patients were CR, 13% were NR, 23% were PR and 37% were R. Progesterone receptor negative and Grade III tumors showed more complete responses. The Rest of the factors, including, initial T and N stage and other factors showed no impact on chemo-response. Survival was significantly poor in NR group (45% OS, 40% DFS), while rest of three groups had comparable survival outcome, with CR group having best survival outcome (86% OS, 80% DFS).

Conclusion: Most of factors studied did not show impact on achieving good chemo response, however good chemo response did show better survival.

Keywords: Neo-adjuvant chemotherapy, Response of neo-adjuvant, serous ovarian carcinoma,

INTRODUCTION

Epithelial ovarian carcinoma accounts for 23% of total cancer cases worldwide and 30% of all cancer deaths[1]. As per World Health Organization (WHO), ovarian cancer affects more than 1.2 million people every year and majority of patients present in advanced stage[2]. According to GLOBOCAN 2018, ovarian cancer is the leading cause of cancer death among females after breast cancer[3]. In Pakistan, incidence of ovarian cancer is 13.6% and 70% of patients present with widespread disease[4].

In the last few decades, neo-adjuvant chemotherapy (NAC) has become a standard treatment in the management of advance stage ovarian cancer. The United States National Cancer data database reported an increase in usage of NAC from 15.7% to 26% in 2015[5, 6].Potential benefits of NAC are killing systemic micro-metastasis right from beginning, achieving higher rates of disease free survival[7].

Response of NAC is variable and it is multi-factorial, as some patients can be either non-responders (NR), complete responders (CR) or partial responders (PR) [8].Patients with highest sensitivity to NAC were expected to have more than five years disease-free survival; however, a subset of patients with hormone receptor positive tumors were resistant to chemotherapy however showed a good 5 years disease free survival ratio[9].

Chemo response variations have led to the researchers focusing on differences among patients that may have influence on achieving better responses; these are patient factors and tumor biomarkers, collectively referred to as Predictive response factors". However, the value of the predictive response factors within the neo-adjuvant scenario is still uncertain, as there are some conflicting results in literature. The rationale of this study are to evaluate all the known factors that may play a role in predicting response to chemotherapy and to see impact of response on five years disease free survival (DFS) and overall survival (OS).

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METHODOLOGY

During 1st January 2012 to 31st December 2012, patients who underwent debulking surgery on ovarian protocolr for high grade serous ovarian cancer after NAC at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC), Pakistan were selected. It is a retrospective study with convenience sampling. Patients who underwent upfront surgery or had distant metastases were excluded from disease.

Variables: Data was collected through human information system (HIS), electronic database of SKMCH&RC. Variables recorded were age, gender, pre surgery histopathology including immunohistochemistry, clinical staging, neo-adjuvant chemotherapy received, type of chemotherapy received, and survival outcomes.

Every patient had detailed history and examination in the walk-in clinic and referred to Gynaecological oncology Clinic for detailed assessment and investigation. Investigations included were baseline blood tests, MRI pelvis and biopsy report if available. Metastatic workup

includes Computed tomography scan (CT)chest and abdomen ,where indicated a Bone scan. Every case was discussed in our Multi-Disciplinary Team (MDT) meeting comprising of trained Gynaecological oncologist, radiologists, pathologists, medical and radiation oncologists.

As a routine, all cadres including doctors, nurses, allied health professionals, put all patient data real time into a computerised Hospital Information System (HIS). Therefore, information like patient demographics, investigations, Multi-Disciplinary Team discussions, Nursing assessments, outpatient, operative notes and post-operative outcomes were collected. As the data is collected in real time and stored, it allows for accurate retrospective review of the data.

Response to chemotherapy was calculated on histopathology of resected specimen. They were categorized into four groups i.e., CR - 100% reduction in tumour mass, R - more than 50% reduction in tumour mass, PR - less than 50% reduction in tumour mass and NR - No reduction seen. The response was measured in percentages. (final size on excision ÷ initial size on ultrasound × 100 -100)

Statistical analyses: Calculations were performed with Statistical Package for the Social Sciences (SPSS 20) for Windows version 20 statistical software. Data was described using median with minimum and maximum value for skewly distributed quantitative variables. For categorical variables, number of observations and percentages were reported. The study is complied with the SKMCH&RC guidelines on research involving human subjects.

RESULTS

A total of 156 patients underwent completion surgery on ovarian protocol after NAC. Median age of patients was 45 years (25-64 years). 14% of the patients had positive family history of cancer. Majority of the patients (68%) were pre-menopausal. 90 patients (57%) had grade II disease, while 64 patients (41%) had grade III disease, while grade-I were 2 patients only (1.3%)

105 patients (67%) underwent non fertility sparing surgery without pelvic nodal dissection, rest underwent hysterectomy on ovarian protocol with pelvic nodal exploration. Estrogen receptors were positive in 81% of patients, while progesterone receptors were positive in 56% of patient.

