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Dose-dense Neoadjuvant Chemotherapy With Paclitaxel and Carboplatin in Cervical Cancer: Efficacy on Pathological Response

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Abstract. *Background/Aim: The role of neoadjuvant chemotherapy (NACT) is under investigation in locally advanced cervical cancer (LACC). Patients and Methods: A total of 49 patients with FIGO stage IB1-IIB cervical cancer who underwent two different regimens of weekly dose-dense NACT were included. The objective was to evaluate clinical/pathological response and toxicity profile. Results: A clinical complete response and partial response were obtained in 43 patients with a clinical overall response rate of 88%. Among the 42 surgically treated patients, 7 (17%) and 35 (83%) achieved a pathological overall optimal response and a suboptimal pathological response, respectively. G3-G4 neutropenia occurred in 16% of patients, whereas no cases of G3 thrombocytopenia, G3 anemia and febrile neutropenia were observed. Conclusion: Dose-dense NACT is safe, has acceptable toxicity, and obtains good clinical response, but is less effective in terms of pathological overall optimal response rates compared to other regimens.*

Since 1999, the National Cancer Institute Alert has strongly supported the use of concurrent radiochemotherapy (CCRT) as standard treatment of locally advanced cervical cancer (1). Recent meta-analysis of 13 randomized trials has confirmed that CCRT significantly improves 5-year overall disease-free survival (DFS) [hazard ratio (HR)=0.78, 95% confidence interval (CI)=0.70-0.87], 5-year loco-regional disease-free survival (HR=0.76, 95%CI=0.68-0.86), 5-year metastases-free survival (HR0.81, 95%CI=0.72-0.91) and 5-year overall survival (OS) (HR=0.81, 95%CI=0.71-0.91) compared with radiotherapy alone (2).

Neoadjuvant chemotherapy (NACT) followed by radical surgery could represent a valid alternative to CCRT in patients with stage Ib-II. Two recent randomized trials have compared NACT plus surgery *versus* CCRT, and both showed similar results, with an improved DFS in the CCRT arm compared to the chemosurgical arm and no differences in OS (3, 4). The combination of paclitaxel, cisplatin and ifosfamide (TIP regimen) every 3-weeks is probably the best regimen with regard to optimal pathological response rate, but this combination is not accepted worldwide due to its toxicity (5, 6).

Considering that the combination of short-interval chemotherapy (<14 days) and higher dosages of cisplatin (>25 mg/mq/week) are associated with better oncological outcomes, some authors have investigated the activity of weekly dose-dense platinum/paclitaxel NACT followed by either radiotherapy or surgery (7, 8). Moreover, it has been shown that the combination of carboplatin + paclitaxel has the same efficacy and a better toxicity profile compared to cisplatin + paclitaxel in recurrent cervical cancer (9).
In this study, we retrospectively analyzed the clinical and pathological response rates as well as the pattern of recurrence in patients with cervical cancer who underwent NACT with weekly dose-dense carboplatin/paclitaxel followed by surgery in two gynecological Italian centers.

Patients and Methods

The study was approved by the appropriate Institutional Review Board (IRB) and written informed consent was obtained from all subjects. Data were extracted from two Italian oncological reference centers database (San Gerardo Hospital, University of Milano-Bicocca in Monza and Department of Gynecology and Obstetrics of University of Pisa). The patients were scheduled for dose-dense weekly carboplatin/paclitaxel-based NACT followed by surgery after an exhaustive discussion within a Multidisciplinary Committee.

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The clinical staging was performed according to the system adopted by 2009 FIGO. Patients with stage IB1-IIB tumors were enrolled (FIGO staging 2009). The included patients with stage IB1 disease wishing to preserve the child-bearing potential had previously undergone laparoscopic pelvic lymphadenectomy or bilateral sentinel node biopsy, with histologically proven negative nodes.
Pre-treatment evaluation included medical history, physical examination, blood tests analysis, colposcopy, pelvic ultrasound, chest-X-ray, abdomino-pelvic MRI, chest-X-ray (and/or PET scan). Inclusion criteria were: histological diagnosis of cervical invasive squamous cell carcinoma or adenocarcinoma cervical cancer (on cervical biopsy or cervical conization), performance status 0-1, adequate bone marrow reserve and renal function, normal liver and cardiac function.

