Chapter 6

Neoadjuvant Chemotherapy for Cervical Cancer: Rationale and Evolving Data

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Additional information is available at the end of the chapter

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1. Introduction

Cervical cancer is still the second most common female malignancy and the second most common cause of cancer-related mortality in women worldwide. [1] In 1999, the National Cancer Institute showed that in addition to radiotherapy, cisplatin chemotherapy produced a therapeutic effect in women with locally advanced cervical cancer (LACC) in 5 randomized trials. [2-7] However, the standard treatments for early cervical cancer have traditionally comprised radical hysterectomy with lymph node dissection or cisplatin-based chemoradiation. [8] Unfortunately, poor prognosis was observed in patients with tumors more than 4 cm in diameter and a poor survival rate of 50–60% was noted in patients with large tumors. To improve the therapeutic results, a new approach with neoadjuvant chemotherapy (NACT) followed by radical surgery or chemoradiation has been introduced. The definition of NACT in cervical cancer is the administration of chemotherapy for the purpose of reducing the cancer volume before the main treatment. In the late 1980s, a pilot study of NACT with cisplatin, bleomycin, and methotrexate performed for 33 patients with a tumor larger than 4 cm showed a response rate of 75.7% (complete response 12.1%, partial response 63.6%) on histologic examination. The sites showing a sensitive response to NACT were the vagina, cervix, and parametrium, in that order. [9] In 1989, Kim et al. performed NACT with vinblastine, bleomycin, and cisplatin (VBP) in 54 patients and reported a high response rate (81.0%), a low incidence of lymph node metastasis (20%), and an improvement in the 2-year tumor free survival rate (94%). [10]

Since 1990, trials evaluating NACT combined with surgery and/or radiation therapy have been undertaken, and this combination therapy has been compared with standard treatments such as radical surgery, radiation therapy, and concurrent chemoradiation.

The aim of this chapter is to investigate the chemotherapy agents used in NACT, know the rationale of NACT before surgery and/or radiation therapy, and review the articles comparing results of NACT with that of surgery or radiation for cervical cancer.

2. Agents used in NACT

Historically, cisplatin has been considered the most active platinum agent drug, with a response rate of 20% in cervical cancer. Although a higher response rate is reported with a dose of 100 mg/m^2 than with a dose of 50 mg/m^2, no differences in complete remission rate, overall survival (OS), and progression-free interval (PFS) were observed between these doses. A high dose of cisplatin was reported to be related to nephrotoxicity and myelosuppression. [11] Moreover, alkylating agent groups also contain an ifosfamide agent, which shows a response rate of 20% at a dose of 1.2 g/m^2 for 5 days in cervical cancer. A higher response rate was noted in patients receiving combination chemotherapy with cisplatin and ifosfamide than in patients receiving cisplatin only (31.1% vs 17.8%, p = 0.004). However, no significant difference in OS was found between these groups. [12] Doxorubicin is an anthracycline antibiotic drug that inhibits the process of cancer cell replication by intercalation into DNA. The response rate of cervical cancer to doxorubicin is reported as 20%. The most severe side effect of doxorubicin is cardiotoxicity, which can be fatal. [13] Paclitaxel, which belongs to the taxane group of drugs, stabilizes polymerized microtubules and inhibits cell division. Paclitaxel shows broad-range activity against a number of solid tumors, including epithelial ovarian cancer, lung cancer, and breast cancer. A dose of 170 mg/m^2 is administered intravenously for 24 hours every 3 weeks. The response rate of cervical cancer to paclitaxel is reported to be 17%. According to pharmacological studies, the sequence of administration is very important when paclitaxel is combined with cisplatin for chemotherapy. Administration of cisplatin before paclitaxel generates more severe hematological toxicity (e.g., neutropenia) than administration of paclitaxel before cisplatin. This distinction arises because of the delayed clearance of paclitaxel when paclitaxel is administered after cisplatin. [14]

