

Neoadjuvant Chemotherapy for Elderly Patients with Advanced Stage Ovarian Carcinoma

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ABSTRACT: **Background:** The treatment of elderly patients with advanced stage ovarian carcinoma is challenging due to a high morbidity. **Objectives:** To evaluate the clinical course and outcome of elderly patients with advanced stage ovarian carcinoma receiving neoadjuvant chemotherapy (NACT). **Methods:** We conducted a retrospective study of all patients with stage IIIC and IV ovarian carcinoma receiving NACT in one medical center (between 2005 and 2017). The study group criteria included age above 70 years. The control group criteria was younger than 70 years old at diagnosis. Demographics and treatment outcomes were compared between groups. Primary outcomes were progression-free survival (PFS) and overall survival (OS). **Results:** Overall, 105 patients met the inclusion criteria, 71 patients (67.6%) were younger than 70 years and 34 patients (32.4%) older. Rates of interval cytoreduction were significantly higher in younger patients (76.1% vs. 50.0%, $P = 0.01$). Of those who underwent interval cytoreduction, no difference was found in rates of optimal debulking between groups (83.35% vs. 100%, $P = 0.10$). Using a Kaplan-Meier survival analysis, no significant differences were observed between the PFS or OS groups, $P > 0.05$. Among the elderly group alone, patients who underwent interval cytoreduction had significantly longer PFS than those without surgical intervention (0.4 ± 1.7 vs. 19.3 ± 19.4 months, $P = 0.001$). **Conclusions:** Elderly patients with ovarian carcinoma who received NACT undergo less interval cytoreduction than younger patients, with no difference in PFS and OS. However, among the elderly, interval cytoreduction is associated with significantly higher PFS.

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KEY WORDS: elderly, interval cytoreduction, neoadjuvant chemotherapy (NACT), ovarian carcinoma, overall survival

Ovarian carcinoma is associated with poor prognosis as it is usually diagnosed at advanced stage with metastatic disease [1,2]. Neoadjuvant chemotherapy (NACT) followed by interval cytoreduction is the primary treatment in cases with advanced stage disease where primary optimal cytoreduction is unlikely, or when perioperative risk is high due to co-morbidities [3]. The incidence of ovarian cancer increases with age, and elderly

women are more likely to have advanced stage disease at presentation [4]. These patients pose a treatment challenge due to higher operative risks and higher rates of co-morbidities. Previous studies have shown that elderly patients with ovarian carcinoma receive standard treatment (a combination of surgery and chemotherapy) less often than younger patients, even in the absence of co-morbidities [5].

A recent retrospective study showed that elderly patients with advanced stage ovarian carcinoma are treated more often with NACT than primary surgery [6]. Although it might seem safe to offer NACT to elderly patients, this is not supported by randomized clinical trials where mainly younger patients were included, and data are scarce on the outcome of older patients receiving NACT [2,7].

In this study, we evaluated the clinical course and outcome of elderly patients with advanced stage ovarian carcinoma receiving NACT.

PATIENTS AND METHODS

STUDY POPULATION

This retrospective cohort study included all women with advanced stage epithelial ovarian carcinoma (stage IIIC and IV) treated with neoadjuvant chemotherapy (NACT) between January 2005 and June 2017 in one medical center. Medical charts were reviewed by the study personnel. Demographic characteristics, staging, histology, NACT protocol, imaging results prior and post NACT, levels of CA-125 during treatment, surgical outcome, and data regarding recurrence and survival were obtained. We compared outcomes between elderly patients, defined as above 70 years old at diagnosis, and younger patients, defined as younger than 70 years of age at diagnosis.

DEFINITIONS

The primary outcome chosen was survival including progression free survival (PFS), defined as the time from end of adjuvant chemotherapy to first recurrence demonstrated on imaging, and overall survival (OS).

Secondary outcomes included: CA-125 normalization (< 35 U/ml) at the end of NACT, CA-125 percentile decrease during NACT treatment, imaging response before interval cytoreduction, surgical outcome including optimal debulking (< 1 cm

residual disease), optimal debulking with no macroscopic residual disease, and post-adjuvant complete response (defined as normal levels of CA-125 and complete imaging response). Surgical intervention was not performed in cases with progressive disease under NACT treatment or according to patient or physician's preference. The study was approved by the local institutional review board (0492-16-RMC). Informed consent was waived due to the retrospective design of the study.

