Neoadjuvant Weekly Paclitaxel-Carboplatin Is Effective in Stage I–II Cervical Cancer

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Objective: Neoadjuvant chemotherapy (NACT) followed by surgery in cervical cancer is widely studied with paclitaxel-ifosfamide-cisplatinum 3 weekly (TIP). Although the response rates with TIP are high, the toxicity is substantial. Therefore, this study evaluates dose-dense paclitaxel-carboplatin (TC) as an alternative.

Methods: In this prospective phase 2 study trial, we included 36 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB1 to IIB cervical cancer, who received 9 weeks' NACT dose-dense TC (median weekly dose paclitaxel 60 mg/m^2, carboplatinum area under the curve 2.7). Radiological response was evaluated by RECIST (Response Evaluation Criteria in Solid Tumors). Optimal pathologic response (OPT) was defined as complete disappearance of tumor (complete response [CR]) or residual disease with less than 3-mm stromal invasion (PR1). Suboptimal pathologic response consisted of persistent residual disease with more than 3-mm stromal invasion (PR2).

Results: Nine patients had a FIGO stage IB1 (25%), 7 had stage IB2(19%), 3 had stage IIA (8%), and 17 had stage IIB disease (47%). Evaluation by magnetic resonance imaging after NACT showed 32 RECIST responses (89%) (CR in 11, PR in 21). Patients who were inoperable had insufficient reduction of the tumor to be operable (4 patients), progressive disease (1 patient), or stable disease (1 patient). Thirty patients were suitable for surgery after NACT. Pathology showed OPT in 50% (CR in 10, PR1 in 5). Thirteen patients had pathologic lymph nodes on radiological evaluation before start of chemotherapy. After chemotherapy, the lymph nodes were negative in 6 (47%) of these patients (pathologic complete remission). Postoperative chemoradiotherapy was administered in 11 patients (2 because of close resection margins, 5 because of metastatic lymph node after surgery, 2 because of close resection margins and metastatic lymph nodes after surgery, and 1 tumor >4 cm after NACT). Hematologic toxicity was acceptable with no febrile neutropenia and a low nonhematologic toxicity. The estimated 5-year overall survival was 70.8%.

Conclusions: Neoadjuvant TC dose-dense in cervical carcinoma has a high response rate, comparable with TIP, and an acceptable toxicity.

Key Words: Cervical cancer, Neoadjuvant chemotherapy, Weekly paclitaxel-carboplatin

Received December 19, 2016, and in revised form January 22, 2017.
Accepted for publication March 10, 2017.

(*Int J Gynecol Cancer* 2017;00: 00–00)

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ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000001021

Early-stage cervical cancer (IA1–IB1) can be treated by primary surgery or concomitant chemoradiation (CCRT), whereas International Federation of Gynecology and Obstetrics (FIGO) stage IIIA or higher is usually treated with CCRT. For locally advanced cervical cancer (FIGO stage IB2–IVA), the most often used therapy is CCRT, but there is evidence that neoadjuvant chemotherapy (NACT) followed by radical hysterectomy (RH) might be an alternative for FIGO stage IB2 to IIB cervical cancer.[1,2]

The principle of NACT followed by RH is to reduce the tumor volume and making the tumor operable. The long-term complications after radiotherapy, castration of the patients, the poor control of metastatic disease, and the lack of possibility for CCRT in less developed countries contribute to the use of NACT followed by surgery.

There have been a number of publications on NACT followed by RH.[3] The meta-analysis published on NACT followed by RH compared NACT with radiotherapy alone. This study consisted of 5 randomized trials with a total of 872 patients and showed a significant benefit for NACT followed by surgery compared with radiotherapy.

A second part of the meta-analysis compared NACT followed by radiotherapy versus radiotherapy alone, showing a significant survival benefit for short-interval chemotherapy (<14 days) followed by surgery and for the higher dosages of cisplatin (>25 mg/m^2). Since the US Food and Drug Administration alert in 1999, radiotherapy in combination with chemotherapy (weekly cisplatin) (CCRT) has become standard of care because of the improved survival results when adding concomitant chemotherapy.[4,5] The results of the randomized study of the EORTC (European Organisation for Research and Treatment of Cancer) comparing NACT followed by RH versus CCRT are still awaited.