3. Rationale of NACT

In 1997, Sardi et al. reported the first randomized trial to investigate the role of NACT in 205 stage 1B women with cervical squamous cell carcinoma. [15] The NACT regimen with 10-day intervals included 3 cycles composed of 50 mg/m^2 cisplatin, 1 mg/m^2 vincristine, and 25 mg/m^2 bleomycin. NACT enabled radical hysterectomy for inoperable bulky cervix cancer and improved the rate of complete resectability. [15, 16] NACT reduced the pelvic recurrence rate significantly and increased the survival rate while decreasing the rate of parametrial invasion

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and lymph node metastasis. An initial tumor size of less than 4.8-cm diameter showed a better response to NACT than a larger tumor size. [16] As the size of the tumor increases, the proportion of hypoxic cancer cells with decreased chemosensitivity increases. Therefore, the potential for complete resection decreases for large tumors. [17, 18] NACT increased the sensitivity of tumor cells to radiation therapy and decreased the proportion of hypoxic cells. Moreover, chemotherapy can be more effectively delivered to tumor volume before blood vessel is destructed by surgery or radiation therapy. [19] However, an undesired delay in the main treatment and resistance to radiation therapy can occur after NACT. [20, 21]

4. Dose of chemotherapy and interval of cycles in NACT

In 2003, the results of a large-scale meta-analysis that systemically reviewed 21 randomized trials were reported. [22] In a comparison of NACT followed by radiation therapy with radiation therapy alone, 2,074 patients in 18 randomized trials were considered for meta-analysis. NACT provided a benefit in survival for cervical cancer patients treated with shorter (interval ≤ 14 days) (hazard Ratio {HR}, 0.83; 95% confidence interval {CI}, 0.69–1.00; p = 0.046) and more dose-intensive (cisplatin ≥ 25 mg/ m^2/cycle) (HR, 0.91; 95% CI, 0.78–1.05, p = 0.20) regimens. In contrast, survival was less favorable in patients treated with longer (interval ≥ 14 days) (HR, 1.25; 95% CI, 1.07–1.46; p = 0.005) and less dose-intensive (cisplatin ≤ 25 mg/m^2/cycle) (HR, 1.35; 95% CI, 1.11–1.14; p = 0.002) regimens. Moreover, in a comparison of NACT followed by surgery with radiation therapy, 872 patients from 5 randomized trials were reviewed and a significant decrease in the risk of death was found (HR, 0.65; 95% CI, 0.53–0.80; p = 0.0004). As a result, a short interval and a high dose of cisplatin appear to offer a great advantage for survival in cervical cancer patients. [22]

5. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

In 2010, the Cochrane Database of Systematic Reviews curated by the MRC Clinical Trial Unit, London, UK, [23] demonstrated the role of NACT in women with early or LACC. This systemic review included 1072 patients, and outcomes such as OS, PFS, pathological response, recurrence rate, and resection rates were investigated. Increased PFS (HR, 0.76; 95% CI, 0.62–0.94; p = 0.01), decreased rate of parametrial invasion (odds ratio {OR}, 0.58; 95% CI, 0.41–0.82; p = 0.002), decreased rate of lymph node metastasis (OR, 0.54; 95% CI, 0.39–0.73; p < 0.0001), reduced recurrence at both local (OR, 0.76; 95% CI, 0.49–1.17; p = 0.21) and distant (OR, 0.68; 95% CI, 0.41–1.13; p = 0.13) sites, and resection rate (OR, 1.55; 95% CI, 0.96–2.50; p = 0.07) were observed in this review. Disappointingly, no OS benefit was noted (HR, 0.85; 95% CI, 0.67–1.07; p = 0.17). Although favorable results were noted in patients treated with NACT followed by surgery, a significant advantage with regard to OS was not seen. Therefore, the beneficial role of NACT over surgery alone is still unclear in women with early-stage or LACC. [23]

