Pharmaceutical Sciences Asia

Pharm Sci Asia 2025; 52(3), 427-432
DOI:10.29090/psa.2025.03.24.3617

Research Article

Incidence of bone marrow suppression and effectiveness of cervical cancer patients receiving concurrent chemoradiotherapy

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ABSTRACT

This study aims to determine the incidence of bone marrow suppression and the effectiveness of concurrent chemoradiotherapy (CCRT) in patients with cervical cancer. This retrospective study investigated cervical cancer patients who received CCRT between January 1, 2015, and December 31, 2018. We included patients aged ≥18 years with Stage IA2 to IVA adenocarcinoma or squamous cell carcinoma. Patients were excluded if they received neoadjuvant or adjuvant CCRT, myeloid growth factors, or erythropoietin within 28 days of the study, or had bone marrow disorders. The primary endpoint was the incidence of bone marrow suppression, with secondary endpoints of progression-free survival (PFS), overall survival (OS), and relative dose intensity (RDI). Descriptive statistics were used to analyze baseline characteristics, bone marrow suppression incidence, and RDI. OS and PFS were estimated using the Kaplan-Meier method. A total of 62 patients were included. The most common any-grade bone marrow suppression incidences were anemia (37.10%), thrombocytopenia (21%) and neutropenia (16.1%), respectively. The median PFS was 63.21 months (95% CI 56.66-69.77), the median OS was 69.25 months (95% CI 64.03-74.47), and RDI was 93.22% ± 7.93. Among cervical cancer patients received CCRT, anemia was the most common incidence of bone marrow suppression. The survival rates were remarkably high, accompanied a noticeably low recurrence rate.

Keywords:
Incidence; Effectiveness; Bone marrow suppression; Concurrent chemoradiotherapy; Cervical cancer

1. INTRODUCTION

Cervical cancer is a significant public health concern in Thailand, ranking as the fifth most common cancer among women and the fifth leading cause of cancer deaths in females. In 2022, approximately 8,662 new cases were reported, accounting for 9.3% of all female cancer cases.[1] The crude incidence rate is 25.6 per 100,000 population, with a crude mortality rate of 13.1 per 100,000, showing an annual increase.[2] Human Papillomavirus (HPV) infection is the predominant cause of cervical cancer, responsible for 90–100% of cases. The HPV vaccine can prevent the disease, and Pap smear tests are available for screening.[3]

For cervical cancer stages IA2 to IVA, the National Comprehensive Cancer Network (NCCN) guidelines recommend concurrent chemoradiotherapy (CCRT), typically combining external beam radiotherapy with weekly cisplatin (40 mg/m^2 for 6 weeks). Carboplatin is used if cisplatin is not tolerated.[4] This combined approach significantly improves outcomes for locally advanced cervical carcinoma, as radiation alone fails to control the disease in 35-90% of cases. Chemotherapy enhances radiation efficacy by sensitizing

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cancer cells, preventing repair of damaged cells, improving tumor oxygenation, and reducing tumor volume.[5] The 2018 Thai guidelines for national health insurance coverage also endorse cisplatin or carboplatin as monotherapy, or cisplatin plus fluorouracil (5-FU) as an alternative for cervical cancer treatment.[6]

Concurrent chemoradiotherapy (CCRT) significantly improves outcomes for cervical cancer patients. Observational study conducted among 11 countries in East and Southeast Asia showed the 2-year local control, progression-free survival, and overall survival rate for all patients were 96%, 78%, and 90%, respectively. 80% patients received 4 or 5 cycles of chemotherapy. Acute grade 3 leukopenia was observed in 20 of the patients (21%), and late grade 3 gastrointestinal toxicity was observed in 3%.[7] Common side effects of CCRT include nausea/vomiting, acute kidney failure, and hematological toxicity, which vary by chemotherapy type and dosage. While meta-analysis showed no significant difference in OS (HR 0.83; 95% CI 0.66-1.06) or PFS (HR 1.03; 95% CI 0.78-1.35) between weekly and every-three-week cisplatin regimens, weekly dosing resulted in significantly lower hematological toxicity (OR 0.62; 95% CI 0.46-0.83, p=0.001). No significant difference was observed in grade ≥3 gastrointestinal side effects (OR 0.72; 95% CI 0.37-1.43, p=0.35).[8] Furthermore, the relative dose intensity (RDI) of chemotherapy was significantly lower in elderly patients (≥65 years) at 0.62, compared to 1.00 in younger patients (<65 years) (p=0.023). Completing prescribed cisplatin cycles is crucial for survival, with incomplete cycles linked to worse outcomes (HR 1.90; 95% CI 1.23-2.96, p=0.004), underscoring the critical importance of RDI in cervical cancer treatment. While CCRT is the standard of care for locally advanced cervical cancer, often faces compromised efficacy due to treatment delays or dosage reductions from adverse effects. Hematological toxicity, is a common dose-limiting side effect, leading to lower Relative Dose Intensity (RDI), which is linked to poorer survival. Consequently, this retrospective study utilized the hospital's electronic database to evaluate the incidence of bone marrow suppression and the effectiveness of CCRT in cervical cancer patients.

