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ORIGINAL ARTICLE

Dose-dense paclitaxel/carboplatin as neo-adjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer: a prospective phase II study

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Abstract

Purpose The role of dose-dense schedules in the neo-adjuvant treatment (NACT) of locally advanced cervical cancer (LACC) has been reported. This phase II study investigated activity of dose-dense paclitaxel/platinum before radical surgery (RS) in LACC patients.

Methods The primary end-point was the rate of optimal pathological response (OPR: pathological complete/microscopic response). NACT (paclitaxel: 80 mg/m^2) and carboplatin (AUC 2) were administered for 6 weeks. Overall response rate (ORR) to NACT was assessed by the RECIST criteria. Patients amenable to surgery were triaged to RS. The null hypothesis was that the OPR rate would improve from 30.0 to 45.0% (α error: 0.05, β error: 0.2). The regimen would be considered active if > 25 OPRs were found.

Results 36 patients were enrolled; 19 patients were stage IIB (52.8%) and 16 (44.4%) patients had pelvic lymph-node involvement at imaging. All patients completed neo-adjuvant chemotherapy; ORR was of 75.0%. RS was performed in 29 (93.5%) patients. Since the OPR was 16.1%, we evaluated the real chances to achieve the number of OPR required by the Simon design and decided to close the study. Grade 3/4 hematological toxicity occurred in 5 patients; surgical morbidity occurred in 14 patients. The 2-year PFS rate was 69.0%.

Conclusion Dose-dense neo-adjuvant paclitaxel/carboplatin is feasible and safe in LACC patients; however, failure to achieve the primary end-point has to be recognized. Given the heterogeneity of the available studies, robust data from an adequately sized prospective study focused on more homogeneous series are required.

Keywords Locally advanced cervical cancer · Neo-adjuvant chemotherapy · Dose density · Radical hysterectomy · Personalized medicine

Introduction

Since 1999, exclusive chemoradiation (CT/RT) has been representing the standard treatment for locally advanced cervical cancer (LACC) patients, with absolute 5-year disease-free survival (DFS) and overall survival (OS) benefit of 8% and 6% compared to radiotherapy, respectively [1, 2]. Moreover, recent data have confirmed the superiority of exclusive CT/RT versus radiotherapy in the subset of stage IIIB patients [3].

However, neo-adjuvant chemotherapy (NACT) followed by radical surgery (RS), which has been employed for decades for the treatment of LACC patients, still remains a frequently adopted therapeutic approach in clinical practice [4–8]. Reasons supporting this strategy are mainly

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represented by the demonstrated activity of NACT in terms of tumor volume reduction, increase of operability rate, as well as control of potential micrometastatic disease [4–8]; in addition, adoption of NACT plus RS is also employed in case of unavailability of radiotherapy units/equipments [9].

While still waiting for the results of the EORTC55994 phase III trial, which compared NACT plus surgery versus CT/RT in stage IB2-IIB patients (http://www.clinicaltrials.gov), very recent results obtained in the same clinical setting have reported improved DFS in CT/RT treated patients compared to those triaged to NACT plus RS, but no difference in terms of OS [10].

Paclitaxel/cisplatin combination administered every 3 weeks is usually considered the best regimen in uterine cervical cancer [11]; however, the recent lines of evidence from a phase III study support the adoption of carboplatin instead of cisplatin, given its equivalent efficacy in face of a better toxicity profile [12].

In addition, publication of some preclinical and clinical evidences supporting the theoretical concept that increased dose density would be more effective and less toxic that dose escalation [13–16] has fuelled the efforts to evaluate increased dose density for either paclitaxel or platinum in different clinical settings of cervical cancer patients [17–24] as well as in combination with CT/RT [25–27].

Here, we report the results of a phase II, non-randomized study aimed at assessing the activity of neo-adjuvant platinum/paclitaxel-based dose-dense chemotherapy followed by radical surgery in LACC patients. Details about acute and late toxicity associated with chemotherapy administration as well as rate and pattern of surgery-related complications have been analyzed.