6. Neoadjuvant chemotherapy plus radical surgery versus radiation therapy

Between 1990 and 1996, a randomized trial was performed in 14 Italian centers, and 441 women were categorized into 2 groups: NACT followed by surgery patients and radiation only patients. For patients with stage IB2 to IIB tumors, treatment with NACT and surgery showed a 5-year survival rate of 64.7% and a PFS rate of 59.7%. These values were significantly greater than those in the radiation only group (18.3% and 13.0%, respectively) ($p = 0.005$ and $p = 0.02$, respectively). [24] However, an analysis of patients with stage III tumors only showed no significant differences in OS and PFS (OS: 41.6% vs 36.7%, $p = 0.36$; PFS: 41.9% vs 36.4%, $p = 0.29$). With this result, it may be suggested that the more progressed is tumor volume, the lesser benefit of NACT and subsequent surgery is noted over radiation therapy. Multivariate analysis showed that OS and PFS were significantly affected by stage, treatment modality, cervical tumor diameter, and lymph node metastasis on computed tomography/lymphangiography. The relative risk of OS in patients treated with NACT plus surgery compared with patients treated with radiation only was 0.63 (95% CI, 0.47–0.86). However, no significant differences were observed in the pattern of recurrence between the NACT plus surgery group and the radiation group. [24] In this study, NACT followed by surgery showed better results with regard to OS and PFS than the radiation only group.

On the other hand, Cervical Cancer Study Group of the Asian Oceanian Clinical Oncology Association [25] performed a chemotherapy of cisplatin 60 mg/m^2 and epirubicin 110 mg/m^2 at 3-week intervals for three cycles, and reported that NACT prior to radiation for cervical cancer patients with stage IIB-IVA showed a significantly higher pelvic recurrence rate compared to those who were treated with radiation therapy alone ($p < 0.003$). Also, lower response rate and inferior survival outcome were noted in patients treated with NACT before radiation compared to patients who received radiation therapy alone. This randomized trial of epirubicin and cisplatin chemotherapy followed by pelvic radiation in LACC failed to demonstrate advantage to NACT prior to radiation over radiation therapy alone in local control and tumor response. [25]

7. Neoadjuvant chemotherapy plus radical surgery versus surgery only and concurrent chemoradiation therapy only

Retrospective review of the follow-up reports of 476 patients with stage IB2-IIB cervical cancer enrolled from 2000 to 2005 indicated that patients treated with NACT followed by surgery showed significantly higher 5-year survival rates than both the radical surgery (OS: HR, 1.813; $p = 0.0175$) and concurrent chemoradiation treatment (OS: HR, 3.157; $p < 0.0001$) groups. [26] Moreover, in the NACT plus surgery group, NACT with a combination of paclitaxel and cisplatin (TP) chemotherapy improved the long-term disease-free survival (DFS) and OS compared NACT with a chemotherapy regimen of vincristine, bleomycin, and cisplatin (VBP) ($p < 0.001$). A tumor size of more than 4 cm caused a significant reduction in both the 5-year

http://dx.doi.org/10.5772/53406

DFS and OS rates (HR, 1.762; 95% CI, 1.131–2.744; p = 0.0122 and HR, 1.669; 95% CI, 1.164–2.392; p = 0.0053, respectively). The limitation of this study is that a selection bias resulted because of the retrospective nature of the investigation. In terms of the proportion of patients with a tumor larger than 4 cm, a higher rate was observed in the concurrent chemoradiotherapy group than in the NACT plus surgery group (77.7% vs 49.7%). [26]

8. The drug combination and regimen of NACT

In 1983, Friedlander reported that a combination of cisplatin (60 mg/m^2 on day 1), vinblastine (4 mg/m^2 on days 1 and 2), and bleomycin (15 mg on days 1, 8, and 15) followed by radiation therapy and/or surgery was performed for 35 cervical cancer patients at 3-week intervals. In this study, 66% of cancer patients showed responsiveness, with 18% showing complete responsiveness, to NACT with radiation and/or surgery. [27]

