Efficacy and tolerability of paclitaxel, ifosfamide, and cisplatin as a neoadjuvant chemotherapy in locally advanced cervical carcinoma

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Objective: To evaluate the efficacy and tolerability of a neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy in patients with locally advanced cervical carcinoma.

Methods: Patients with histologically confirmed locally advanced cervical carcinoma, aged ≥18 years, were treated with intravenous ifosfamide 5,000 mg/m^2 and mesna 5,000 mg/m^2, on day 1; intravenous paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2, on day 2; every 3 weeks for three cycles. Following chemotherapy, operable patients underwent radical hysterectomy and pelvic lymphadenectomy, and, if necessary, adjuvant radiotherapy.

Results: One hundred fifty-two patients with median age 53 years (range, 24 to 79 years), FIGO stage IIB in 126 (89%), were treated with chemotherapy for median 3 cycles (range, 1 to 3). Treatment was delayed or withdrawn in 23 patients (15%). One hundred thirty-nine patients (91%) underwent surgery. Postchemotherapy pathological complete response rate was 18% (25 patients). Postoperative radiotherapy was administered in 100 patients (72%). The 5-year overall survival and progression-free survival were 87.3% (95% confidence interval [CI], 84.5 to 90.3) and 76.4% (95% CI, 73.5 to 79.5), respectively.

Conclusion: Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy was feasible and effective in the treatment of locally advanced cervical carcinoma patients with older age and more advanced disease stage than reported in previous studies. Hematological and renal toxicity could be carefully prevented.

Keywords: Antineoplastic Combined Chemotherapy Protocols; Disease-Free Survival; Retrospective Studies; Uterine Cervical Neoplasms

INTRODUCTION

Concomitant cisplatin-based chemoradiotherapy is the standard care for patients with locally advanced cervical carcinoma (LACC) [1]. The use of a neoadjuvant chemotherapy (NACT) approach followed by surgery may offer some specific advantages over chemoradiotherapy such as better potential activity against micrometastatic disease and a debulking effect that may improve subsequent surgical outcome.

NACT followed by radical surgery could be an alternative to chemoradiotherapy in the treatment of LACC based on several studies showing a 5-year overall survival (OS) rate ranging from 45% to 83% [2-9]. A direct comparison of NACT followed by surgery versus concurrent chemoradiotherapy is still lacking and is being addressed by the ongoing EORTC-55994/NCT00193739 trial.

The Studio Neo-Adjuvante Portio 02 Italian collaborative study confirmed the superiority of a three-drug induction

chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP) compared to a two-drug combination of cisplatin and paclitaxel (TP), in terms of response rate. However, TIP was associated with significantly higher rates of grade 3 or 4 hematological toxicity than the TP schedule (78% vs. 29%, p<0.0001) and more drug-related serious adverse events that required hospitalization [10].

We explored the efficacy and tolerability of a TIP NACT performed in a real-life setting of LACC patients.

MATERIALS AND METHODS

1. Patient eligibility

Women aged 18 years or more, with a histological diagnosis of LACC were consecutively treated at the Division of Gynecological and Medical Oncology, Maternal and Child Department of the Cannizzaro Hospital, Sicily, Italy, from July 1997 to November 2013. Patient data on histology and disease stage, treatment response and toxicity, and survival were retrospectively evaluated.

Pretreatment evaluation included history, physical examination, tumor biopsy, and complete blood analysis. Tumor extension was assessed clinically and by abdominal magnetic resonance imaging (MRI), three-dimensional (3D) ultrasound, and, where necessary, ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET), at baseline. Patients with International Federation of Gynecology and Obstetrics (FIGO) [11] stages IB2 to IVA cervical carcinoma were treated. Further eligibility criteria included: World Health Organization performance status of ≤2; adequate bone marrow reserve (i.e., absolute granulocyte count ≥2.0×10^3/L, platelet count ≥100×10^3/L, hemoglobin ≥8.0 g/dL); adequate renal, hepatic, and cardiac function. Informed consent was obtained from all patients.