Materials and methods

Study design and end-points

This prospective, non-randomized phase II study aimed at assessing the activity of neo-adjuvant dose-dense platinum/paclitaxel chemotherapy (NACT) followed by radical surgery (RS) in LACC patients (FIGO stage IB2-IVA).

The primary end-point was represented by rate of pathologically assessed complete and microscopic response (optimal pathological response, OPR); the secondary end-points were progression-free survival (PFS), overall survival (OS), toxicity associated with NACT, as well as rate and pattern of surgery-related complications.

Eligibility

Patients with stage IB2–IVA cervical cancer were evaluated for enrolment into the study by our Institutional Tumor Board. The trial was approved by the local Ethics Committee and Institutional review Board (CICOG231653), and all patients signed a written informed consent agreeing to be submitted to all the procedures described, and for their data to be collected.

Inclusion criteria were: biopsy-proven carcinoma of the cervix (any histotype), no evidence of distant disease, age $\leq$75 years, no previous treatment, ECOG performance status 0–1, adequate bone marrow function (WBC > 3000/mm^3, platelets > 120,000/mm^3), adequate renal function (blood urea nitrogen < 25 mg/dl, creatinine < 1.5 mg/dl), normal liver function (bilirubin < 2 mg/dl), and no prior cancer other than basal cell carcinoma. Exclusion criteria were as follows: previous or concurrent malignancies at other sites with the exception of basal or squamous cell carcinoma of the skin, uncontrolled severe infection, and/or medical problems unrelated to malignancy which would limit full compliance with the study or expose the patient to extreme risk.

Pre-treatment work-up included the collection of medical history, clinical examination, abdomino-pelvic MRI, and PET/CT scan; cystoscopy and proctoscopy were carried out in case of clinical suspicion of bladder and/or rectum invasion.

Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy was administered for 6 consecutive weeks, and included paclitaxel (80 mg/m^2, 1 h infusion) and carboplatin (AUC 2, 1 h infusion). Premedication was represented by dexamethasone taken the night before and the same day of chemotherapy administration.

Hematological toxicity was managed as follows: none of the drugs would be administered if neutrophils < 1000/mm^3 or platelets < 100,000/mm^3 were registered the day of treatment; if recovery did not occur the subsequent week, dose of drugs would be reduced by 15% (i.e. 68 mg/m^2 for paclitaxel and AUC 1.7 for carboplatin). In case of further toxicity, treatment administration would be stopped. Paclitaxel would be stopped in case of $\geq$G2 neurotoxicity. Monitoring of toxicity was planned on a weekly schedule.

Assessment of clinical response and surgery details

Clinical response to NACT would be assessed by abdomino-pelvic MRI, according to RECIST criteria [28]; PET/CT was also performed to exclude distant disease and better characterize response to treatment. Overall response rate (ORR) included complete and partial responses. Responsive patients were triaged to radical hysterectomy (RH) according to Querleu–Morrow classification [29], and pelvic ± aortic lymphadenectomy. Aortic lymphadenectomy was performed in case of (1) positive pelvic lymph nodes at frozen section analysis routinely performed during completion surgery; (2)

positive pelvic lymph nodes at imaging at the initial staging work-up; (3) intra-operative finding of palpable or indurated or fixed aortic lymph nodes.

Surgery would be abandoned in case of progressive disease, stable disease, or partial tumor regression not considered amenable to be successfully managed by surgery. Patients with stable disease, otherwise, considered operable were triaged to surgery.

Patients progressing during treatments were triaged to salvage chemotherapy and/or chemoradiation according to the pattern of relapse.

Assessment of pathologic response and follow-up

Pathologic response to therapy was evaluated based on the examination of uterus, vaginal cuff, parametrium, pelvic and aortic lymph nodes: residual disease at any site was expressed in millimeters (mm), and response was defined as complete (absence of any residual tumor after treatment at any site level), microscopic (persistent tumor foci ≤ 3 mm maximum dimension), and macroscopic (persistent tumor foci > 3 mm maximum dimension).

Adjuvant treatment included systemic chemotherapy, or radiation, or chemoradiation according to pathologically assessed risk factors (residual macroscopic disease, close margins, and parametrial and/or lymph-node involvement).