2. MATERIALS AND METHODS

2.1 Study design, Setting and Oversight

This descriptive retrospective research involves collecting data from an electronic database. The study has received approval from the Naresuan University Human Research Ethics Committee (IRB No. 487/2021, dated November 29, 2021) and the Human Research Ethics Committee of Buddhachinnarat Phitsanulok Hospital (IRB No. 119/64, dated December 13, 2021). Cervical cancer patients who underwent concurrent external beam radiotherapy 2 Gy fractions/5 days/week plus 40 mg/m^2 cisplatin weekly at Buddhachinnarat Phitsanulok Hospital, from January 1, 2015, to December 31, 2018, were included in this study.

2.2 Study participants

Inclusion criteria were patients aged ≥18 years with stage IA2-IVA adenocarcinoma or squamous cell cervical cancer and an ECOG score of 0–2. All patients had to have confirmed absence of distant metastasis via chest CT, abdominal CT, or pelvic MRI, with tumor size assessed by RECIST criteria. They received first-line definitive CCRT with cisplatin, with no prior treatment for their cervical cancer (e.g., chemotherapy, targeted drugs, or radiotherapy). Laboratory test results were required to be within normal limits: hemoglobin (Hb) ≥10 g/dl, absolute neutrophil count (ANC) ≥1,500 cells/mm^3, platelet count ≥100,000 cells/mm^3, and creatinine clearance ≥50 ml/min. Exclusion criteria included receipt of myeloid growth factors or erythropoietin within 28 days before study entry, bone marrow abnormalities (e.g., atrophy, other cancers), or lack of available CT/laboratory data. Patients without CT or MRI evaluations of disease stage within 2 months before CCRT were also excluded.

2.3 Statistical analysis

The primary outcome was the incidence of bone marrow suppression and secondary outcomes included PFS, OS and RDI. Continuous data were described as means, median and standard deviation. Time to event data were analyzed using the Kaplan-Meier method. Bone marrow suppression was defined as neutropenia, anemia, thrombocytopenia and febrile neutropenia according to Common Terminology Criteria for Adverse Events (CTCAE) version 5. PFS duration were defined as the time from start CCRT to progressive disease or death. OS duration was defined as the time from start CCRT to death, defined as death from any cause. For patients alive at the time of analysis, duration of survival was censored at November 11, 2021. Assessment of the response to treatment was based on the Response Evaluation Criteria In Solid Tumors (RECISRT, version1.1), briefly, complete response (CR) was defined as disappearance of all target lesions, partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions, progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions, and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD[11]. SPSS 21 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Table 1 Patient characteristics

Characteristic	Number (%)
Age (years)	
Mean ± SD	52.13 ± 11.65
BSA (m^2)	
Mean ± SD	1.61 ± 0.17
ECOG performance status	
0	1 (1.61)
1	60 (96.78)
2	1 (1.61)
Histologic type	
Squamous cell carcinoma	55 (88.71)
Adenocarcinoma	7 (11.29)
FIGO Stage	
I	
IB1	3 (4.84)
IB2	2 (3.23)
IB3	0 (0.00)
II	
IIA	1 (1.61)
IIB	37 (59.68)
III	
IIIA	1 (1.61)
IIIB	10 (16.13)
IIIC	3 (4.84)
IVA	5 (8.06)
Tumor size (cm)	
Mean ± SD	5.19±1.29
Pelvic nodal status	
Positive	26 (41.94)
Negative	35 (56.45)
Unknown	1 (1.61)
Para-aortic lymph node status	
Positive	7 (11.29)
Negative	52 (83.87)
Unknown	3 (4.84)
Hemoglobin (g/dl)	
Mean ± SD	12.15 ± 1.06
Platelet ($x10^3$ cells/mm^3)	
Mean ± SD	297.50 ± 79.02
ANC ($x10^3$ cells/mm^3)	
Mean ± SD	5.18 ± 1.72

