GYNECOLOGY

Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer

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OBJECTIVE: The objective of the study was to analyze in a large series of unresectable advanced ovarian cancer (AOC) patients the prognostic role of pathological response to neoadjuvant chemotherapy (NACT).

STUDY DESIGN: We retrospectively evaluated 322 unresectable AOC patients treated with NACT followed by interval debulking surgery (IDS). Pathological response was classified as follows: complete (cPR) in the absence of residual disease, microscopic (microPR) in the presence of microscopic tumor foci (maximum diameter $\leq$3 mm), and macroscopic (macroPR) when macroscopic residual disease was detected.

RESULTS: cPR was observed in 21 (6.5%), microPR in 104 (32.3%), and macroPR in 197 (61.2%) patients. No differences were observed in the distribution of baseline clinicopathological characteristics between the groups. Median progression-free survival was 36 months in cPR, 16 in microPR, and 13 in macroPR ($P = .001$). Median overall survival was 72 months in cPR, 38 in microPR, and 29 in macroPR ($P = .018$). The survival differences between microPR and macroPR patients were not confirmed when the analysis included only cases resected to no gross residual disease at IDS. cPR retained the independent prognostic role in the multivariate analysis. International Federation of Gynecology and Obstetrics stage IV was the only negative independent predictor of cPR ($\chi^2 = 5.362$, $P = .021$).

CONCLUSION: cPR is an uncommon event in AOC patients receiving NACT and is associated with a longer progression-free survival and overall survival compared with women showing no cPR, even in patients receiving IDS with no gross residual disease. The proposed classification of pathological response may serve in the next future as an easily assessable and highly valuable prognostic tool in this clinical setting.

Key words: advanced ovarian cancer, complete pathological response, interval debulking surgery, neoadjuvant chemotherapy, prognosis

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Consolidated evidences from retrospective series demonstrated that residual tumor at first surgery represents the most powerful predictor of clinical outcome in advanced ovarian cancer (AOC).[1-6] Therefore, extensive primary debulking surgery (PDS) is considered the cornerstone in the management of women even with late-stage disease. On the other hand, novel evidences suggest that neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) may provide similar survival benefit, with fewer surgical morbidities.[7,8] In this context, it is urgently needed to develop novel prognostic tools able to identify which patients benefit most from PDS or NACT followed by IDS.

It is well known that the vast majority of women with AOC respond to platinum-based NACT, experiencing a tumor shrinkage, which allows the disease removal, at the time of IDS. However, the magnitude of response to NACT is highly variable, thus identifying specific cohorts of patients, potentially characterized by different clinical outcome.[9,10] In particular, it has been documented that NACT can determine the complete disappearance of all the neoplastic lesions in a small proportion of women with a highly chemosensitive disease.[10] Therefore, it can be hypothesized that this very selected cohort of women may represent the clinical setting that gains the highest benefit from the NACT-based approach. However, very

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few data are currently available about the prognostic role of complete pathologic response (cPR) to NACT. Furthermore, the early identification of these women would be highly valuable, in order to properly tailor the upfront management.

For these reasons, here we investigate the prognostic role of an easily assessable classification of pathologic response to NACT, emphasizing the relevant favorable impact of cPR in terms of overall and progression-free survival. Furthermore, we investigated the potential clinicopathological predictors of cPR.

TABLE 1
Distribution of patients' clinicopathological characteristics and treatment details in the overall population and according to pathological response to NACT

Characteristics	All cases, n (%)	cPR, n (%)	microPR, n (%)	macroPR, n (%)	*P* value[a]
All	322	21 (6.4)	104 (31.5)	197 (59.7)	
Age, y					
≤65	226 (70.2)	16 (76.2)	75 (72.1)	135 (68.5)	
>65	96 (29.8)	5 (23.8)	29 (27.9)	62 (31.5)	.688
FIGO stage					
IIIC	251 (77.7)	18 (85.7)	77 (74.0)	155 (78.7)	
IV	72 (22.3)	3 (14.3)	27 (26.0)	42 (21.3)	.430
Carcinomatosis at diagnosis					
No	37 (11.5)	5 (23.8)	12 (11.5)	20 (10.2)	
Yes	285 (88.5)	16 (76.2)	92 (88.5)	177 (89.8)	.175
Ascites					
No	75 (23.3)	6 (28.6)	25 (24.0)	44 (22.3)	
Yes	247 (76.7)	15 (71.4)	79 (76.0)	153 (77.7)	.794
Tumor histotype					
Serous	264 (82.0)	15 (71.4)	90 (86.5)	159 (80.7)	
Others	58 (18.0)	6 (28.6)	14 (13.5)	38 (19.3)	.196
Tumor grade					
G1	9 (2.7)	1 (4.8)	0 (0.0)	8 (4.1)	
G2-3	313 (97.3)	20 (95.2)	104 (100.0)	189 (95.9)	.108
CA-125, IU/mL[b]					
Median serum levels (range)	548 (9—9.999)	404 (9—9.999)	888 (9—9.999)	516 (4—9.999)	.328
First-line chemotherapy regimen					
Carboplatin alone	51 (15.8)	4 (19.0)	11 (10.6)	36 (18.3)	
Carboplatin/paclitaxel or PLD	271 (84.2)	17 (81.0)	93 (89.4)	161 (81.7)	.202
NACT cycles					
3-4	216 (82.3)	16 (76.2)	78 (75.0)	122 (61.9)	
6	57 (17.7)	5 (23.8)	26 (25.0)	75 (38.1)	.047
Clinical response to NACT					
Complete	41 (15.8)	15 (71.4)	10 (9.6)	26 (13.2)	
Partial/Stable disease	271 (84.2)	6 (28.6)	94 (90.4)	171 (86.8)	.001

cPR, complete pathological response; *FIGO*, International Federation of Gynecology and Obstetrics; *macroPR*, macroscopic pathological response; *microPR*, microscopic pathological response; *NACT*, neoadjuvant chemotherapy; *PLD*, pegylated liposomal doxorubicin.

[a] Calculated by χ^2 test. Patients with progressive disease at clinical revaluation, not receiving surgery after NACT, were excluded from the analysis; [b] Calculated by a Kruskal-Wallis nonparametric test.

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