Gemcitabine and Radiotherapy in the Treatment of Uterine Cervical Cancer Patients at Phramongkutklao Hospital

Phanida Jarruwale MD*,
Yawana Tanapat MD*, Pote Aimpun MD, MSc, DrPH**

** Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand*
*** Department of Military and Community Medicine, Phramongkutklao College of Medicine, Bangkok 10400 Thailand*

Objectives: *To determine response, complication and survival of uterine cervical cancer patients treated with concurrent gemcitabine radiotherapy.*
Material and Method: *A retrospective review of medical records of 41 patients with uterine cervical cancer patients, stage IIB and above treated with concurrent gemcitabine radiotherapy from August 2000 to August 2003.*
Results: *At 6 and 12 months of follow up, the complete response rate was 75.6% and 65.9%. The cumulative probability of survival at 6 and 12 months after treatment was 0.93 and 0.85. The main complications were mild hematologic and nonhematologic toxicities.*
Conclusion: *Concurrent gemcitabine radiotherapy provided a satisfactory response in patients with uterine cervical cancer with mild toxicity. Long term follow up data is necessary to determine the recurrent rate of this regimen.*

Keywords: *Cervical cancer, Gemcitabine, Radiotherapy*

J Med Assoc Thai 2005; 88(Suppl 3): S19-24
Full text. e-Journal: *http://www.medassocthai.org/journal*

Uterine cervical cancer is the most common gynecologic malignancy found in Thai women[1]. Currently, the main treatment of patients with uterine cervical cancer stage IIB or above is radiotherapy alone[2,3]. Radiotherapy has limited a result in the bcontrol of cancer in patients with bulky tumor or advanced local disease resulting in decreased survival[4-7]. Improving pelvic tumor control can increase survival, but it was limited by normal pelvic tissue tolerance causing limited radiation dosage[7,8]. Chemotherapeutic agents such as cisplatin, 5-fluorouracil, hydroxyurea and mitomycin-C used concurrently with radiotherapy have resulted in improved control of pelvic tumor which resulted in improved survival[9-12].

Gemcitabine (2 , 2 -difluoro-2 -deoxycytidine or dFdC) is a synthetic pyrimidine nucleoside analog that exerts antitumor activity by multiple mechanism of action[13]. Gemcitabine was found useful against a variety of cancers either alone or in combination with other chemotherapeutic agents[14-16]. In vitro studies have demonstrated radiosensitizer potential of gemcitabine[17-19].

The objective of the present study was to determine the responses, complications and survival of patients with uterine cervical cancer treated with concurrent gemcitabine radiotherapy at Phramongkutklao Hospital.

Correspondence to: Jarruwale P, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Phramongkutklao Hospital, 315 Rajavithee Rd., Rajthavee, Bangkok 10400, Thailand. Phone: 0-2354-7600 ext. 94061, Fax: 0-2354-7630, E-mail address: phanidajw@yahoo.com

Material and Method

From August 2000 to February 2003, 41 patients with histologically confirmed uterine cervical cancer, FIGO stage IIB to IVA were treated with concurrent gemcitabine and radiotherapy. Prerequisite for inclusion were hematocrit equal or greater than 30%, creatinine clearance equal or greater than 50 ml/min and serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (AP) not more than 1.5 times of normal limit.

Treatment included external radiotherapy 2 Gy per fraction per day with a total dose of 56 Gy to the whole pelvis according to stage plus weekly intravenous gemcitabine 300 mg/m^2 of the total body surface area until external radiation was completed, and intracavitary brachytherapy with 2 applications of Cesium-137. Laboratory parameters were measured weekly. Gemcitabine administration was delayed if any of the prerequisite criteria stated above was violated. Chemotherapy was given as soon as the violated parameters had returned to normal.