Several chemotherapeutic agents have been tested as NACT in cervical cancer, with cisplatin, paclitaxel, and ifosfamide considered among the most active drugs.[6–9] An Italian group showed in the SNAP (Studio Neo-Adjuvante Portio) 01 trial that TIP (paclitaxel, ifosfamide, and cisplatin) resulted in a higher response rate than IP, without a statistically significantly different effect on overall survival.[10] The SNAP-02 trial of Lissoni et al[11] compared TP with TIP and showed TIP to be the most active (25% vs 43% pathological optimal response rate). However, TIP also has an important higher morbidity compared with TP (neutropenia in 26% and 76%, respectively).[11]

Recently, it has been shown that 3-weekly paclitaxel-carboplatin has similar efficacy compared with 3-weekly paclitaxel-cisplatinum in recurrent cervical cancer.[12] In the meantime, Mori et al[13] showed in 2010 that weekly paclitaxel and carboplatin at a dose of paclitaxel 60 mg/m^2, carboplatin (area under the curve [AUC] 2), as NACT for cervical cancer, to be promising. These findings together with the meta-analysis showing the importance of using dose-dense regimens[4] and our encouraging results with dose-dense paclitaxel-carboplatin in the recurrent setting resulted in the current prospective nonrandomized phase 2 trial investigating the role of dose-dense paclitaxel-carboplatinum as NACT in cervical cancer.[14]

In this study, we present 36 patients treated with weekly TC for locally advanced cervical cancer (IB2–IIB) followed in case of response by RH or early-stage (IB1) cervical cancer followed by conization.

METHODS

We started this prospective phase 2 trial to investigate the aim of pathologic complete remission after treatment of neoadjuvant paclitaxel and carboplatin in dose-dense doses. Patients were recruited between 2005 and 2014 in the University Hospitals Leuven in Belgium. A data analysis of all patients treated with neoadjuvant paclitaxel-carboplatin chemotherapy was done between 2005 and 2016 in the University Hospitals Leuven. All these patients were planned to receive NACT followed by surgery. Only patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix were included. Patients with high-risk histology such as small cell, neuroendocrine, and glassy cell tumors were excluded.

An optimal pathological response of 43% has been reported with TIP.[10,11] A sample size of 36 patients was planned to provide for an OPT of 50%, with a more than 90% power and 95% confidence intervals of the maximum half width equal to 16% (confidence interval, 34%–66%).

The study was approved by the ethical committee of University Hospitals Leuven (S57619).

At diagnosis, all patients had a pretreatment evaluation with medical history, physical examination including pelvic examination under anesthesia and cystoscopy, preoperative blood test including tumor markers (SCC if squamous histology and CA-125 if adenocarcinoma), magnetic resonance imaging scan of the pelvis, and systemic examination by computed tomography (CT) of the thorax and abdomen or whole-body positron emission tomography–CT.

Chemotherapy was administered in a dose-dense regimen at a mean weekly dose of paclitaxel 60 mg/m^2 and carboplatin AUC 2.7 (either at weekly infusions at this dose or paclitaxel 90 mg/m^2, carboplatin (AUC 4) on days 1 and 8, every 3 weeks. The 2 regimens were given for 9 weeks preoperatively.

After NACT clinical examination of the pelvis, magnetic resonance imaging of the pelvis and CT of the thorax and abdomen or positron emission tomography–CT was repeated. Response was reported according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).[15] Surgery was done 4 weeks after the last course of chemotherapy in patients showing response and who were operable. If the patient was inoperable, chemoradiation was advised.

Pathologic response was defined as in the SNAP-1 trial[10] as OR, including a complete disappearance of tumor in the cervix with negative pelvic lymph nodes (CR), or a residual disease with less than 3-mm stromal invasion or in situ carcinoma (PR1). Suboptimal response consisted of persistent residual disease with more than 3-mm stromal invasion in the surgical specimen (PR2).

Adjuvant chemoradiation was standard prescribed if pathology showed positive lymph nodes or in case of involved resection margins.

Overall survival and progression-free survival were both calculated by Kaplan-Meier curves. SPSS Statistics version 21 by IBM Corporation (Armonk, NY) was used for the statistical

calculations. Hematologic and nonhematologic toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 criteria.[16]

RESULTS

The median age of the patients was 45 years (range, 25–75 years). Most patients received a diagnosis of a squamous carcinoma (29 patients, 81%), whereas 5 patients received a diagnosis of an adenocarcinoma (14%), and 2 patients had an adenosquamous carcinoma (6%). At start, 13 patients (36%) had suspected lymph nodes. Median weight was 64 kg (range, 45–104 kg). Nine patients had a FIGO stage IB1 (25%), 7 patients had stage IB2 (19%), 3 patients had stage IIA (8%), and 17 patients had stage IIB disease (47%). Twelve patients were treated with the d1, 8 regimen every 3 weeks (33%), and 24 patients with the weekly regimen (67%). The median number of treatment weeks was 9 (range, 6–9 weeks).

Evaluation according to the RECIST criteria after chemotherapy showed 11 patients with complete remissions (31%), 21 with partial remissions (58%), 2 with stable diseases (6%), and 2 with progressive diseases (2%) (Table 1).