2. Chemotherapy and supportive therapy

TIP regimen included: 24-hour continuous intravenous infusion of ifosfamide 5,000 mg/m^2 and mesna intravenous 5,000 mg/m^2, each in one liter of saline solution, on day 1; 3-hour intravenous paclitaxel 175 mg/m^2 and 1-hour intravenous cisplatin 75 mg/m^2, each in 500 mL of saline solution, on day 2; every 3 weeks for 3 cycles.

Premedication included: intravenous 8 mg ondansetron and intravenous 50 mg ranitidine, 30 minutes before the administration of ifosfamide, on day 1; intravenous 250 mg methylprednisolone 60 minutes before, intravenous 8 mg ondansetron and intravenous 50 mg ranitidine 30 minutes before the administration of paclitaxel, on day 2. Two and a

half liters of saline solution, with the addition of 10 mEq/L of potassium chloride and 10 mEq/L of MgSO$_4$, were intravenous administered over 6 hours, on day 2. On day 3, supportive therapy included: 1 L of saline solution with the addition of 8 mg ondansetron, 50 mg ranitidine, and 4 mg dexamethasone, in a 2-hour intravenous infusion.

Since 2003, granulocyte-colony stimulating factor (G-CSF) prophylaxis, administration of erythropoietin with iron implementation in those patients with hemoglobin values below 10 g/dL, and accurate urological evaluation for possible nephrostomy or ureteral stenting, along with the assessment of creatinine clearance before the start of each chemotherapy cycle have been implemented for all patients.

The administration of each TIP cycle was based on the evaluation of blood cell count, renal and hepatic function. Treatment was administered if absolute granulocyte count was ≥1.5×10^3/L and platelet count was ≥100×10^3/L. Treatment was delayed for a maximum of 2 weeks; thereafter, it was withdrawn. Treatment was discontinued in cases of: grade 4 toxicity, or not resolved grade 2 to 3 toxicity [12].

3. Feasibility and chemotherapy response evaluation

All patients who had received at least one cycle of TIP NACT were assessed for feasibility, which was defined by the following parameters: the median number of cycles of TIP delivered, the number of patients who had to delay or withdraw TIP, the toxicity that determined the delay or withdrawal of TIP (i.e., treatment-related limiting toxicity).

Tumor extension was re-evaluated clinically and by abdominal MRI, 3D ultrasound, and possible ^{18}F-FDG-PET after the three cycles of TIP. Clinical objective tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [13].

4. Treatment following chemotherapy and follow-up

All patients underwent surgical evaluation for radical hysterectomy and pelvic lymphadenectomy within 4 weeks following the administration of the third cycle. The surgery was performed according to Piver, Rutledge, and Smith classification; radical hysterectomy and pelvic lymphadenectomy was done via laparotomy, laparoscopy was never done. Patients with inoperable tumors because of progressive disease (PD) were offered radiotherapy.

Based on the histopathology report of the surgical specimen, pathological response to chemotherapy was classified as: pathologic complete response (pCR), if no tumor was found in the cervix and/or in the lymph nodes; pathological partial response-1 (pPR1), in cases of residual tumor infiltrating less than 3 mm (microinvasion); pathological partial response-2

(pPR2), in patients with response, but persistent residual disease infiltrating more than 3 mm; and stable disease (SD), if tumor size was unchanged.

Postoperative adjuvant radiation was considered in high-risk patients with positive surgical margins, metastatic lymph nodes, or parametria involvement. The volume of external beam radiation therapy (EBRT) included parametria, uterosacral ligaments, vaginal margin from the gross disease (3 cm), presacral nodes, and other nodal volumes at risk. For patients with negative nodes the radiation volume included the entirety of the external iliac, internal iliac, and obturator nodal basins. For patients with confirmed nodes confined to the lesser pelvis the radiation volume was increased to cover the common iliac nodes. In those patients with common iliac and/or para-aortic nodal involvement, extended field pelvic and para-aortic radiotherapy up to the level of renal vessels was delivered. An EBRT dose of approximately 50 Gy (in conventional fractionation of 1.8 to 2.0 Gy daily), and highly conformal boost of an additional 10 to 15 Gy were considered for limited volume of gross unresected adenopathy. In the last 5 years, intensity-modulated radiation therapy has been used to minimize the dose to the bowel and other clinical structures and to treat the para-aortic nodes, when necessary. Brachytherapy was not performed.