Patients underwent follow-up examination every 3 months for the first 2 years and every 6 months thereafter. Chest radiography and abdomino-pelvic MRI were performed every 6 months for the first 3 years and every 12 months thereafter.

Toxicity assessment

Assessment of NACT-related toxicity was performed according to the Common Terminology Criteria for adverse events (CTCAE version 4.0) (https://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Surgery-related morbidity was classified according to the Chassagne' grading system [30]. Postoperative early and late complications were defined as any adverse event occurring within or after 30 days from surgery, respectively.

Data collection and statistical analysis

Study data were stored and managed by the RedCap™ database system (http://www.redcap.org) with sensitive data tied to the patient's unique ID.

Sample size was quantified based on the previous studies reporting a rate of pathologically assessed OPR to treatment around 30%, on average [18, 21, 23]. Based on the mini-max two-stage design by Simon [31], we tested the null hypothesis that the true rate of OPR to treatment would improve from 30.0% to the clinically relevant alternative of 45.0%, using an α error of 0.05 (two-sided), and a β error of 0.2. Thus, the first step was planned to include 46 patients; if > 16 patients successfully achieved OPR, the study would enroll additional patients up to a total of 65 patients. The regimen would be considered active if > 25 OPR were registered. Considering a dropout rate around 5%, at least 70 cases were planned to be enrolled.

The Chi-square test or Fisher's exact test for proportion was used to analyze the distribution of clinico-pathological variables according to different subgroups. Wilcoxon rank sum non-parametric test was used to analyze the distribution of continuous values. Progression-free survival (PFS) and was calculated from the date of surgery to the date of relapse or the date of the last follow-up; overall survival (OS) was calculated from the date of diagnosis to the date of death or the date last seen. Medians and life tables were computed using the product limit estimate by the Kaplan–Meier method [32], and the log-rank test was used to assess the statistical significance [33].

Statistical analysis was carried out using SOLO (BMDP Statistical Software, Los Angeles, CA, USA).

Results

Between January 2016 and January 2018, 41 patients were screened, and 36 were considered eligible for enrolment into the study due to the occurrence of screening failure in 5 cases (Fig. 1). Clinical and pathological characteristics of enrolled patients are summarized in Table 1: median age was 45 years (range 28–65), and all, but one, showed PS-ECOG = 0. Nineteen (52.8%) patients were FIGO stage IIB, and 4 cases (11.1%) had stage IIIB disease. At staging work-up, pelvic lymph-node involvement was documented in 16 (44.4%) patients.

Dose-dense NACT was administered to all patients enrolled. Table 2 shows the details of clinical response based on MRI assessment: complete and partial responses to NACT were achieved in 1 and 26 patients, respectively, thus totaling an objective response rate (ORR) of 75.0%; stable disease was documented in 8 patients (22.2%) and 1 patient experienced progression of disease. Excluding the patient with progressive disease, 3 cases with stable disease, and 1 patient who achieved partial response but were considered not operable, 31 patients were triaged to surgery. As shown in Supplementary Table 1: radical hysterectomy was performed in 29 (93.5%) patients, pelvic lymphadenectomy was performed in all patients, while aortic lymphadenectomy was carried out in 58.1% of cases. Minimally invasive surgery was carried out in 21 (67.8%) patients.

As shown in Table 3, pathologic complete response to treatment was documented in only 1 case out of 31 patients