34% of patients had recurrence either local or distant.22% of patient died within five year after completion of treatment. Median disease free survival and median overall survival after surgery for ovarian cancer was 58±22 months and 60±19.2months respectively.

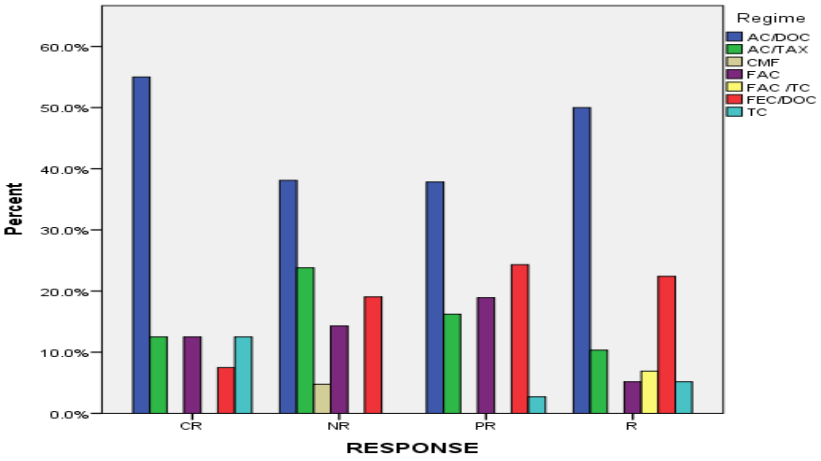
After NAC, 40 patients (25%) showed CR. 58 patients (37%) were in R, 37 patients (23%) showed PR, 21 patients (13%) showed no response (NR) at all. As the groups were categorized only on tumor response i.e. T stage after chemotherapy, so LNs response was not taken in account. In complete responders' 36 patients (out of 40) showed complete pathological response. Out of all variables, only Grade of tumor, progesterone receptors (PR) showed relationship with the chemo response with significant P- values (Table 1).

Grade III tumors distribution was highest in complete responder group (40%), which was not observed in rest of the groups. Similarly, PR negative distribution was highest in complete responder group (41%), but not seen in rest of the groups. Estrogen positivity was 81% in whole group so it showed higher distribution in each group, however among the 19% ER- tumors most were in CR group (48%). Menopausal status, multicentricity and family history and parity were also not related to chemo response. Majority i.e. 90% of tumors were stage-II, so its impact on chemo response was not significant.

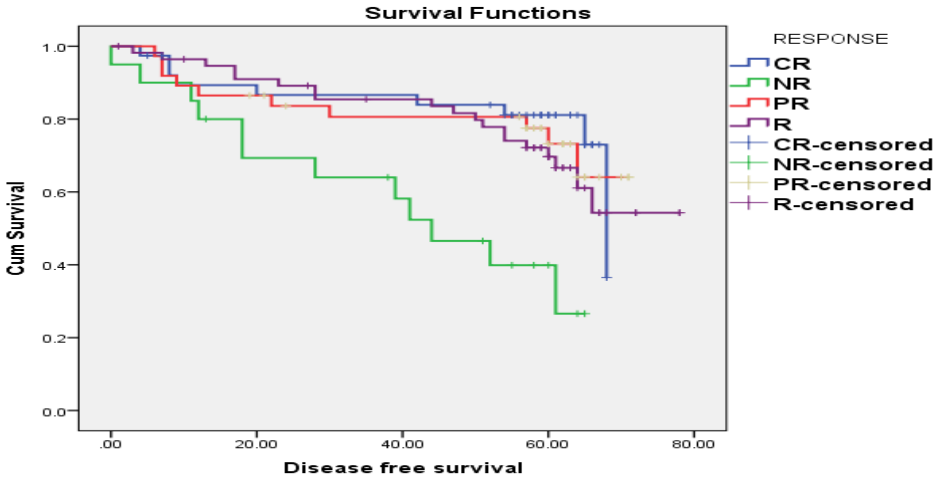
Table: 1. Predictive factors distribution in each group