After completion of treatment, patients were evaluated by pelvic examination and Pap smear by a gynecologic oncologist and radiologist, and scheduled for follow up at 1 month, then every 2 months during the first year. Follow up was every 4 months during the second year and every 6 months thereafter. Complete response was defined as complete disappearance of a visible gross tumor, partial response was at least 50% decrease in visible tumor size. Stable disease was defined as less than 50% decrease or less than 25% increase in visible tumor size. Progressive disease was defined as equal to or more than 25% increase in a visible tumor or new tumor was identified. Toxicity was assessed using WHO criteria[20]. Cumulative probability for survival at 6 and 12 months was calculated using the Kaplan-Meier method.

Table 1. Patient Characteristics

Characteristic	Number (%) (N = 41)
Age	
31-40 years	7 (17.1)
41-50 years	15 (36.6)
51-60 years	10 (24.4)
61-70 years	8 (19.5)
>70 years	1(2.4)
Tumor morphology	
Exophytic 2-3 cm	5 (12.1)
4-5 cm	18 (44.0)
6-7 cm	8 (19.5)
Infiltrative	1 (2.4)
Not described	9 (22.0)
Stage	
IIB	6 (14.6)
IIIA	1 (2.4)
IIIB	32 (78.0)
IVA	1 (2.4)
Unclassified	1 (2.4)
Histologic type	
Squamous cell carcinoma	35 (85.4)
Adenocarcinoma	5 (12.2)
Adenosquamous	1 (2.4)

Table 2. Toxicity during treatment[20] (182 Cycles)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematology					
Hemoglobin	106	53	22	1	-
WBC	110	41	22	9	-
Granocyte	137	25	13	7	-
Platelet	182	-	-	-	-
Gastrointestinal					
SGOT	173	8	1	-	-
SGPT	168	9	5	-	-
AP	179	3	-	-	-
Kidney					
Creatinine	179	3	-	-	-

Results

The patients were between 34 and 73 years old with a median age of 49 years. Most patients were in stage IIIB (78%), with tumor size of 4-7 centimeters (63.5%) and had squamous cell carcinoma (85.4%) as shown in Table 1. A total of 182 cycles of gemcitabine were given, median cycle per patient was 5 with a range of 1-7 cycles. Gemcitabine was stopped in 4 patients after the first cycle due to severe neutropenia (2 cases), previously undetected Beta-thalassemia/HbE (1 case), rising transaminase (1 case) and not willing to continue therapy at this hospital (1 case). Among the three patients in whom gemcitabine had to be stopped, one was switched to concurrent cisplatin-radiotherapy and two continued treatments by radiation alone.

Toxicity resulting in delay of gemcitabine administration included myelotoxicity (30 cycles), abnormal liver function test (5 cycles), severe diarrhea (1 cycle), fever with cystitis (1 cycle) and abnormal creatinine level (1 cycle). Details of toxicity are shown in Table 2. Hematologic toxicity was not common with grade 3 anemia (1 cycle), grade 3 neutropenia (9 cycles), grade 3 granulocytopenia (7 cycles). Grade 0 thrombocytopenia was found in all treatment cycles. Mild abnormal liver profiles were common but only 5 cycles were found with grade 2 gastrointestinal toxicity. Other complications were 17 patients with diarrhea and one patient with alopecia.

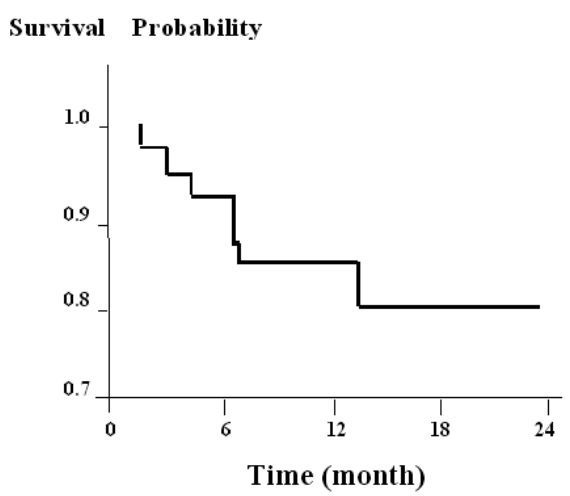

Fig. 1 Kaplan-Meier survival curve for patients with uterine cervical cancer treated with concurrent gemcitabine and radiotherapy