Disease assessment was performed 1 month after completion of treatment, every 3 months for the first year and every 6 months for 5 years thereafter. Follow-up included pelvic examination and vaginal cytology, pelvis and abdomen MRI or computed tomography scan and chest X-ray at each follow-up examination.

5. Statistical analysis

The primary end point was pCR and the sum of pCR and pPR1. Secondary endpoints included: pPR2, surgical resection

Table 1. Patient characteristics (n=152)

Characteristic	No. (%)
Age (yr), median (range)	53 (24–79)
Histological subtype	
Squamous cell carcinoma	147 (97)
Adenocarcinoma	5 (3)
FIGO stage	
IB2	2 (1)
IIB	126 (89)
III	12 (8)
IVA	2 (1)
Missing	10 (7)

FIGO, International Federation of Gynecology and Obstetrics.

rate, clinical response rate (according to the RECIST criteria), OS and progression-free survival (PFS), and toxicities (according to the common toxicity criteria ver. 2.0) [12].

The responses rates were reported as relative proportions to the total number of patients. Percentages were approximated to the nearest unit. Continuous variables were expressed as medians with related value ranges. The PFS was calculated from the date of diagnosis until the date of PD, or death from any cause. The OS was calculated from the date of diagnosis until death, or last date of follow-up. Patients who had not died or progressed at the time of the final analysis were censored at the date of last contact. The PFS and OS were estimated using the Kaplan-Meier method [14]. All analyses were performed according to the intention to treat. In order to study the possible influence of prognostic or predictive factors, the log-rank test was used to assess survival differences between groups by univariate analysis. The multivariate Cox proportional hazards regression modeling was used to identify the prognostic clinical-pathological features from univariate analysis and independently associated with OS and PFS [15].

RESULTS

1. Patient characteristics

Between July 1997 and November 2013, 152 women were

Table 2. Feasibility of paclitaxel, ifosfamide, and cisplatin (n=152)

Parameter	No. (%)
Cycles of treatment, median (range)	3 (1–3)
Treatment delay	10 (7)
Toxicity	10 (7)
Treatment withdrawal	13 (9)
Toxicity	12 (8)
Refusal	1 (1)
Treatment limiting toxicities*	23
Neutropenia	11 (48)
Anemia	10 (43)
Thrombocytopenia	7 (30)
Renal failure	3 (13)
Allergic reaction	3 (13)
Vomiting	3 (13)
Febrile neutropenia	2 (9)
Hypopotassemia	2 (9)
Atrial fibrillation	1 (4)

*Toxicities requiring treatment delay or withdrawal.

treated with TIP NACT and were assessable for response. Patient characteristics are reported in **Table 1**. Median age was 53 years (range, 24 to 79 years). The majority of patients (89%) had FIGO stage IIB disease.

2. Treatment feasibility

Feasibility data are summarized in **Table 2**. Median numbers of delivered cycles of TIP was 3 (range, 1 to 3). Treatment was delayed in 10 patients (7%) and withdrawn in 13 patients (9%). In all cases treatment was delayed due to toxicity; in all cases except one it was withdrawn due to toxicity. The most frequent treatment-related limiting toxicity included: hematological toxicity such as neutropenia, anemia and thrombocytopenia in 48%, 43% and 30% of patients, respectively; renal failure in 13% of patients; allergic reaction in 13% of patients; vomiting in 13% of patients; febrile neutropenia in 9% of

patients; and hypokalemia in 9% of patients. No treatment-related deaths occurred. Fifteen of these treatment-related limiting toxicities (63%) occurred in the first 50 patients. In the subsequent 102 patients, it was observed in only eight of them (36%).

3. Treatment efficacy

Efficacy data are reported in **Tables 3, 4**. Following NACT, 35 patients (23%) had clinical CR, and 93 patients (62%) a clinical PR; clinical SD was observed in 20 patients (13%); only three patients (2%) had a clinical PD.