Variables		CR	R	PR	NR	TOTAL	P-value
Grade of tumor	1	0	2 (3%)	0	0	2 (1.2%)	0.014
	2	14 (35%)	38(65.5%)	25(67.7%)	13 (62%)	90 (57%)	
	3	26 (65%)	18 (31%)	12 (32%)	8 (38%)	64 (41%)	
ER status	Negative	14(35%)	4 (7%)	5 (13.5%)	6 (29%)	29 (19%)	0.002
Positive		26 (65%)	54 (93%)	32(86.5%)	15 (71%)	127 (81%)	
PR status	Negative	28 (70%)	20(43.5%)	12 (32%)	9 (43%)	69 (44%)	0.002
Positive		12 (30%)	38(65.5%)	25(68%)	12(57%)	87 (56%)	
Age	≤ 35 years	6(15%)	13(22.4%)	2(5.4%)	2(9.5%)	23(14.7%)	0.126
	36-50 years	22(55%)	33(56.9%)	21(56.8%)	9(42.9%)	85(54.5%)	
	≥ 51 years	12(30%)	12(20.7%)	14(37.8%)	10(47.6%)	48(30.8%)	
Family history	Yes	8 (20%)	7 (12%)	3 (8%)	3 (14%)	21 (14%)	0.478
of cancer	No	32 (80%)	51 (88%)	43 (92%)	18(86%)	135(86%)	
Menopausal	Yes	12 (30%)	14 (24%)	15 (40%)	9 (43%)	50 (32%)	0.251
Status	No	28 (70%)	44 (76%)	22 (60%)	12 (57%)	106 (68%)	
T stage	T1	3 (7.5%)	3 (5%)	0	2 (9.5%)	8 (5%)	0.674
(At Presentation) T2		39 (90%)	52 (90%)	34 (92%)	19(90.5%)	144 (90%)	
	T3	0	2 (3%)	2(5%)	0	4 (2.6%)	
	T4	1(2.5%)	1 (1.7%)	1(2.7%)	0	3 (1.9%)	
LN Status	Negative	12 (30%)	18 (31%)	15(40.5%)	8 (38%)	53 (34%)	0.711
(At presentation)	Positive	28 (70%)	40 (69%)	22(59.5%)	13 (62%)	103 (66%)	

Figure 1: Out of total 156, 105 patients underw ent completion on ovarian protocol w ith out pelvic nodal dissection and 51 patients underw ent nodal dissection along w ith debulking surgery.



Overall Survival (Each group):



Disease Free Survival (Each group)

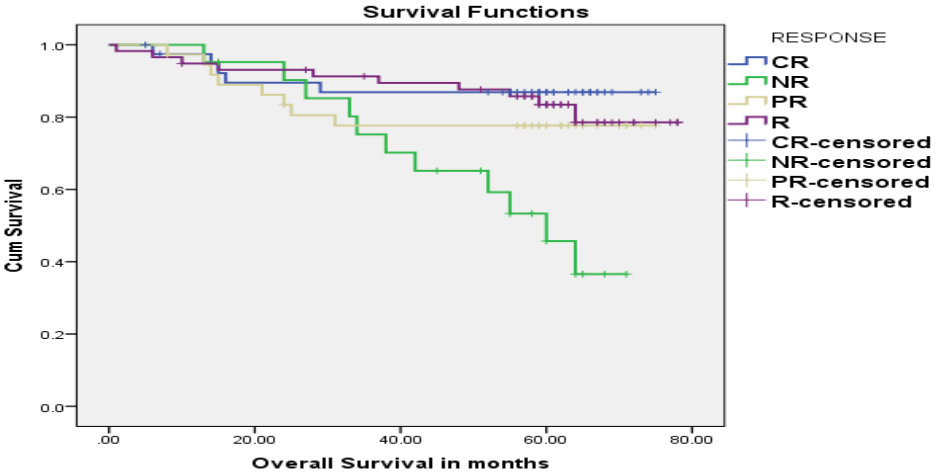


Table: 2

Response	Overall survival	Disease free survival
CR (100% response)	86%	80%
R (>50% response)	84%	70%
PR (<50% response)	78%	73%
NR (No response at all)	45%	40%

Table: 3. Recurrence

	CR	R	PR	NR	Total
Yes	25%	34%	27%	62%	34%
No	75%	66%	73%	38%	66%

Table: 4. Type of recurrence

	CR	R	PR	NR	Total
AML	0	0	1	1	2
Distant	6	14	5	8	33
Local	0	3	3	2	7
Distant + Local	2	1	1	2	7
Local + Contralateral	0	0	1	0	1
Contralateral	2	2	0	1	5
Total	10 (25%)	20 (34%)	11(AML excluded) (30%)	13(AMLexcluded) (61%)	53 (AML excluded) (34%)

Table: 5. Alive and Dead status:

	CR	R	PR	NR	Total
Dead	5 (12.5%)	10 (17%)	8 (22%)	11 (52%)	34 (22%)
Alive	35(87.5%)	48 (83%)	29 (78%)	10 (48%)	122 (78%)

The Chemotherapy regimens were also studied. Most common regimen used was AC/DOC (in 46% of total), rest were used less frequently (AC/TAX, FAC, FAC/TC, TC, FEC/DOC). The distribution of various chemotherapy regimens among all four groups was not significantly different. Only one patient received CMF and did not respond (non-responder group) (Figure 1).