3. RESULTS

3.1 Patient population

During the study period, 202 patients with cervical cancer stages IA2-IVA who underwent CCRT. However, 140 patients did not meet the inclusion criteria due to receiving CCRT pre- or post-operatively, abnormal laboratory results, or the inability to access treatment information or follow up on treatment. Finally, a total of 62 patients were included in this study. The average age of patient was 52.13 years. Majority of patients belonged to stage IIB cervical cancer (59.7%). Squamous cell carcinoma comprised the most common type of cervical cancer (88.7%). The characteristics of the patients in our study are shown in Table 1.

3.2 Bone marrow suppression during concurrent chemoradiotherapy

A total 62 patients, at all severity grades, the majority of bone marrow suppression had anemia (37.10%), followed by thrombocytopenia (21%), and neutropenia (16.1%). The incidence of bone marrow suppression in our study is shown in Table 2.

3.3 Effectiveness outcome

A total of 62 patients received an average dose of cisplatin 38.89 mg/m^2, and the majority completed a course of chemotherapy consisting of 4 cycles. The mean dose of pelvic External Beam Radiation Therapy (EBRT) is 55.97 ± 0.25 Gy, and the Intracavitary Radiation (ICR) dose is 27.73 Gy. 98.39% of patients

Table 2 The incidence of bone marrow suppression

bone marrow suppression	Severity grade of bone marrow suppression (%)		
	All grade	Grade 1 – 2	Grade 3 - 4
Anemia	23 (37.10)	22 (35.49)	1 (1.61)
Thrombocytopenia	13 (21.00)	13 (21.00)	0 (0.00)
Neutropenia	10 (16.13)	10 (16.13)	0 (0.00)
Febrile neutropenia	0 (0.00)	0 (0.00)	0 (0.00)

adhere to complete chemotherapy plan (4 weeks) but only 22.58% adhere to complete radiation plan (6 weeks). In 48 patients who did not complete radiation plan, 30 patients (48.39%) delay less than 1 week. (Table 3).

The PFS was 63.21 months (95%CI 56.66-69.77) and OS was 69.25 months (95% CI 64.03-74.47). At the end of follow up period, 8 (12.90%) patients experienced tumor recurrence. Two patients (3.23%) had recurrence in uterus, 1 patient (1.61%) had para-aortic lymph nodes recurrence (PALN), 3 patients (4.84%) had local and distant metastasis, and 2 patients (3.23%) had recurrences in distant organs excluding PALN. At the time of last follow-up, 7 patients (11.29%) died. The median RDI% of cisplatin was 93.22% ±7.93. Two patients had 80% dose of cisplatin, 1 patients had experienced of adverse event and one patient had lower dose at cycle 1. Three patients had experienced delay and dose reduction dueto adverse event.

4. DISCUSSION

Cervical cancer stages IA2–IVA are commonly managed with CCRT; however, treatment effectiveness may be influenced by adverse reactions. Among these, hematological toxicities are frequently encountered as the most prevalent acute toxicity. The systematic review indicated that grade 1 to 2 hematological toxicities were morehigher in regimens combining radiation with cisplatin-containing chemotherapy compared to radiation therapy alone.[12] According to Tangjitgamol S, et al., our study revealed a higher frequency of hematological toxicities; there were grade 1 to 2 hematological toxicities occurrences, which included 20.2% anemia, 14.7% neutropenia and 2.3% thrombocytopenia. These effects occur rapidly during the course of the five-week treatment.[13] In contrast, grade 1 to 2 hematological toxicities were detected more frequently than in our study by Reig A, et al., 94.6% anemia, 50% leukopenia, and 100% thrombocytopenia were discovered.[14] According to Motala F, et al., there was a grade 1 to 2 hematological toxicities that included 68% anemia, 16% neutropenia and 22% thrombocytopenia. However, our study shown grade 3 to 4 hematological toxicities less than previous.[13-16] The alterations typically revert upon discontinuation of the treatment. Hemoglobin (Hb) experienced a notably greater decrease compared to other cellular components in both groups, followed by white blood cells (WBC). Anemia is characterized by Hb levels below 10 g/dL. The primary cause of anemia is impaired erythropoiesis due to the release of inflammatory cytokines, alongside reduced production of hematopoietic growth factors, malabsorption, and impaired iron recycling. Additional causes of anemia encompass nutritional deficiencies,