Resection rate was 91%. The median time from the initiation of TIP to surgery was 3 months (range, 2 to 4 months). Thirteen patients did not undergo surgery; this was due to clinical SD in 10 patients and PD in three patients. The mean duration of surgery was approximately 150 minutes. Lymphadenectomy was performed in 121 patients (87%). A median number of 20 lymph nodes were removed (range, 4 to 64). Ninety-one patients (75%) were pN0, 30 patients were pN1 (25%) (**Table 4**). Perioperative and postoperative complications included: the need for blood transfusions in 13 patients (9%); three cases (2%) of bladder denervation requiring suprapubic catheterization; four cases (3%) of rectovaginal fistulas all occurred in patients who subsequently received radiotherapy. During surgery, the mean blood loss was 300 mL.

Postchemotherapy pathological response in 137 assessable patients was: pCR in 25 patients (18%), pPR1 in 18 patients (13%), pPR2 in 83 patients (61%), SD in 10 patients (7%), and PD in one patient (1%). Overall, 43 patients (31%) had a pCR

Table 3. Treatment efficacy (n=152)

Parameter	No. (%)
Clinical tumor response*	
CR	35 (23)
PR	93 (61)
SD	20 (13)
PD	3 (2)
NA	1 (1)
Resection rate	139 (91)
Pathologic tumor response	
CR[†]	25 (18)
PR1[‡]	18 (13)
PR2[§]	83 (61)
SD	10 (7)
PD	1 (1)
Missing	2 (1)
Follow-up (mo), median (range)	48 (5–173)
Death	20 (13)
Relapse	31 (20)
Local	15 (48)
Distant	16 (52)
5-Year OS (95% CI)	87.3 (84.5–90.3)
5-Year PFS (95% CI)	76.4 (73.5–79.5)

CI, confidence interval; CR, complete response; NA, not available; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease.
*As assessed by magnetic resonance imaging or transvaginal ultrasonography on all 152 patients according to Response Evaluation Criteria in Solid Tumors criteria. [†]Pathological CR, defined by pT0. [‡]Pathological PR1, defined by residual disease with ≤3 mm stromal invasion including pTis. [§]Pathological PR2, defined by persistent residual disease with >3 mm stromal invasion on surgical specimen.

Table 4. Postchemotherapy pathological TNM stage* (n=139)

Parameter	No. (%)
T stage	
ypT0	26 (21)
ypTis	7 (6)
ypT1a1–2	11 (9)
ypT1b1–2	45 (36)
ypT2a1–2	16 (13)
ypT2b	19 (15)
ypT3b	1 (1)
ypT4	1 (1)
Missing	13 (10)
N stage	
ypN0	91 (75)
ypN1	30 (25)

*According to tumor, node, and metastasis (TNM) classification. Prefix p indicates stage given by pathologic examination of a surgical specimen; y indicates stage assessed after neoadjuvant therapy.

A

B
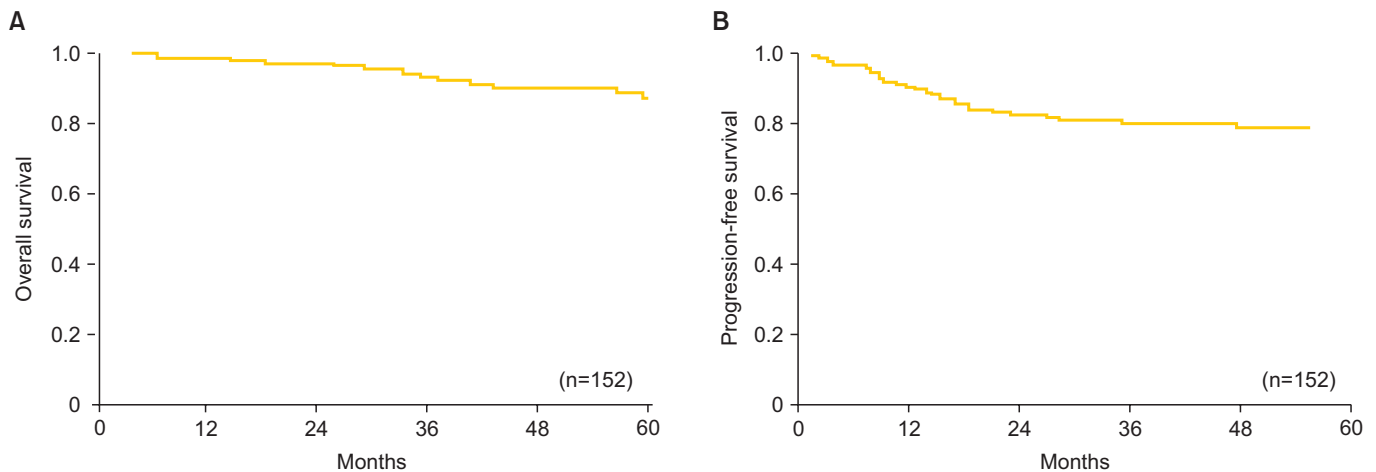
Fig. 1. (A) Probability of overall survival. (B) Probability of progression-free survival.