Follow up period ranged between 1.7-26 months with median at 14.2 months. At 6 months of follow up 31 patients (75.6%) achieved complete response and 3 (7.3%) had progressive disease. In the patients with progressive disease, two had supraclavicular lymph node metastasis and one patient died. Four patients were lost to follow up at 6 months resulting in 36 patients available for follow up at 12 months. At 12 months, 27 patients were in complete response (65.9%), 2 patients had local recurrence (4.9%) and 2 patients had stable disease (4.9%), 1 patient had progressive disease (2.4%), 1 patient died and 3 patients were lost to follow up. Cumulative probability of survival at 6 and 12 months were 0.93 and 0.85 as shown in Fig. 1.

Discussion

Concurrent chemotherapy and radiotherapy in patients with uterine cervical cancer has improved local tumor control and patient survival[11,12,19,21-25]. Gemcitabine has shown potential as a radiosensitizer[18,19] in various forms of cancer cells including cervical cancer cells thus making it a logical choice for patients with advanced or bulky uterine cervical cancer. In the present study the complete response at 6 and 12 months was 75.6% and 65.9%. This response rate is lower than the 84% complete response at 3 months after treatment found in a previous study[23]. This may be due to the inclusion of patients with stage IIB to IVA and the longer follow up period in the present study. However, cumulative probability of survival at 6 and 12 months were favorable. The reason for this may be better tumor control, especially local tumor control was good with 4.9% stable disease, 4.9% local recurrence and 2.4% progressive disease at 12 months. This was better than the 28% pelvic failure reported in concurrent cisplatin radiotherapy[26]. Complications of treatment were not severe and included only mild hematologic and nonhematologic toxicity which were managed without undesirable sequelae, which was similar to toxicity found in other concurrent chemo-radiotherapy studies[23,27,28].

The retrospective nature of the study design that may lead to biases in patients included data collection and quality of data obtained. According to the present study, the authors tried to determine responses, complications and survivals of uterine cervical cancer patients who were treated with concurrent gemcitabine and radiotherapy. Although there was switched treatment in some cases (such as one patient was switched to concurrent cisplatin-radiotherapy and two remained

with radiotherapy alone after chemotherapeutic toxicity), the authors still included every collected data because all patients were intention-to-treat cases. In order to determine the effectiveness of concurrent gemcitabine radiotherapy, a prospective controlled study should be undertaken with an adequate number of patients.

Conclusion

Concurrent gemcitabine radiotherapy seems to provide a favorable response and survival in patients with bulky or advanced uterine cervical cancer without severe toxicity. However, the limited number of patients, the follow-up period and the retrospective design of the present study does not provide conclusive evidence for effectiveness of this therapy and further studies should be conducted.

Acknowledgements

The authors wish to thank the staff of the Division of Radiation Oncology, Department of Radiology, Phramongkutklao Hospital in the treatment program for uterine cervical cancer patients.