TREATMENT PROTOCOL

NACT was offered to women with advanced stage ovarian carcinoma who had a low likelihood of achieving optimal debulking in primary cytoreduction or those with a high perioperative risk profile [2]. Prior to starting NACT, histologic or cytologic diagnosis of ovarian, fallopian tube, or primary peritoneal malignancy was confirmed. The standard NACT given was three weekly doses of carboplatin and paclitaxel. Usually, three to four cycles of chemotherapy were administered prior to interval cytoreduction. In patients with significant co-morbidity, carboplatin alone was initiated as a single agent. Following NACT, women were offered interval cytoreduction surgery, which included total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph nodes dissection, and resection of all macroscopic disease when possible. In certain cases of radiologic treatment, complete response following NACT, where high morbidity from surgical intervention was likely, patients were offered follow-up without any surgical intervention.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA).

All data were summarized and displayed as mean \pm standard deviation for all continuous variables, and as number and percentage within each group for categorical variables. Continuous variables were compared using Student's *t*-test and the Mann-Whitney U test. Chi-square and Fisher's exact tests were used for categorical variables, as appropriate. PFS and OS were analyzed using Kaplan-Meier survival analysis. $P \leq 0.05$ was considered statistically significant.

RESULTS

During the study period, 105 patients were treated with NACT for advanced stage ovarian carcinoma. Seventy-one (67.6%) patients were above 70 years of age at diagnosis and 34 patients (32.4%) were younger than 70 years old. Patient characteristics are presented in Table 1. There was no significant difference in stage of disease, levels of CA-125 at diagnosis, and histology between groups. Elderly patients had significantly higher rates of initial treatment with carboplatin compared to younger patients (35.3% vs. 4.2%, $P < 0.001$) [Table 2]. There were no

Table 1. Patient characteristics

Variable	Age < 70 N=71	Age \geq 70 N=34	P value
Age, years	57.8 \pm 8.9	75.5 \pm 4	< 0.001
Stage			
IIIC	58 (81.7%)	27 (79.4%)	0.79
IV	13 (18.3%)	7 (20.6%)	0.79
CA-125 at presentation	1910 \pm 2320	1465 \pm 3473	0.44
Ca-15-3 at presentation	206 \pm 193	131 \pm 95	0.03
Imaging at presentation			
Ascites	62 (87.3%)	25 (73.5%)	0.08
Omental involvement	66 (92.9%)	30 (88.2%)	0.43
Enlarged lymph nodes	24 (33.8%)	8 (23.5%)	0.57
Ovarian mass	46 (64.7%)	27 (82.3%)	0.17
Histology			
Serous	46 (64.8%)	21 (61.7%)	0.26
Endometrioid	3 (4.2%)	1 (2.9%)	1.0
Other	4 (5.6%)	1 (2.9%)	1.0

Continuous variables are presented as mean \pm standard deviation and categorical variables are presented as n (%)

Table 2. Treatment characteristics and outcome

Variable	Age < 70 N=71	Age \geq 70 N=34	P value
Initial treatment carboplatin + paclitaxel	68 (95.8%)	22 (64.7%)	< 0.001
Initial treatment carboplatin only	3 (4.2%)	12 (35.3%)	< 0.001
> 4 cycles of NACT	43 (60.6%)	12 (35.3%)	0.03
CA-125 levels following 1st cycle	1989 \pm 2518	823 \pm 788	0.001
NACT modifications*	20 (28.2%)	11 (32.4%)	0.65
CA-125 normalization post NACT	39 (54.9%)	16 (47.1%)	0.32
CA-125 % decrease	85.8 \pm 34.3	93.2 \pm 8.4	0.08
Post NACT imaging response			0.88
Complete response	20 (28.2%)	8 (23.5%)	
Partial response	38 (53.5%)	14 (41.2%)	
Stable disease	6 (8.5%)	2 (5.8%)	
Progressive disease	7 (9.8%)	10 (29.4%)	
Interval cytoreduction	54 (76.1%)	17 (50.0%)	0.01
Recurrence	37 (52.1%)	14 (41.2%)	1.0
Progression-free survival, months	14.8 \pm 21.7	10.2 \pm 16.8	0.28

Continuous variables are presented as mean \pm standard deviation and categorical variables are presented as n (%)

*NACT modifications included delay in treatment and dose reduction
NACT = neoadjuvant chemotherapy

differences in post NACT CA-125 normalization between older and younger patients (47.1% vs. 54.9%, $P = 0.32$).