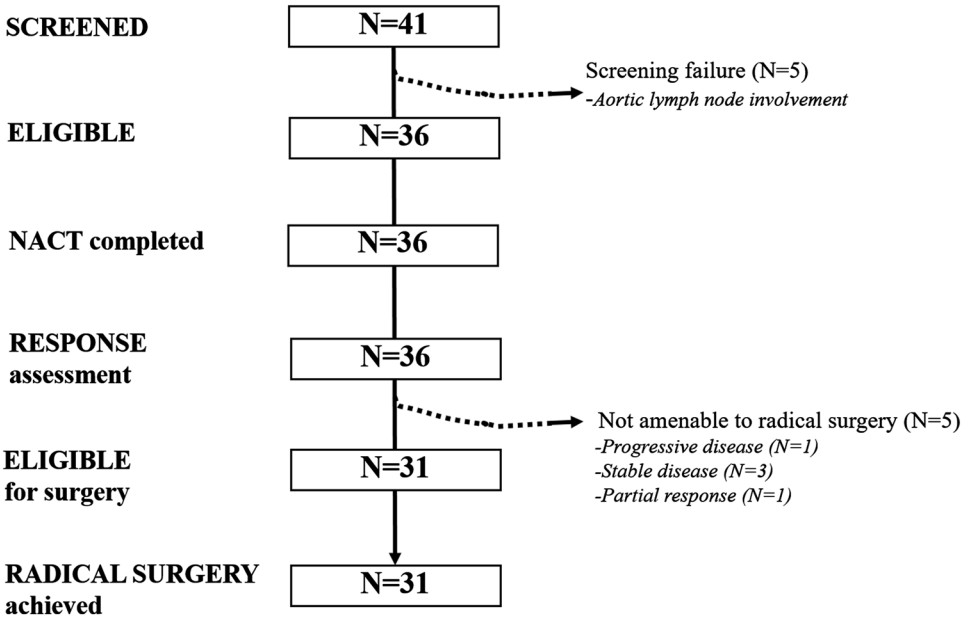

Fig. 1 Flowchart of patient population

undergoing radical surgery (3.2%), while 4 cases (12.9%) showed microscopic response. Considering the rate of OPR, we were prompted at evaluating the real chances to achieve the number of OPR required by the original sample size calculation; after a careful analysis carried out by the multidisciplinary Tumor Board, we decided to close the study for ethical reasons.

Overall, median residual tumor in the uterine cervix was 20 mm (range 1–70 mm). Pathologic involvement of pelvic and aortic lymph nodes was reported in 7 (22.6%), and in 1 out of 18 patients (5.5%), respectively (data not shown).

Adjuvant treatment was administered to 23 patients (chemoradiation: 16, chemotherapy: 7).

Details on NACT administration and toxicity

Completion of the planned 6 weekly administrations was achieved in all the cases, and the total number of weekly administrations was 216. Median cumulative dose was 1344 mg/m^2 (range 846–2200) for carboplatin and 791 mg/m^2 (range 604–960) for paclitaxel. Carboplatin reduction was required in two patients (5.5%) due to grade 3 anemia, and delay of administration was necessary in four patients (11.1%) (grade 3 anemia, $N=2$; grade 4 neutropenia, $N=2$). None of patients suspended the treatment. Toxicity was evaluated in all patients (Table 4): grade 3/4 hematological toxicity occurred in five patients.

Surgery-related morbidity

We did not register any intra-operative complications; during the observation period, 7 of 31 (22.6%) patients experienced the early postoperative complications for a total of 11 complications; of them, most were urinary (Table 5). Seven patients (22.6%) had late postoperative sequelae (total complications: 10, mostly vascular and urinary). Among early and late postoperative adverse events, there were no grade 3–4 complications.

Clinical outcome

As of August 2018, median duration of follow-up in the whole series was 12 months (range 6–21). As far as secondary end-points are concerned, the 2-year PFS in the whole series was 69.0% (data not shown). Relapse/progression of disease was documented in ten cases (27.8%): in particular, four patients developed central pelvic recurrence, four patients had mixed sites of disease relapse, and two had peritoneal carcinomatosis. Death of disease was documented in one patient.

Discussion

To our knowledge, this is the first prospective phase II study investigating activity and safety of neo-adjuvant dose-dense paclitaxel (80 mg/m^2) and carboplatin (AUC 2) followed by surgery in LACC patients.