or pPR1 following TIP and surgery. Following chemotherapy, disease downstaging was observed in 105 patients (of the 138 with an initial clinical stage more than IB2, 86%), including: 27% of all operated patients with ypT0/pTis stage, 9% with ypT1a, 36% with ypT1b, and 13% with ypT2a (**Table 4**).

Postoperative radiotherapy was administered in 100 patients (72%). With a median follow-up of 48 months (range 5 to 173 months), 132 patients (87%) are alive and 121 patients (80%) are alive and disease-free. Among the 31 patients with relapse 15 patients (10% of all patients) had pelvic recurrences and the remaining 16 patients (11%) had distant metastases.

The probability of 5-year OS and PFS were 87.3% (95% confidence interval [CI], 84.5 to 90.3) and 76.4% (95% CI, 73.5 to 79.5), respectively (**Fig. 1**). None of the clinicopathological features studied resulted prognostic factors by univariate analysis (**Table 5**).

DISCUSSION

With a 5-year OS of 87.3% and PFS of 76.4%, this study confirms the efficacy and tolerability of NACT with TIP in a large series of 152 patients with LACC homogenously treated in a real-life setting with older age and more advanced FIGO disease stage than reported in previous studies [10,16,17]. In comparison with the two Italian randomized clinical trials that used TIP as NACT [10,16], the observed OS and PFS were slightly higher. One possible reason for these unexpected results may lie in the high proportion of patients (72%) who underwent adjuvant radiotherapy at the completion of surgery. In fact, this treatment could have contributed as consolidation or salvage therapy for these patients. Indirect evidence supporting this hypothesis could be the low occur-

rence of pelvic relapse, reported in only 15 of the 31 patients with PD. Moreover, though NACT followed by radical surgery have been used to reduce the long-lasting adverse effects of radiotherapy [17], the role of adjuvant radiotherapy following NACT and radical surgery is still not clear. Another factor that should be taken into account is the role of surgery following NACT, since the efficacy of NACT still remains suboptimal as is evident from the high proportion of SD, PR2 or even disease progression. For this reason, the expertise and surgical aggressiveness of a single well-experienced surgical team and the meticulous sharp dissection performed to achieve excellent clearance despite the presence of postchemotherapy fibrosis, may contribute to improve the outcome of patients.

As shown in **Table 5** the absence of a significant difference of survival outcomes could depend on the large number of patients who received postoperative adjuvant radiotherapy. These patients underwent adjuvant radiotherapy because of advanced FIGO stage at the diagnosis or postchemotherapy pathological response after radical surgery, except for microlesions, T0 or Tis TNM stage. So, the selection of most patients for this treatment probably over-rides the significant difference of survival outcomes between FIGO stages and between negative and positive parametrium. In addition, the reason of better survival in patients with positive parametria could be related to NACT or sequence of the three treatments.