Between 1983 and 1990, Hwang et al. enrolled 80 women with stage IB to IIB cervical cancer with a tumor diameter of more than 4 cm. A NACT regimen of VBP followed by radical hysterectomy with pelvic lymphadenectomy showed overall 5-year and 10-year DFS rates of 82.0% and 79.4%, respectively. The VBP regimen is considered a tolerable combination with low hematological toxicity and a favorable response rate. [28] In 1990, Lara et al. reported that the administration of cisplatin and ifosfamide chemotherapy was an effective anti-cancer remedy for cervical cancer IIIB patients as a neoadjuvant treatment. The chemotherapy schedule was composed of 20 mg/m^2 cisplatin on days 1–5 and 1.5 g/m^2 ifosfamide on days 1–5. Thereafter, radiotherapy was performed, and 62.5% of patients experienced at least a 50% reduction in tumor size. The authors reported that these results were superior to those for radiotherapy alone. [29]

The SNAP01 (Studio Neo-Adjuvante Portio) randomized trial was performed in 21 Italian centers from 1997 to 2000, and 219 patients were divided into 2 groups: 113 women were treated with the ifosfamide, and cisplatin (IP) combination regimen and 106 received the paclitaxel, ifosfamide, and cisplatin (TIP) combination regimen. [30] The response rate of patients treated with the IP regimen was 23%, whereas that of patients treated with the TIP regimen was 48% (p = 0.0004). However, the HR was not significant for patients treated with the TIP regimen (HR, 0.66; 95% CI, 0.39–1.10; p = 0.11) and those treated with the IP regimen with respect to OS. Hematological toxicity was more severe in the TIP regimen group; therefore, women older than 70 years or those with renal problems were not recommended for intense NACT. The authors suggested that the optimal response rate could be used as a surrogate marker for survival. Thus, optimal response rate can be used as a cornerstone to quickly monitor the therapeutic results in cervical cancer patients.

Helena et al. [31] performed NACT in 141 women with cervical cancer 1B (1B1: 30 patients, 1B2: 111 patients) from 1998 to 2008. A regimen of cisplatin (75 mg/m^2) and ifosfamide (2 g/m^2) was used in patients with squamous cell cervical cancer and a combination of cisplatin (75 mg/m^2) and doxorubicin (35 mg/m^2) was used in women diagnosed with adenocarcinoma. The NACT cycle was 3 days, and the interval was 10–14 days. The most common hematological

toxicity was neutropenia. Interestingly, 69.5% of women who were treated with NACT experienced a reduction in tumor size of more than 50%, and 11.3% of patients showed no residual malignancy on pathological examination after NACT. Further, the 5-year survival rate was 80.6%, and 56.8% of patients are now disease free.

From 1999 to 2004, Bae et al. [32] enrolled 112 patients with stage IB to IIB tumors who were treated with 3 cycles of NACT composed of cisplatin (60 mg/m^2 on days 1 and 2) and etoposide (100 mg/m^2 on day 1). Etoposide is a topoisomerase inhibitor that inhibits the re-ligation of DNA strands and induces breaks in DNA strands. Etoposide can induce cell death through autophagy. The authors demonstrated that NACT followed by surgery resulted in 5-year OS and PFS rates of 88.1% and 60.5%, respectively.