The rates of interval cytoreduction were significantly lower in elderly patients compared to the younger group (50.0% vs. 76.1%, $P = 0.01$). Treatment with chemotherapy alone, without any surgical intervention, was administered to 17 elderly patients (50%) vs. 17 younger patients (23.9%). This treatment was mostly used when the disease was stable or progressive following NACT.

All elderly patients who underwent interval cytoreduction achieved optimal debulking. There were no differences in

rates of optimal debulking between old and younger patients (100% vs. 83.35%, $P = 0.10$) who underwent interval cytoreduction. In addition, in rates of post-adjuvant chemotherapy, complete responses were comparable between younger and older patients (70.4% vs. 82.4%, $P = 0.53$). PFS was comparable between elderly and younger patients (10.2 ± 16.8 vs. 14.8 ± 21.7 months, $P = 0.28$). Using Kaplan-Meier survival analysis, no differences were observed in PFS or OS between groups [Figures 1,2].

We compared the outcome between elderly patients who underwent interval cytoreduction ($n=17$) and elderly patients without any surgical intervention ($n=17$). Patients who underwent interval cytoreduction were significantly younger (73.7 ± 3.4 years vs. 77.3 ± 3.9 , $P = 0.008$). The younger patients had longer PFS than elderly patients without surgical intervention (0.4 ± 1.7 vs. 19.3 ± 19.4 months, $P = 0.001$). Although not statistically

significant, patients who had surgery were found to have longer OS (22.7 ± 18.1 vs. 36.9 ± 24.4 , $P = 0.67$).

DISCUSSION

We evaluated the clinical course and outcome of elderly patients with advanced stage ovarian carcinoma initially treated with neoadjuvant chemotherapy. In our cohort, elderly patients were not treated as often as younger patients with standard protocol (combination platinum-based and paclitaxel chemotherapy followed by interval cytoreduction). These results are in concordance with previous studies [5,8-10]. A study conducted by Fourcadier et al. [8] found that elderly patients with ovarian carcinoma are less often treated than younger counterparts. They reported that 21.5% of older patients received no treatment at all compared to 4% in the younger group. While this difference is clinically significant, the reasons for avoiding treatment were not detailed. Maas and colleagues [5] found that elderly patients (above 70 years of age) with stage II or III ovarian cancer often did not receive the recommended treatment of surgery and chemotherapy. In the study, only 45% of elderly patients received standard combination treatment. Nevertheless, the reason behind lower rates of surgical intervention was not explained.

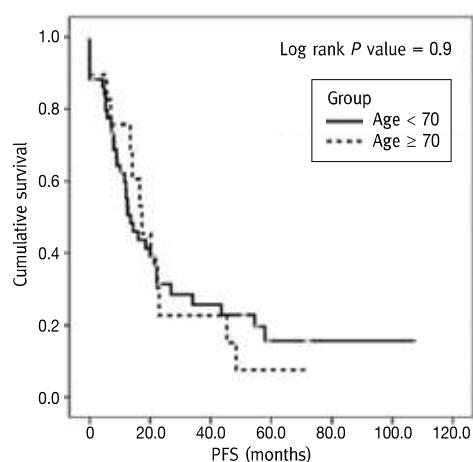
Although it did not reach statistical significance, elderly patients had lower rates of complete response and higher rates of progressive disease following NACT compared to younger patients. This finding could be explained by the lower rates of combination chemotherapy treatment in this group.

In our study, 50% of elderly patients received chemotherapy alone. In 14 out of 17 elderly patients who received chemotherapy alone, surgery was omitted due to stable or progressive disease. In these cases, interval cytoreduction is rarely performed due to the expected lower rates of complete surgical debulking [11].

Another reason to avoid standard treatment in older patients is the higher rates of co-morbidities and less favorable performance status in this population [12]. Nevertheless, a recent study has shown that even in the absence of co-morbidities, standard treatment was less prescribed for elderly patients. In addition, co-morbidities did not seem to have any impact on survival outcome [6]. Data regarding the existence of co-morbidities is lacking in our study; therefore, it is hard to draw conclusions on its impact on treatment decisions and survival in our cohort.