No prognostic factors for PFS and OS were identified in our series. In particular, response to NACT was not associated with PFS or OS, similarly to the results of a Korean case series of 112 patients with FIGO stage IB-IIB cervical carcinoma that were treated with cisplatin/etoposide NACT [18]. However, the observed overall response rate of 92% (including 18% pCR, 13% pPR1, and 61% pPR2 rates) is in agreement with the range of response rates (between 70% and 90%) reported in other

Table 5. Univariate analyses for prognostic factors

Variable	At risk	Progression-free survival			Overall survival		
		No. of events	5-Year survival (%)	p-value	No. of events	5-Year survival (%)	p-value
FIGO stage							
IB2	2	0	100	0.45	0	100	0.27
IIB	133	25	78		18	88	
III–IVA	16	6	62		2	80	
NACT withdrawal							
Yes	17	6	59	0.11	4	86	0.86
No	135	25	79		16	88	
Response to NACT							
pCR+pPR1	62	13	76	0.95	7	90	0.48
pPR2	77	15	78		12	84	
SD	9	0	100		1	100	
TNM stage							
ypT0–Tis	36	10	72	0.18	5	81	0.58
ypT1a	31	4	86		4	92	
ypT1b	48	9	79		5	91	
ypT2	33	5	83		6	93	
ypN0	91	16	81	0.62	8	91	0.29
ypN1	30	7	70		5	88	
Parametrial status							
Negative	111	23	77	0.54	15	87	0.93
Positive	21	3	79		3	87	
Adjuvant RT							
Yes	100	22	75	0.60	12	88	0.75
No	51	9	80		7	87	

FIGO, International Federation of Gynecology and Obstetrics; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; pPR1, pathological partial response 1; pPR2, pathological partial response 2; RT, radiotherapy; SD, stable disease.
Prefix p indicates stage given by pathologic examination of a surgical specimen; y indicates stage assessed after neoadjuvant therapy.

trials [4,9,10,16]. A plausible explanation for that may lie in the administration of adjuvant radiotherapy discussed above, and its possible positive effect on the outcome of patients. Feasibility of TIP in this study was acceptable, with 85% of patients completing the planned 3 cycles of chemotherapy. However, the high toxicity profile of TIP was confirmed as a relevant issue, with hematological, renal, gastrointestinal toxicity, and allergic reaction being the more frequent causes of treatment delay or withdrawal. It should be noted that 63% of treatment-related limiting toxicities occurred in the first 50 patients, suggesting the relevance of adequate management of TIP side effects. In the subsequent 102 patients, a treatment limiting toxicity was reported in only eight patients (36%), due to the introduction of routine G-CSF prophylaxis, as well as the administration of erythropoietin with iron implementation in those patients with hemoglobin values below 10 g/dL, and accurate urological evaluation for possible nephrostomy

or ureteral stenting, along with the assessment of creatinine clearance before the start of each chemotherapy cycle. These measures may have significantly contributed to the reduction of severe hematological and renal toxicity.

The question of whether NACT or chemoradiotherapy is a more effective treatment for patients with LACC (FIGO stage IB2-IIB) remains unanswered [17]. The results of the ongoing EORTC RCT (EORTC-55994, NCT00193739), comparing these two strategies in patients with LACC, are expected to reveal the most effective treatment protocol. TIP NACT demonstrated a significant advantage in terms of optimal disease response when compared with a two-drug regimen with ifosfamide and cisplatin (IP) or TP, though it was associated with significantly higher rates of grade 3 or 4 hematological toxicity than the TP schedule [10,16]. Based on the efficacy and tolerability of TIP, which were confirmed in this large series of LACC patients, efforts should be addressed to tailor chemotherapy using pre-

dictive biomarkers, thus avoiding patients with chemoresistant disease from unnecessary toxicity.

Some limitations of this study include its retrospective nature, with the possible related lack of some relevant clinical data, and the inclusion of patients treated over a long period of time, that may have affected disease staging, as well as supportive therapy. Another major limitation of this study may be the broad indication for adjuvant radiotherapy that was not restricted to those patients with positive surgical margins, metastatic lymph nodes, or parametria involvement, but also to those not achieving a pCR or pPR1.

In conclusion, this study confirms the efficacy and tolerability of NACT with TIP in a single center large series of LACC patients treated in a real-life setting characterized by older and higher disease stage than reported in other similar previous studies. Hematological and renal toxicity remain the major issues of this strategy that should be carefully considered by adequate urological evaluation and supportive care. The role of adjuvant radiotherapy following NACT and radical surgery is still not completely clear.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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