Between 2000 and 2002, Park et al. [19] administered a NACT regimen of paclitaxel (60 mg/m^2 on day 1) and cisplatin (60 mg/m^2 on day 1) for 43 stage IB2 to IIB cervical cancer patients, with 3 cycles every 10 days. The authors reported a high response rate of 90.7%, with a complete response rate of 39.5% (11.6% confirmed by pathology), a partial response rate of 51.2%, and no cases of progression. Thirty-one of 43 patients (72.1%) experienced downstaging of cervical cancer. The 43 patients underwent radical hysterectomy and lymph node dissection after NACT. The 2- and 5-year DFS rates were 94.5% and 89.2%, respectively. Response after NACT, differentiation of cancer cells, and metastasis were reported to be associated with survival. The authors insisted that the reduced delay because of the shorter interval of NACT had a positive effect on survival. [33]

In 2004, NACT was successfully used in fertility-preserving radical trachelectomy for young women with early-stage cervical cancer. The chemotherapy regimen was composed of paclitaxel (175 mg/m^2 on day 1), cisplatin (75 mg/m^2 on day 2), and ifosfamide (5 g/m^2 over 24 hours). [34]

Between January 2006 and December 2009, 123 women with stage IB2 to IIA cervical cancer were randomly divided into 4 groups. The NACT combination was cisplatin (50 mg/m^2) and 5-fluorouracil (750 mg/m^2) at a 2-week interval. No significant differences in 3-year PFS and OS were observed between the 4 groups. [35]

Between 2007 and 2010, 46 cancer patients with stage IB2 to IIIB tumors were enrolled. The NACT schedule was topotecan (0.75 mg/m^2 on days 1–3) followed by cisplatin (75 mg/m^2 on day 1). The authors examined the therapeutic results in patients treated with NACT followed by surgery. They found that 89.5% of patients experienced a pathological response and 15.8% achieved a complete response. The 2-year PFS and OS of the 38 patients treated with NACT and surgery were 79% and 95%, respectively. [36]

In 2012, the Japanese Gynecologic Oncology Group reported a phase II NACT study with irinotecan hydrochloride and nedaplatin followed by radical hysterectomy for bulky stage IB2 to IIB cervical squamous cell carcinoma. Sixty-six patients were treated with irinotecan (60 mg/m^2 on days 1 and 8) and nedaplatin (80 mg/m^2 on day 1) with a 21-day interval. Radical hysterectomy was performed after NACT, and the response rate was 75.8%. Of these patients, 72.2% complained of neutropenia, and the side effects of NACT were acceptable. [37]

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9. Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy

Between 2000 and 2007, NACT (cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2, 3 cycles every 3 weeks) plus surgery followed by 4 cycles of platinum-based adjuvant chemotherapy was performed by Angioli et al. The authors reported that the 5-year OS and DFS rates were 81% and 70%, respectively. The 5-year OS rates of cervical cancer patients with positive and negative lymph nodes were 75% and 88%, respectively. The authors showed that adjuvant chemotherapy after NACT and surgery could be useful for patients with LACC. [38]

10. Currently ongoing randomized trial

A randomized phase III trial comparing the effectiveness of cisplatin-based NACT followed by radical hysterectomy with the effectiveness of concomitant radiotherapy and chemotherapy in patients with stage IB2 or stage II cervical cancer has been undertaken by the European Organization for Research and Treatment of Cancer (55994). However, the results of that phase III trial have been not yet published.

11. Conclusion

A review of the literature associated with NACT showed that most chemotherapy regimens included cisplatin (Table 1 and Table 2). Recently, the number of clinical trials that include the use of paclitaxel chemotherapy has gradually increased. A short interval between cycles and a high dose of cisplatin were considered optimal for NACT. Three cycles was the most frequently used method in NACT for cervical cancer. In general, the side effects and toxicity of NACT seemed acceptable for patients with cervical cancer. In a review of medical literatures, high response rate after cisplatin-based NACT provided an advantage to surgery and prevention of lymph node metastasis. Moreover, NACT prior to surgery showed acceptable improvement in survival rate in phase III trial. However, no definitive agreement on the best management strategy for NACT has been determined for early and LACC. Therefore, clinicians should carefully compare the efficacy of NACT with the disadvantages of the delayed start of the main treatment and the toxicities associated with chemotherapy.