During this period two different regimens of NACT were used: 1) Carboplatin area under curve (AUC) 2 plus paclitaxel 80 mg/m^2 for 6 consecutive weeks (regimen A). 2) Carboplatin AUC 2.7 plus paclitaxel 60 mg/m^2 for 9 consecutive weeks (regimen B).

The schedule was chosen according to Center's policy at the time of treatment, and it was not based on stage at diagnosis. Premedication was administered according to standard institution policy. Blood tests were repeated before each cycle; treatment was administered if absolute granulocyte count was ≥1000/μl and platelets count was ≥100,000/μl.

In case of toxicity, the treatment was to be delayed from week to week until minimum hematological parameters were met. Toxic effects were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (10). Clinical response was determined according to RECIST criteria, version 1.1 (11). Clinical and abdomino-pelvic MRI were performed after NACT and the patients who were operable, underwent radical surgery (radical hysterectomy plus pelvic lymphadenectomy or cone) within 3 or 6 weeks.

The pathological responses of the patients who underwent surgery were assessed as follows: Complete response (pCR) was defined as the complete disappearance of the tumor in the cervix with negative nodes; optimal partial response (pPR1) was defined as persistent residual disease with <3 mm stromal invasion including in situ carcinoma on the surgical specimen and negative nodes; and suboptimal partial response consisted of persistent residual disease with >3 mm stromal invasion on the surgical specimen and negative nodes or positive nodes (regardless of response of primary tumor) or positive parametria and/or surgical margins (pPR2). Pathological overall optimal response (pOR) rate was the sum of pCR and pPR1.

Post-operative management was discussed by a multidisciplinary team and the adjuvant therapy was administered on the basis of histological findings on surgical specimen; the considered variables were the types of pathological response, deep stroma infiltration, lymph vascular space invasion (LVSI) and millimeter of free margins (thickness of uninvolved cervical stroma).

Results

From June 2015 to September 2020 a total of 49 patients were retrospectively reviewed. Patient characteristics and NACT details are shown in Table I. Fifty-five percent (27/49) of patients had stage IB1/IIA1 and IB2/IIA2 and, among them, 7 had positive pelvic lymph node. The squamous histotype was the most represented with 61% of cases (30/49). Seventy-five percent of patients completed at least six cycles of NACT and six patients (6/49, 12%) suspended the chemotherapy (five after delays in treatment, 1 upfront). The treatment was delayed in 6 patients for a total of 7 one-week delays. Two of this six patients completed the cycles and four stopped the chemotherapy treatment due to toxicity (they completed three, five, seven and seven cycles, respectively).

Table I. *Characteristics of the whole population.*

Population	Total 49
Age	
Median	44,5
Range	25-70
Figo Stage 2009	
IB1	9/49 (18%) (3 N+)
IIA1	2/49 (4%)
IB2/IIA2	16/49 (33%) (4 N+)
IIB	22/49 (45%) (9 N+)
Histology	
Squamous cell	30/49 (61%)
Adenocarcinoma	15/49 (31%)
Adenosquamous	2/49 (4%)
others	2/49 (4%)
N° cycles	
3	1
4	/
5	2
6	37
7	3
9	6
N° delays	7 in 6 patients
Suspension	6

Toxicity data were as follows: 16% of patients (8/49) experienced neutropenia G3-G4 whereas no cases of trombocytopenia G3, anemia G3 and febrile neutropenia were observed. Neurological toxicity never exceeded grade 1-2; alopecia grade 2 was observed in the majority of patients (85%) irrespective of the schedule. A clinical complete response and partial response were obtained by 7 and 36 patients, respectively, with a clinical overall response rate of 88% (Table II). After NACT, surgery was not performed in 7 patients: four of these seven patients had a unsatisfactory clinical response whereas three patients, after an exhaustive discussion within a Multidisciplinary Team, proceeded to CCRT due to their morbidity and/or the consequent high surgical risk. With regard to pathological response, the pOR was achieved by 7 patients of 42 (17%) submitted to surgery whereas 83% of patients (35/42) had a

Table II. *Clinical response*.