References

1. Deerasamee S. Cervical cancer in Thailand. Proceedings of Scientific Program Cervical Cancer Screening Problems in South East Asia; 2000 Nov 6-8; Nakorn Nayok, Thailand.
2. Hacker NF. Cervical cancer. In: Berek JS, Hacker NF, editors. Practical Gynecologic Oncology. 3rd ed. Philadelphia: Lippincott Williams&Wilkins, 2000: 345-405.
3. DiSaia PJ, Creasman WT. Invasive cervical cancer. In: DiSaia PJ, Creasman WT, editors. Clinical Gynecologic Oncology 6th ed. St.Louis: Mosby, 2002: 53-111.
4. Perez CA, Camel HM, Kuske RR, Kao MS, Galakatos A, Hederman MA, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix: a 20-year experience. Gynecol Oncol 1986; 23: 127-40.
5. Kramer C, Peschel RE, Goldberg N, Kohorn EI, Chambers JT, Chambers SK, et al. Radiation treatment of FIGO stage IVA carcinoma of the cervix. Gynecol Oncol 1989; 32: 323-6.
6. Perez CA, Grigsby PW, Nene SM, Camel HM, Galakatos A, Kao MS, et al. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 1992; 69: 2796-806.
7. Coia L, Won M, Lanciano R, Marcial VA, Martz K, Hanks G. The patterns of care outcome study for cancer of the uterine cervix: results of the second national practice survey. Cancer 1990; 66: 2451-6.
8. Sasaoka M, Fuwa N, Asano A, Matsumoto A, Katou E, Ito Y. Patterns of failure in carcinoma of the uterine cervix treated with definitive radiotherapy alone. Am J Clin Oncol (CCT) 2001; 24: 586-90.
9. John M, Flam M, Sikic B, Rotman M, Cooper J, Malec M, et al. Preliminary results of concurrent radiotherapy and chemotherapy in advanced cervical carcinoma: a phase I-II prospective intergroup NCOG-RTOG study. Gynecol Oncol 1990; 37: 1-5.
10. Koumantakis E, Haralambakis Z, Koukourakis M, Mazonakis M, Haldeopoulos D, Papageorgiou N, et al. Short communication. A pilot study on concurrent platinum chemotherapy and intracavitary brachytherapy for locally advanced cancer of the uterine cervix. Br J Radiol 1998; 71: 552-7.
11. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999; 340: 1144-53.
12. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs III CL, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical cancer. N Engl J Med 1999; 340: 1154-61.
13. Storniolo AM, Allerheiligen SRB, Pearce HL. Preclinical, pharmacologic, and phase I studies of gemcitabine. Semin Oncol 1997; 24(2 Suppl 7): S7-2-7.
14. Burris III HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer : a randomized trial. J Clin Oncol 1997; 15: 2403-13.
15. Iaffaioli RV, Tortoriello A, Facchini G, Caponigro F, Gentile M, Marzano N, et al. Phase I-II study of gemcitabine and carboplatin in stage IIIB -IV non-small-cell lung cancer. J Clin Oncol 1999; 17: 921-6.
16. Burnett AF, Roman LD, Garcia AA, Muderspach LI, Brader KR, Morrow CP. A phase II study of gemcitabine and cisplatin in patients with

advanced, persistent, or recurrent squamous cell carcinoma of the cervix. Gynecol Oncol 2000; 76: 63-6.
17. Shewach DS, Hahn TM, Chang E, Hertel LW, Lawrence TS. Metabolism of 2 , 2 -Difluoro-2 - Deoxycytidine and radiation sensitization of human colon carcinoma cells. Cancer Res 1994; 54: 3218-23.
18. Lawrence TS, Eisbruch A, Shewach DS. Gemcitabine - mediated radiosensitization. Semin Oncol 1997; 24 (Suppl 7): S7-24-8.
19. Hernández P, Olivera P, Dueñas-Gonzalez A, Pérez-Pastenes MA, Zárate A, Maldonado V, et al. Gemcitabine activity in cervical cancer cell lines. Cancer Chemother Pharmacol 2001; 48: 488-92.
20. DiSaia PJ, Creasman WT. Gynecologic oncology group common toxicity criteria grade-October 1988. In : DiSaia PJ, Creasman WT, editors. Clinical Gynecologic Oncology. 6th ed. St. Louis: Mosby, 2002, 621-4.
21. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrent after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 2001; 358: 781-6.
22. Pearcey R, Brundage M, Drouin P, Jeffrey J, Johnston D, Lukka H, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002; 20: 966-72.
23. Pattaranutaporn P, Thirapakawong C, Chansilpa Y, Therasakvichya S, Ieumwananontachai N, Thephamongkhol K. Phase II study of concurrent gemcitabine and radiotherapy in locally advanced stage IIIB cervical carcinoma. Gynecol Oncol 2001; 81: 404-7.
24. Poggi MM, Kroog GS, Russo A, Mutr C, Cook J, Smith J, et al. Phase I study of weekly gemcitabine as a radiation sensitizer for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2002; 54: 670-6.
25. Runowicz CD, Wadler S, Rodriguez-Rodriguez L, Litwin P, Shaves M, O Hanlan KA, et al. Concomitant cisplatin and radiotherapy in locally advanced cervical carcinoma. Gynecol Oncol 1989; 34: 395-401.
26. Fields AL, Anderson PS, Goldberg GL, Wadler S, Beitler J, Sood B, et al. Mature results of a phase II trial of concomitant cisplatin/pelvic radiotherapy for locally advanced squamous cell carcinoma of the cervix. Gynecol Oncol 1996; 61: 416-22.
27. Pearcey RG, Stuart GCE, MacLean GD, Nation JG, Arthur K, Lukka H, et al. Phase II study to evaluate the toxicity and efficacy of concurrent cisplatin and radiation therapy in the treatment of patients with locally advanced squamous cell carcinoma of the cervix. Gynecol Oncol 1995; 58: 34-41.
28. de Lange SM, van Groeningen CJ, Meijer OWM, Cuesta MA, Langendijk JA, van Riel JMGH, et al. Gemcitabine-radiotherapy in patients with locally advanced pancreatic cancer. Eur J Cancer 2002; 38: 1212-7.