As far as the primary end-point is concerned, we reported the data relative to only 36 patients due to the documentation of a low rate (16.1%) of OPR to treatment; indeed, after a careful evaluation of the poor chances to comply with the criteria required by the Simon design for calculation of the original sample size, the multidisciplinary Tumor Board considered not ethical to proceed with further patient enrollment. Comparison of these results with the previous

Table 1 Clinical and pathological features of study population

Group	No. (%)
All cases	36
Age, years	
Median (range)	45 (28–65)
Body Mass Index (kg/m^2)	
Median (range)	23.7 (19.0-39.7)
No. > 30 BMI	4 (11.1)
PS-ECOG	
0	35 (97.2)
1	1 (2.8)
Patients with comorbidities	8 (22.2)
No. comorbidities	9
Hypertension	6
Diabetes	1
Thyroid disorders	1
Dyslipidemia	1
Tumor diameter (mm)	
Median (range)	47.5 (25–70)
Histotype	
Squamous	28 (77.8)
Adenocarcinoma	5 (13.9)
Adenosquamous	1 (2.8)
Glassy cell	1 (2.8)
Signet-ring cell carcinoma	1 (2.8)
Grade	
G1/2	27 (75.0)
G3	4 (11.1)
n.a.	5 (13.9)
FIGO stage	
IB2	9 (25.0)
IIA2	4 (11.1)
IIB	19 (52.8)
IIIB	4 (11.1)
Pelvic LN status at imaging	
Negative	20 (55.5)
Positive	16 (44.4)

Table 2 Clinical response to neo-adjuvant dose-dense chemotherapy

Response	No. (%)	95% confidence intervals
All	36	
Complete	1 (2.78)	−2.59, 8.13
Partial	26 (72.22)	57.58, 86.85
ORR[a]	27 (75.0)	60.85, 89.14
Stable disease	8 (22.22)	8.64, 35.80
Progression	1 (2.78)	−2.59, 8.13

[a]ORR = overall response rate includes clinical complete and partial response

Table 3 Pathologically assessed response to neo-adjuvant dose-dense NACT in patients undergoing radical surgery

Group	No. (%)	95% confidence intervals
All	31	
Complete	1 (3.20)	−2.99, 9.43
Microscopic	4 (12.90)	1.10, 24.69
OPR	5 (16.12)	3.17, 29.06
Macroscopic	26 (83.87)	70.92, 96.81

OPR optimal pathological response

Table 4 Worst hematological and non-hematological toxicity per patient during neo-adjuvant dose-dense chemotherapy

Toxicity	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Hematological				
Anemia	1 (2.8)	1 (2.8)	3[a] (8.3)	–
Leukopenia	1 (2.8)	2 (5.5)	–	–
Neutropenia	2 (5.5)	1 (2.8)	–	2[b] (5.5)
Thrombocytopenia	–	–	–	–
Non-hematological				
Asthenia	2 (5.5)	1 (2.8)	–	–
Nausea/vomiting	7 (19.4)	2 (5.5)	–	–
Diarrhoea	2 (5.5)	1 (2.8)	–	–
Constipation	1 (2.8)	–	–	–
Arthralgia	3 (8.3)	–	–	–
Aminotransferase elevation	1 (2.8)	–	–	–

[a]Managed by blood transfusion

[b]Managed by G-CSF administration

studies adopting dose densification of both drugs (Supplementary Table 2) shows that the earlier Japanese experience reported just one pathological complete response (3.6%) in a series of stage IB2–IVA patients administered paclitaxel (60 mg/m^2) plus carboplatin (AUC 2) before surgery [17]; this figure does not differ from our results. Moreover, the retrospective study by Gadducci et al. [23], who utilized the same regimen adopted in the current study, reported the OPR rate of 21.4%, a figure to be considered with caution considering the very small sample series. The above cited studies, and our experience too, cannot provide consistent and robust suggestions about the role of weekly PTX, regardless of whether it is dose intensified or not [17, 23]. In this context, the role of potential dependence of drug(s)/schedule(s) according to ethnic patient differences has been emphasized on the basis of conflicting results documented in other malignancies [16, 34].