Table 3 Chemotherapy and radiation treamtent

Treatment	Number (%)
Radiation (mean ± SD)	
pelvic EBRT (Gy)	55.97±0.25
ICR (Gy)	27.73±0.68
Number of days receiving radiotherapy	27.98±0.13
Chemotherapy (mean ± SD)	
Total cycle number	3.98±0.13
Dose of weekly cisplatin (mg/m^2)	38.89±8.20
%RDI	93.22±7.93
Adherence	
chemotherapy	
complete plan (4 cycle)	61(98.39)
not adhering to the plan	
1 cycle	1(1.61)
2 cycles	0(0.00)
3 cycles	0(0.00)
Radiation	
complete plan (6 weeks)	14 (22.58)
not adhering to the plan	48 (77.42)
≤ 1 week	30 (48.39)
>1 week	18 (29.03)

hemolysis, infiltration of malignant cells into the bone marrow, and bone marrow infections.[15]

Based on findings from a randomized clinical trial, the standard of care for stage IB–IVA cervical cancer disease is concurrent chemoradiation with platinum-containing chemotherapy. Our study has demonstrated significant results in terms of PFS (63.21 months, 95% CI 56.66-69.77) and OS (69.25 months, 95% CI 64.03-74.47). Only 8 (12.90%) patients experienced tumor recurrence. Previous studies have reported PFS rates of 60.3% ± 14.3% at 3 years and 53.0% ± 15.7% at 5 years, along with OS rates of 95.1% ± 6.4% at 3 years and 80.4% ± 13.1% at 5 years.[14] The occurrence of adverse effects of treatment leads to treatment limitations, resulting in deviations from the treatment plan. Some patients are diagnosed to postpone treatment period, decrease chemotherapy dose, or delay treatment rounds combined with dosage adjustments. For patients who unable to tolerate according to treatment plan, can impact treatment outcomes. Our study of 57 patients revealed an average RDI of ≥ 85%, with only five patients falling below this. Notably, our hospital's standard protocol of four chemotherapy cycles delivered concurrently with radiotherapy diverges from findings in previous studies and established guidelines. For instance, a previous study reported a significantly lower median RDI in older patients (≥ 65 years) at 0.62 (range, 0.20–1.00) compared to 1.00 (range, 0.04–1.00) in younger patients ($p = 0.023$). However, this difference in RDI did not translate to significant differences in 5-year progression-free survival ($p = 0.685$) or 5-year overall survival ($p = 0.791$) between those groups.[9]

Strengths of our study include patients had relatively long-term follow-up and real -world practice. Our study also had limitations, as a retrospective study, it is subject to limitations related to data completeness, which can arise from changes in data collection systems and the inclusion of patients referred from other hospitals, leading to inaccessible and missing data. Furthermore, the study is constrained by a small sample size. The treatment practice for cervical cancer patients in this study deviated from standard practice. Therefore, it is advisable for future studies to augment the sample size by including additional research sites or extending the duration for recruiting patients.

5. CONCLUSIONS

In conclusion, cervical cancer patients treated with cisplatin concurrent chemoradiotherapy showed the acute hematological toxicities especially anemia. Nonetheless, these adverse effects are typically tolerable and manageable. The survival rates were very high, with a noticeably low recurrence rate.

6. ACKNOWLEDGEMENTS

Author contribution

KD: conceptualization, data curation, data analysis and interpretation, statistical analysis, writing original draft preparation, manuscript preparation, supervision. NW and CK: conceptualization, data collection, data analysis and interpretation, statistical analysis, manuscript preparation. OK: conceptualization, data analysis and interpretation, manuscript preparation, supervision. KT and SK: data collection, data analysis and interpretation, manuscript preparation. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This research received no external funding

Ethics approval

The study was approved by the the Naresuan University Human Research Ethics Committee (IRB No. 487/2021, dated November 29, 2021) and the Human Research Ethics Committee of Buddhachinnarat Phitsanulok Hospital (IRB No. 119/64, dated December 13, 2021).

Article info:
Received December 29, 2024
Received in revised form July 13, 2025
Accepted July 15, 2025

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