ผลการรักษาผู้ป่วยมะเร็งปากมดลูกด้วยเจมไซทาบีนร่วมกับรังสีรักษาในโรงพยาบาลพระมงกุฎเกล้า

พนิดา จารุเวฬ, เยาวนา ธนะพัฒน์, พจน์ เอมพันธุ์

บทนำ: *ปัจจุบันการให้เคมีบำบัดร่วมกับรังสีรักษามีบทบาทในการรักษามะเร็งปากมดลูกมากขึ้น เพื่อเพิ่มการควบคุมมะเร็งเฉพาะที่, ลดการแพร่กระจายของมะเร็ง และเพิ่มระยะเวลาการมีชีวิตอยู่ ผู้วิจัยมีความประสงค์ที่จะศึกษาว่าการให้เจมไซทาบีนร่วมกับรังสีรักษาในผู้ป่วยมะเร็งปากมดลูกมีผลการรักษาเป็นอย่างไร*

วัตถุประสงค์: *เพื่อศึกษาอัตราการตอบสนอง, ภาวะแทรกซ้อน และการมีชีวิตรอดของผู้ป่วยมะเร็งปากมดลูกที่รักษาด้วยเจมไซทาบีนร่วมกับรังสีรักษา*

วัสดุและวิธีการ: *การศึกษาแบบย้อนหลัง เก็บข้อมูลจากเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกตั้งแต่ระยะ IIB ขึ้นไปและได้รับการรักษาด้วยเจมไซทาบีนร่วมกับรังสีรักษา 41 ราย ระหว่างเดือนสิงหาคม พ.ศ. 2543 ถึง เดือนสิงหาคม พ.ศ. 2546*

ผลการศึกษา: *อัตราการตอบสนองแบบ complete response ที่ 6 และ 12 เดือน หลังสิ้นสุดการรักษาเท่ากับร้อยละ 75.6 และ 65.9 และอัตราการมีชีวิตรอดสะสม (cumulative probability of survival) เท่ากับ 0.93 และ 0.85 ตามลำดับ ภาวะแทรกซ้อนที่พบส่วนมากไม่รุนแรง*

สรุป: *การรักษาผู้ป่วยมะเร็งปากมดลูกด้วยเจมไซทาบีนร่วมกับรังสีรักษา ให้ผลเป็นที่น่าพอใจ และเกิดการเป็นพิษน้อย ส่วนการติดตามผลการรักษาในระยะยาวยังคงมีความจำเป็นต้องดำเนินเพื่อติดตามการกลับเป็นซ้ำของมะเร็งต่อไป*