	IB1 9	IIA1 2	IB2/IIA2 16	IIB 22	Total 49
CR	3/9 (33%)	/	/	4/22 (18%)	7/49(14%)
PR	2/9 (22%)	2/2 (100%)	16/16 (100%)	16/22 (73%)	36/49 (74%)
SD	4/9 (45%)	/	/	1/22 (4.5%)	5/49 (10%)
PD	/	/	/	1/22 (4.5%)	1/49 (2%)

CR: Complete response; PR: partial response; SD: stable disease; PD: progression disease.

pPR2. pOR was observed in 44%, 15% and 6% of cases at stages IB1, IB2/IIA2 and IIB, respectively. After NACT, 38 patients underwent radical hysterectomy with pelvic lymphadenectomy and 4 patients underwent conization. Pathological response by different regimens is shown in Table III: 11% and 28% of patients obtained an pOR in regimen A and B, respectively. After surgery, 14 patients (33%) did not receive further treatments (5 patients with pCR, 2 patients with pPR1 and 7 patients with pPR2). Among 35 patients with pPR2, 26 (74%) underwent adjuvant treatment after surgery (Table IV). Two patients with pPR2 waiting for adjuvant radiotherapy after surgery had an early progression of disease and therefore received palliative chemotherapy. At the time of the present analysis, 5 of the 42 surgically treated patients (12%) experienced recurrence after a median time of 12 months. All the five patients with recurrence had pPR2 on surgical specimen and 4 of these had received adjuvant treatment. The sites of recurrence were central pelvic in 1 patient (20%), both central pelvic and nodal in 2 patients (40%), both nodal and distant in one case (20%) and distant in only one patient (20%).

Table III. *Pathological response by Dose dense regimen*.

	Regimen A	Regimen B	Total
	28	14	42
CR	2/28 (7%)	3/14 (21%)	5/42 (12%)
PR1	1/28 (4%)	1/14 (7%)	2/42 (5%)
PR2	25/28 (89%)	10/14 (72%)	35/42 (83%)

Regimen A: Carboplatin area under curve (AUC) 2 plus paclitaxel 80 mg/m^2 for 6 consecutive weeks; Regimen B: Carboplatin AUC 2.7 plus paclitaxel 60 mg/m^2 for 9 consecutive weeks; CR: complete response; PR1: optimal partial response; PR2: sub-optimal partial response.

Table IV. *Types of adjuvant treatment*.

	Regimen A	Regimen B	Total
CHT	2	3	5
CCRT	13	3	16
RT+/– BRT	4	/	4
No therapy	8	6	14
Hysterectomy after cone	/	1	1
Progression disease	1	1	2

CHT: Chemotherapy; RCT: concurrent radiochemotherapy; RT: radiotherapy; BRT: brachytherapy.

Discussion

CCRT is the standard of care for locally advanced cervical cancer since 1999. NACT followed by radical surgery is an interesting alternative therapeutic option, especially in young women, able to avoid the high potential morbidity of CCRT like the long-term incidence of vaginal, bowel and bladder toxicity and the worsening of sexual life (12). The two randomized trials comparing NACT followed by radical hysterectomy *versus* CCRT have shown improved DFS in the patients treated with CCRT with no differences in OS (3, 4). Despite these trials had a similar study design, they have several critical points as different primary endpoints (OS or DFS), presence/absence of stage IIA, difference in NACT regimen and histotype.

In Gupta's trial three cycles of paclitaxel 175 mg/m^2 and carboplatin AUC 5-6 every 3 weeks were administered whereas in the study of Kenter *et al*. different cisplatin–based regimens were used: cisplatin alone (46%), cisplatin + paclitaxel (20%), cisplatin + paclitaxel + ifosfamide (TIP regimen) (19%), cisplatin + others agents (15%). The EORTC trial has reported a pOR rate of 38% in the whole series and of 45% in the group of patients who received the TIP regimen (4). No data on pathological response were available in the study of Gupta *et al*. (3). The achievement of a pOR is a strong predictor of survival as confirmed by our previous series (13). The TIP regimen has been found to obtain higher response rate compared to ifosfamide + cisplatin and compared to regimen with cisplatin+ paclitaxel (5, 6). In the studies of Buda and Lissoni *et al*. (5, 6) the TIP regimen had obtained similar results in terms of pOR rates,