Prognosis was taken from date of end of active treatment (completion of either radiotherapy or Surgery). Five year OVS for whole study group was 78%, while DFS was 70%. While 80 months OVS was 75% and DFS was 52%. Two of the deaths were due to acute myeloid leukemia (within 2 years of primary diagnosis), and 2 died of worsening medical condition (one heart failure and one liver cirrhosis). Impact of chemo response on prognosis was very evident. The best survival was shown by complete responder group with 86% overall survival and 80% DFS. The survival functioned declined proportionately according to decreasing response, the non-responder group showed least percentages (Table: 2).

The highest recurrences were observed in Non-responder group (62%) and lowest in complete responder group (25%). The commonest recurrence in all groups was distant (Table 3 & 4).

DISCUSSION

This retrospective study studied few clinical and pathological factors that may act as predictive factors in determining response to NAC in ovarian cancer and then the impact of chemo response on survival. Researchers are trying to find a way by which chemo-response can be predicted before subjecting the patient to this potentially hazardous treatment mode. So, chemotherapy cycles might be tailored in a subset of patients who may not respond well to chemotherapy, thus not delaying onset of other mode of treatment[9-12]. The goal of chemotherapy in neo-adjuvant settings is to shrink the size of tumor and lymph nodes and if any micro metastasis.It would be a big breakthrough in the field of science if we know before starting chemotherapy that who will achieve this goal and who will not.

Younger age and lesser BMI were shown to have better chemo response [13-16].Among the pathological factors grade of tumor, receptor status, proliferation index (Ki-67), P53 mutation and other rarer genes are extensively studied in the past. Some patients despite having good predictive factors, show resistance to chemotherapy or have early recurrences, suggesting there might be certain cellular characteristics at the molecular level[17-20].

In this study the degree of response was graded in 4 groups, however in most of the studies done previously pCR was studied in relation with predictive factors. Response meant tumor size reduction only, lymph node response was separately studied but it was not the main focus of study. The four grades were the complete responders and non-responders with 2 groups of variable responses in between (< and > 50% response). The distribution of each factor was observed across the 4 grades. None of the clinical factors like age, menopausal status, family history and parity showed any effect.BMI was not evaluated in this study. Another problem was lack of fluorescence in suit hybridization (FISH) testing for 2+ score on immunohistochemistry

In our study population, ER and PR positivity was high (81% ER+, 56% PR+). So, ER positive tumors was almost evenly distributed in all response groups, however ER- tumor were more clustered in complete responder group (14 out of 29 patients).In complete responder group 70% of patients were PR- tumors showing PR negativity may be favorable predictive factor towards chemo response (0.002). Grade III tumors showed more complete response (P=0.014) compared to grade II. Large majority, i.e. 92% of our population was T- II tumors (T1 are less

frequent presentation in this part of world and T3 tumors usually doesn't fulfill hospital acceptance criteria), so T size also showed not impact on chemo response. 64% of study population was lymph node positive at presentation and showed no propensity towards better or worst response (P= 0.711).

Although, a pCR does not mean a definitive cure, however it can predict a more favorable outcome with reduced relapse rates [18]. Patients with residual disease have significantly lesser survival[19]. In one study, the 5-year survival for patients achieving complete pathologic response was 96% compared with 75% in those with partial response[21-24].

In our study, 61% of the patients' responded partially after neo-adjuvant chemotherapy, 13.5 did not respond at all. 25.5% of patients had no residual tumor (T0)out of which pCR was shown in 22% of patients (T0N0).Survival for each response group was measured separately; the worst survival was shown by non-responder group (OS 45%, DFS 40%). In rest of three groups, if survival is compared, it fell proportionately as the response decreased (0S= 86% CR, 84%R, 78%PR). The survival in complete responder group (which had 36 T0N0 out of 40) was not as good as in other published studies [19], perhaps because only 5% patients had T1 disease at presentation, almost all the rest were T2 disease, and because 28 patients out of 40 were LN+ at diagnosis.

Most common type of recurrence in the whole cohort as well as in each response group was distant (41 out of 53 patients) implying breast cancer is either a systemic disease or because NAC induces changes in microenvironment that may cause distant metastasis [25-28]. Rest (12 out of 53 patients) were local or contralateral only. Two patients developed acute myeloidleukemia within 2 years of completion of treatment.

In Summary, the more a tumor responds to chemotherapy the better is survival. The goal is to predict the response before starting chemotherapy. In this study, only PR + and Grade III tumors had better chemo response. More work is needed on molecular and genetic level to better understand variability of chemo-response.

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