TABLE 1. RECIST and pathological response in relation to FIGO stage, surgical margins, and histological type (neoadjuvant dose-dense paclitaxel-carboplatin in cervical cancer)

Patient No.	FIGO Stage	Response After Chemo	Positive Surgical Margins	Pathologic Response
1	IB2	PR	0	PR1
2	IIB	PR	0	PR1
3	IIB	PR	—	Inoperable*
4	IB2	PR	0	PR2
5	IIB	PR	0	PR2
6	IIB	PR	1	PR2
7	IIA	SD	1	PR2
8	IIB	PR	—	Inoperable*
9	IIB	SD	—	Inoperable*
10	IIB	PR	0	PR2
11	IIA	CR	0	CR
12	IIA	PR	0	PR2
13	IIB	PR	—	Inoperable*
14	IB2	CR	1	PR2
15	IB1	CR	0	CR
16	IB1	CR	0	CR
17	IB1	CR	0	CR
18	IB1	CR	0	CR
19	IB1	CR	0	CR
20	IB1	CR	0	CR
21	IB1	CR	0	CR
22	IB1	PD	0	PR2
23	IIB	PR	0	PR2
24	IB2	PD	—	Inoperable*
25	IIB	PR	0	PR2
26	IB2	PR	0	PR2
27	IIB	PR	0	PR1
28	IIB	PR	—	Inoperable*
29	IB2	PR	0	PR2
30	IIB	CR	0	CR
31	IIB	PR	0	PR2
32	IB1	CR	0	CR
33	IIB	PR	0	PR2
34	IB2	PR	0	PR1
35	IIB	PR	0	PR1
36	IIB	PR	—	PR2

RECIST response with CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease). Pathologic response with CR (complete remission), PR1 (residual disease with <3-mm stromal invasion including in situ carcinoma), PR2 (suboptimal response consisted of persistent residual disease with >3-mm stromal invasion on surgical specimen). Positive surgical margins are described as 1, and negative surgical margins as 0. If inoperable and no pathology was obtained: —.

*Patients were judged to be inoperable when no RECIST response was observed or when a partial remission was seen but with insufficient reduction of the tumor in order to be operable.

After NACT, 21 patients underwent an RH (58%), and 9 patients underwent a conization (25%). Five patients were judged to be inoperable because of no RECIST response or when a partial remission was seen but with insufficient reduction of the tumor in order to be operable. They were treated with chemoradiation (20%). Pathological CR was seen in 10 patients, 5 patients showed a PR1 (OPT pathological response in 50% of the patients operated on), and 15 patients had a PR2. In 1 patient, adjuvant radiotherapy was administered after surgery because of close resection margin. Five patients received radiotherapy because of a positive lymph node after surgery, 2 because of close resection margins and metastatic lymph nodes after surgery, 1 because of tumor of more than 4 cm after NACT, 1 patient with a large tumor before chemotherapy and extended lymphovascular invasion and 1 patient because of young age, with positive lymph node before starting NACT and massive lymphovascular invasion.

Another patient was planned for chemoradiation, but at the start of the radiotherapy, progression with distant metastases was observed. She was further treated with chemotherapy.

The median time from the last chemotherapy to surgery was 32 days (range, 13–45 days).

Grades 3 and 4 neutropenia was seen in 20 patients (56%) and is the most observed adverse event. Fifteen patients (42%) had grade 3 neutropenia, and 5 patients (14%) had grade 4. There were no cases of neutropenic fever. None of the

TABLE 1. *(Continued)*

TABLE 2. Number of patients with adverse events of chemotherapy according to the CTCAE classification, version 3.0*

	Neutropenia	Thrombocytopenia	Anemia	Neuropathy	Kidney
Grade 0	8 (22%)	20 (56%)	3 (8%)	30 (83%)	33 (92%)
Grade 1	1 (3%)	13 (36%)	19 (53%)	5 (14%)	3 (8%)
Grade 2	7 (19%)	2 (6%)	10 (28%)	1 (3%)	0 (0%)
Grade 3	15 (42%)	1 (3%)	4 (11%)	0 (0%)	0 (0%)
Grade 4	5† (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Described toxicity is worst reported grade per patient during administration of chemotherapy.
*CTCAE version 3.0; available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
†No cases of febrile neutropenia.

patients needed colony-stimulating factors. Grade 3 thrombocytopenia was seen in 1 patient. Grade 3 anemia was seen in 4 patients (11%), whereas grades 1 and 2 anemia was seen in 22 patients. Two of the patients with grade 3 anemia were treated with erythropoietin in combination with intravenous iron therapy. Grade 2 sensoric neuropathy was seen in only 1 patient. Kidney toxicity grade 1 was seen in 3 patients. No deaths related to chemotherapy were seen (Table 2).