Table V. *Dose- dense data by international literature.*

Authors	Stage	Histology	CT regimen	Pts	Overall clinical response rate	Optimal pathological response
Mori	Ib2-IIb	SCC, AD-ADS	CBDCA AUC2 q7 + PTX 60 mg/m^2 for 6 cycles	30	86.7%	NA
Benedetti	IIa-IIIb	SCC	CDDP 50 mg/m^2 q 10+ PTX 60 mg/m^2 for 5 cycles	22	52.6%	31.6%
Tanioka	Ib2-IIb	SCC, AD-ADS	cCDDP 75 mg/m^2 d1-PTX 80 mg/m^2 d 1, 8, 15 q21 for 3 cycles	51	94.0%	28% (pCR)
Gadducci	Ib1-IIb	SCC,AD	CBDCA AUC2 q7+PTX 80 mg/m^2 for 6 cycles	17	82.3%	17.6%
Salihi	Ib1-IIb	SCC, AD-ADS	CBDCA AUC2.7 q7+PTX 60 mg/m^2 for 6 and 9 cycles	36	88.9%	50%
Ferrandina	Ib2-IIIb	SCC,AD	CBDCA AUC2 +PTX 80 mg/m^2 for 6 cycles	36	75%	16.1%

SCC: Squamous cell cervical carcinoma; AD: adenocarcinoma; ADS: adenosquamous; CBDCA: carboplatin; PTX: paclitaxel; CDDP: cisplatin; AUC: area under curve.

ranging from 43% to 48%, associated with high toxicity. In the SNAP01 study, there were four (2%) deaths related to toxicity: three patients received an ifosfamide+ cisplatin schedule and one patient received the TIP regimen. In the SNAP02, grade 3 and 4 neutropenia was observed in 55 patients (76.4%), grade 3-4 thrombocytopenia in 17 patients (23.3%) and anemia grade 3 and 4 in 24 patients (32.8%); no toxic deaths had been recorded.

The use of weekly schedule is expected to overcome tumor resistance compared to more prolonged schedule, associated with a faster admission and hopefully lesser toxicity. Some authors have investigated the feasibility and the clinical activity of a dose–dense platinum/paclitaxel based NACT, taking into consideration its low toxicity. In our study, we experienced a very favorable toxicity profile with only 16% of patients with neutropenia G3-G4, no cases of trombocytopenia G3-G4, anemia G3-G4 and febrile neutropenia. In the prospective phase II study of Ferrandina *et al*. (14), three patients (8.3 %) reported anemia, two patients (5.5%) reported neutropenia and there were no cases of thrombocytopenia; Salihi *et al*. (15) have reported similar rates of anemia and thrombocytopenia, associated with higher incidence of G3-G4 neutropenia (56%).

As far as pathological and clinical response is concerned, few data are available in the literature about the activity of a dose–dense platinum/paclitaxel based NACT followed by radical surgery in locally advanced cervical cancer. Mori *et al*. (16) have reported that NACT with weekly paclitaxel (60 mg/m^2) + carboplatin (AUC2) for six cycles obtained a clinical overall response in 86.7% of 30 patients. Twenty-eight patients underwent radical hysterectomy, followed by adjuvant radiotherapy in 13 cases with high–risk factors. No data were available about pathological response. In the study of Benedetti *et al*. (17), 20 of 22 the patients (91.9%) completed all the five planned cycles of paclitaxel (60 mg/m^2) + cisplatin (60 mg/m^2) every 10 days, 19 (86.4%) underwent radical surgery, and 6 of them (31.6%) received adjuvant radiotherapy or CCRT. Clinical overall response rate was 52.6% and pOR rate was 31.6%.

In the present series, a clinical overall response was observed in 88% of 49 patients, and a pOR rate was achieved in 17% of 42 patients who underwent surgery. pOR rate was higher in the patients who received–weekly carboplatin (AUC 2.7) + paclitaxel (60 mg/m^2) for 9 cycles compared to those who received weekly carboplatin (AUC 2) + paclitaxel (80 mg/m^2) for 6 cycles (28% *versus* 11%), but the limited number of patients does not allow to draw any firm conclusion. Our data are aligned with prior studies using the combination of weekly paclitaxel 80 mg/m^2 plus carboplatin (AUC 2) for 6 cycles as NACT. Gadducci *et al*. (18) have reported a pOR in 17.6% and a pPR2 in 41.2% of the surgical specimens, whereas Ferrandina *et al*. (14) reported a pOR rate of 16% (3.2% of patients with complete response and 12.9% with microscopic disease). In the phase II study of Salihi *et al*. (15), 36 patients received the modified scheme of dose-dense NACT with the combination of weekly paclitaxel 60 mg/m^2 + carboplatin AUC 2.7 for 9 cycles. Nine patients were stage IB1 (25%), seven were stage IB2(19.4%), three with stage IIA and 17 patients were stage IIB (47.2%). Eleven and 21 patients achieved a complete and partial clinical response, respectively, with a clinical overall response of 89%. Twenty-one patients (58%) underwent a radical hysterectomy and nine patients