Focusing on the studies exploring the role of increased dose intensification of platinum agents in dose-dense

Table 5 Type of early and late postoperative complications according to organ system and grade

Organ system	Early	Type	Late	Type
ALL	11		10	
Urinary	7		5	
G1	5	Acute symptoms of cystitis lasting > 2 weeks ($N=4$) Abnormal bladder functions lasting > 2 weeks ($N=1$)	4	Abnormal bladder functions lasting > 2 weeks and < 6 months ($N=2$) Acute symptoms of cystitis > 2 weeks ($N=1$) Urinary incontinence ($N=1$)
G2	2	Uretero-vaginal fistula requiring surgery with subsequent normal renal function ($N=1$) Any symptoms or signs of abnormal bladder functions lasting < 6 months ($N=1$)	1	Ureteral stenosis requiring surgery with subsequent normal function ($N=1$)
Vascular	3		5	
G1	3	Lymphocele not requiring drainage ($N=2$) Leg edema not interfering with normal activity ($N=1$)	4	Thrombophlebitis settling on medical treatment ($N=1$) Lymphocele not requiring drainage ($N=2$) Leg edema not interfering with normal activity ($N=1$)
G2	–	–	1	Leg edema interfering with normal activity ($N=1$)
Other	1		–	–
G2	1	Neurologic sensory symptoms with moderate functional impairment ($N=1$)	–	–

schedules, it has to be acknowledged that the group of Benedetti Panici et al. [18] reported the rates of pathological complete or microscopic response in 26.2% and 5.3%, respectively. However, the study was closed due to the documentation of rates of grade 3–4 extra-hematological grade higher than the pre-planned stopping rule [18]. On the other hand, the Belgian study documented up to 33% of pathological complete, and 17.7% of microscopic response to the weekly schedule with paclitaxel (median dose = 60 mg/m^2) plus carboplatin (AUC 2.7), thus leading to support the data provided by the meta-analysis published in 2003 that platinum intensification would be more active, in principle [3]. However, it has to be taken into account that the vast majority of pathological complete response to NACT in the Belgian study were registered in stage IB1 patients, and that about one-third of cases had been treated with a different regimen (paclitaxel 90 mg/m^2 and carboplatin AUC 4, day 1, and day 8 on a tri-weekly schedule) [21]. In addition, despite the use of the less toxic carboplatin, the study reported grade 3–4 neutropenia in 56% of cases.

In this context, it seems that the issues relative to the extent of activity, and to the benefit/toxicity ratio of weekly schedules (regardless of presence or absence of drug(s) dose intensification) versus the tri-weekly ones remain elusive and require clarification [6, 7, 17, 20–23].

When focusing on clinical response after NACT, it appears that the weekly schedule provided an ORR of 75%, which is in the range of previously reported experiences with weekly or tri-weekly platinum-based combinations [6–8, 17, 18, 21–23]. This is clinically relevant to achieve a high rate of operability, associated with a reduction of rate and severity of surgery-related complications. Indeed, careful pre-operative clinical and imaging evaluation as well as adoption of minimally invasive approaches in 67.8% of patients could also have resulted in documentation of only grade 1 and 2 early and late postoperative complications.

As far as the toxicity profile of chemotherapy is concerned, the weekly schedule allowed completion of planned 6 weekly administrations in all patients, who experienced a low rate of hematological and non-hematological adverse events. This favourable toxicity profile could be reasonably ascribed to the use of carboplatin, which has been recognized to provide equivalent efficacy to cisplatin in cervical cancer patients, in face of less adverse events [12], but also to the choice of the weekly schedule. Finally, dose intensification of paclitaxel (which led to increase up to 37% the dose intensity compared to the standard), did not seem to result in worse toxicity.

As far as clinical outcome is concerned, the 2-year PFS in the whole series was 69.0%; these data are hardly comparable to the previous results given the heterogeneity of the studies and, more important, to the relatively short follow-up of our series [17, 18, 21, 23].

In conclusion, we showed that adoption of dose-dense paclitaxel/carboplatin as neo-adjuvant chemotherapy before RS is feasible and safe in LACC patients; however, failure to achieve the primary end-point has to be recognized.

Despite the potential advantages expected on the basis of the theoretical concepts relative to the dose densification/intensification (increased activity, better toxicity profile), results from the available studies on this issue have to be considered just preliminary, if any, given the small sample size, heterogeneity of regimens, and limited data on outcome. Therefore, it seems that more efforts should be done

to provide robust data from an adequately sized, prospective study focused on more homogeneous settings.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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