The median follow-up time was 17 months (range, 3–100 months). In that period, 8 patients had progressive disease. The mean time to progression was 16 months. The different sites of recurrence are described in Table 3. The estimated mean overall survival in all patients is 76 months with a 95% confidence interval of 59 to 91 months. The estimated mean progression-free survival is 67 months, with a 95% confidence interval of 51 to 84 months. The 5-year overall survival is 70.8%. The 5-year progression-free survival is 61.8%.

DISCUSSION

Neoadjuvant chemotherapy for cervical cancer is still debated. Promising results have been reported by many retrospective and several prospective randomized studies, but the results of the randomized controlled EORTC 55994 trial comparing NACT followed by RH versus CCRT in stage IB2–IIB are still eagerly awaited.

The search for effective and well-tolerated chemotherapy regimens for NACT is ongoing. TIP has been shown to be one of the most active regimens but is associated with a high toxicity and even mortality. Additional ifosfamide has an important gonadotoxic effect. TIP was compared with TP and IP in the 2 SNAP trials, with lower hematologic toxicity but also lower response rate for the 2-drug combinations.[10,11] TC in a 3-weekly scheme showed promising results in 1 study with a clinical response rate of 95%.[17] These results together with the meta-analysis showing the importance of using dose-dense regimens[4] and our results with dose-dense paclitaxel-carboplatin in the recurrent setting[14] resulted in the start of current prospective trial to investigate the pathologic complete response (CR) and toxicity of dose-dense paclitaxel-carboplatin as NACT in cervical cancer.

In this study, we present our results of paclitaxel-carboplatin in dose-dense regimens. We already showed that TC weekly is an effective regimen in recurrent cervical cancer, with a low toxicity profile.[14] The most severe toxicity was grade 3–4 neutropenia (56%), but no febrile neutropenia was observed. Grade 2 sensoric neuropathy was seen in only 1

TABLE 3. Site of recurrence

Patient No.	Type of Tumor	FIGO Stage	RECIST Response	Type of Surgery	Size of Tumor on Pathology	Central Pelvis	Pelvic Lymph Node	Upper Abdomen	Extra Abdominal
5	Squamous	IB2	PR	Wertheim	3.5 × 2 × 1.5	0	1	0	1
6	Squamous	IIB	PR	Wertheim	4 × 2.6	0	0	0	1
8	Adenocarcinoma	IIA	SD	Wertheim	32 × 25 × 17	0	0	0	1
11	Squamous	IIB	PR	Wertheim	11 × 20 × 30	1	1	1	1
14	Squamous	IIB	PR	Inoperable	—	1	0	0	0
16	Adenosquamous	IB1	CR	Conization	NRT	1	0	0	0
23	Squamous	IB1	PD	Wertheim	20 × 25 × 28	0	1	0	1
29	Squamous	IIB	PR	Inoperable	—	0	1	1	0

RECIST response with CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease). Sites of recurrences are denoted as 1.
NRT, no residual tumor.

patient. No alopecia is seen, especially since the use of cold caps in our hospital.

In the current study with dose-dense paclitaxel-carboplatin, we observed excellent clinical (89%) and pathological response rates in patients operated on (no tumor on pathology or invasion of <3 mm in 50% of the patients). This compared with the 84% clinical response (CR or PR) seen in TIP.[18] These results are also comparable with those seen by Mori et al[13] (87% objective response rate).[13]

The main difference between our study and that of Mori et al[13] is the dose of carboplatin. We used a mean weekly dose of paclitaxel 60 mg/m^2 and carboplatin (AUC 2.7) (TCw) or paclitaxel 80 mg/m^2 and carboplatin (AUC 4) d1,8 every 3 weeks (TCdd), whereas Mori et al[13] used the same paclitaxel dose but a carboplatin dose of AUC 2.0.

The pathologic response rate in our population is comparable to the SNAP-02 trial[11] with a pathologic response of 43% with TIP and 25% with TP, 3 weekly. The SNAP-01 trial showed an optimal response rate of 23% for IP. We should, however, remark that in our series 9 patients with FIGO stage IB1 tumors were included. Table 1 confirms that the highest response rate radiologically and pathologically is seen in the more prognostically favorable tumors (FIGO stage IB1).

The 5-year overall survival and progression-free survival were 70% and 66%, respectively. The SNAP trial showed a similar overall survival of 78% for TIP and 71% for TP.[11]

We therefore propose that weekly paclitaxel carboplatin should be considered as an alternative to TIP.[10,11] Using our doses described in this study in combination with the weekly administration, in our experience, we find an intensive continuous dose of paclitaxel and carboplatin, with similar results of effectiveness but with less toxicity and better toleration.[14]

In conclusion, dose-dense paclitaxel-carboplatin is a well-tolerated regimen with promising efficacy as NACT in cervical cancer.

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