In the future, early markers or clinical variables for monitoring the effect of NACT during the early phase may be helpful for determining the optimal treatment for cervical cancer patients. Further, drugs that are highly effective for cervical cancer will need to be developed for the NACT regimen. For the determination of optimal treatment in cervical cancer, advantages of NACT should be evaluated in phase III trial compared to standard treatments.

Authors	Publication	Number	Stage	Comparison	Response rate
Friedlander [27]	1983	35	IIB	cisplatin (60 mg/m^2 day1), vinblastine (4 mg/m^2, days 1 and 2), and bleomycin (15 mg, days 1, 8, and 15) followed by radiation therapy and/or surgery	66% (complete response 18%)
Lara [29]	1990	26	IIIB	cisplatin (20 mg/m^2 on day 1-5) and ifosfamide (1.5 g/ m^2 on day 1-5)	62.5%
Hwang [28]	2001	80	IB-IIB	cisplatin (50 mg/m^2 day1), vinblastine (4 mg/ m^2, days 1), and bleomycin (16 mg/ m^2, days1, 2)	93.7% (complete response 50%)
Park [19]	2004	43	IB-IIB	paclitaxel (60 mg/m^2, day 1) and cisplatin (60 mg/m^2, day 1)	90.7%
Buda [30]	2005	113	IB-IV	cisplatin 75 mg/m^2 paclitaxel 175 mg/m2 ifosfamide 5 g/m2	48%
Bae [32]	2008	112	IB-IIB	cisplatin (60 mg/m^2, days 1, 2) and etoposide (100 mg/m^2, day 1)	69.7%
Helena [31]	2010	141	IB	cisplatin (75 mg/m^2) and ifosfamide (2 g/m^2)	69.5%

Table 1. Pilot study of neoadjuvant chemotherapy for cervical cancer

Authors	Publication	Number	Stage	Comparison	Neoadjuvant chemotherapy
Souhami [39]	1991	107	IIIB	NACT+RT vs RT	Bleomycin 15U IM days 1-4, vincristine 1mg/m^2 day 1, mitomycin C 10 mg/m^2 day 1, cisplatin 50 mg/m^2 day 1,
Chauvergne [40]	1993	151	IIB~III	NACT+RT vs RT	methotrexate, chlorambucil, vincristine, cisplatin
Tattersall [25]	1995	260	IIB~IVA	NACT+RT vs RT	cisplatin 60 mg/m^2 and epirubicin 110 mg/m^2 day 1
Sardi [15]	1997	205	IB	NACT+RT vs RT	vincristine 1mg/m^2 day 1, cisplatin 50 mg/m^2 day 1, bleomycin 25 mg/m^2 days 1-3
Kumar [41]	1998	184	IIB~IVA	NACT+RT vs RT	bleomycin, ifosfamide, cisplatin
Symonds [42]	2000	204	IIB~IVA	NACT+RT vs RT	methotrexate 100 mg/m^2, cisplatin 50 mg/m^2
Chang [43]	2000	124	IB~IIA	NACT+RS vs RT	vincristine 1mg/m^2 day 1, cisplatin 50 mg/m^2 day 1, bleomycin 25 mg/m^2 days 1-3
Herod [44]	2000	172	IB~IVA	NACT+RS vs RT	bleomycin 30 units/24-hour infusion, ifosfamide 5 g/m^2/24 hours, cisplatin 50 mg/m^2
Benedetti-Panici [24]	2002	441	IB~III	NACT+RS vs RT	cisplatin-based NACT (with a "/>240 mg/m^2 total cisplatin dose)
Wen [35]	2012	123	IB-IIA	NACT+RS vs RS vs BT +RS vs IACT	cisplatin (50 mg/m^2) and 5-fluorouracil (750 mg/m^2) at a 2-week interval

NACT:neoadjuvant chemotherapy, RS: radical surgery, RT: radiation therapy, BT:Brachy radiation, IACT:Intra-arterial chemotherapy

Table 2. Randomized controlled trial about neoadjuvant chemotherapy for cervical cancer

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