(25%) underwent a conization, and 50% of the surgically treated patients achieved a pOR. Nevertheless, we have to remark that 25% of patients were in stage IB1 and if we excluded the patients in this stage, the percentage of pOR decreased to 33%. These data are worse than those reported in the literature concerning the use of TIP. Table V shows the experience of the dose-dense regimens by international literature. Even considering the limitations of the retrospective analysis and single-center experience, Buda *et al*. (13) have reported a pOR rate of 51.6% in the whole population; by stage, pOR rate was 35.8%, 52.6%, 30.8% and 15.1% for cases at stage IB2, IIa, IIb and III/IV, respectively. The achievement of a pOR was a strong predictor of survival and should be used to obtain information about the efficacy of a new treatment. The dose-dense carboplatin/paclitaxel-based regimen NACT is safe, has acceptable toxicity, obtains good clinical response rates but it is less effective in terms of pOR rates compared with TIP. A randomized phase III trial that enrolled 253 patients with metastatic or recurrent cervical cancer, found that paclitaxel+carboplatin every 3 weeks is not inferior to paclitaxel+cisplatin in terms of OS. In addition, among the patients who had not received prior cisplatin, median OS was shorter in the paclitaxel/carboplatin group (13.0 months; 95%CI=10.0-20.4 months) than in the paclitaxel/cisplatin group (23.2 months; 95%CI=17.4-27.4 months; HR=1.571; 95%CI=1.062-2.324) (8). Considering that the patients with primary cervical cancer scheduled for NACT followed by surgery are chemo-naive, the use of cisplatin-based regimen rather than carboplatin–based regimen should be investigated in future dose-dense trials. To date, despite the publication of two randomized trials, many issues are debated with regards to the best treatment between NACT followed by surgery *versus* CCRT for patients with locally advanced cervical cancer. In the patients already scheduled for definitive CCRT, the dose-dense NACT seems to be feasible with acceptable toxicity, and does not compromise subsequent CCRT (19). Furthermore, the proportion of patients who achieved complete/partial clinical response increased at the end of full treatment (NACT followed by CCRT) (19). The results of the ongoing NCT01566240 trial comparing dose–dense carboplatin + paclitaxel-based NACT followed by CCRT *versus* CCRT alone in patients with locally advanced cervical cancer are not yet available (INTERLACE study). Conversely, the choice of the NACT regimen prior to surgery should be based on the regimen that ensures the higher chance of pOR, since this represents an independent prognostic factor for survival.

The EORTC study showed better 5-year DFS in the CCRT arm in the whole population but better results for NACT followed by surgery in young women with disease stage Ib2. Similarly, in the subgroup analyses of Gupta's trial, the detrimental effect of NACT plus surgery on DFS was even greater in patients with stage IIb disease (67.2% *versus* 79.3%, HR=1.90; 95%CI=1.25-2.89; p=0.003), whereas no significant DFS difference was observed between the two arms in patients with stage Ib2 or IIa disease.

In conclusion, NACT plus radical surgery could be a valid alternative to CCRT, especially in young patients with stage IB2-IIa disease and negative node at baseline diagnostic imaging. In our opinion, the critical issues regarding future randomized studies are: 1) carboplatin vs. cisplatin in chemo-naive patients with weekly schedule (9 cycles) and 2) the use of TIP (3 cycles) *versus* weekly paclitaxel + cisplatin (9 cycles) in patients judged amenable to surgery in case of good clinical response.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Study concepts: G.D.M., A.G., A.A.L; Recruitment and quality control of data: M.L.D.M, D.F., G.D.M., S.C.; Data analysis and interpretation: A.G., F.L., G.D.M., A.A.L; writing: G.D.M, A.A.L review: A.G, F.L; editing: All Authors.

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