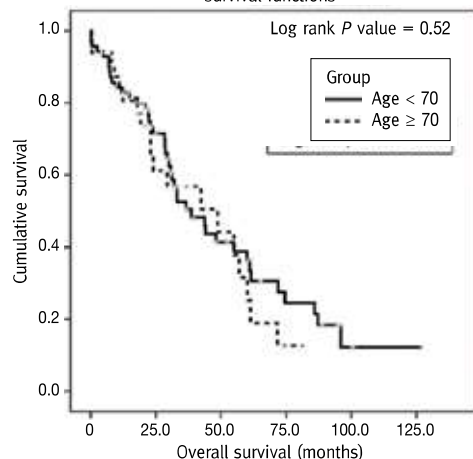
Although there were differences in rates of surgical intervention and standard chemotherapy treatment between elderly and younger patients, we did not find any difference in PFS and OS between the groups. Small numbers in the study groups might have influenced the results, and perhaps with larger cohorts the difference in survival outcome would have reached statistical significance. However, the standard treatment of surgical intervention and combination chemotherapy seems to result in minor improved survival in cases with stage IIIC and IV ovarian cancer, where extremely poor prognosis is expected.

Figure 1. Kaplan-Meier curve for progression free-survival



PFS = progression free survival

Figure 2. Kaplan-Meier curve for overall survival survival functions



While choosing the appropriate treatment tailored for each patient can be challenging, especially when it is not according to standard protocols, this approach does not have any adverse effect on survival. Petignat and co-authors [13] found that elderly patients had decreased 5-year survival and ovarian cancer mortality even after adjusting for stage of disease, tumor characteristics, and treatment. Another study, which included patients with stage II and III ovarian carcinoma, found that 3-year survival was significantly worse for elderly patients compared to young (22% vs. 51%) [5]. Since patients elected for NACT are already at higher risk for poor prognosis due to advanced disease [14], it may be that advanced age at diagnosis has a minor impact on survival.

No significant difference in optimal cytoreduction between groups was observed and rates of optimal debulking in the elderly group were 100%. This result is probably secondary to meticulous selection of patients eligible for surgery. Patients who elected for interval cytoreduction in the elderly group had significantly longer PFS than patients treated with chemotherapy only, with no statistical difference in OS. This finding is challenging to explain since many factors could influence this result. The reason for offering or opposing interval cytoreduction could directly impact PFS. One reason for choosing to avoid interval cytoreduction is advanced age. As noted earlier, in the elderly group, patients who opted for interval cytoreduction were significantly younger. Another reason could be due to progressive disease, which directly impacts PFS. Notwithstanding, as previously reported by Eitan and colleagues [15], patients with ovarian cancer treated with chemotherapy only, without any surgical intervention, responded only partially to first line chemotherapy and had a short disease-free interval.

As for OS, patients who underwent surgery had 14 months longer OS. Although this result was not statistically significant, it is clinically important and might have reached statistical significance with a larger cohort. Since we had a small cohort in the elderly group, we did not perform multivariate regression analysis on these results. However, the difference in PFS was significant using the Student's *t*-test and the non-parametric Mann-Whitney U test. Although OS was not significantly different between groups, it was almost double in elderly patients undergoing interval cytoreduction. The small numbers in each group make it underpowered for evaluating overall survival, but this difference is clinically important and should be further studied in prospective trials.

To the best of our knowledge, this is the first study to evaluate surgical and clinical outcome in this specific cohort of elderly patients. Previous studies have included patients with different stages including stage II, while we solely examined advanced stage (stage IIIC and IV) elected for NACT.

LIMITATIONS

The main limitation lies in the retrospective design. Data are partly missing, such as co-morbidities and performance status of patients, which could have influenced the results.

STRENGTHS

The strength of our study is that it included a defined sub-population of patients with advanced stage ovarian carcinoma chosen for NACT treatment at a single gynecologic oncology unit with standard protocols.

CONCLUSIONS

Older patients with advanced stage ovarian carcinoma treated with NACT do not receive standard treatment of both chemotherapy and surgery as often as do younger patients, but this has no significant impact on PFS and OS. Nevertheless, among the older patients, interval cytoreduction is associated with higher PFS.

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