Consolidation Chemotherapy for Locally Advanced Cervical Cancer

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Abstract

Cervical cancer is a major health problem of women all over the world. Most of cervical cancer cases and deaths occurred in developing countries, such as Thailand, China, and India, etc. This is probably due to a suboptimal screening coverage leading to a high proportion of locally advanced cervical cancer (LACC) or advanced stage disease, resulting in a poor overall prognosis. Although concurrent chemoradiation therapy is a standard treatment for LACC, high rates of local and distant failures are still encountered. New treatment modalities e.g. new chemotherapeutic regimens, combining chemotherapy with novel target agents or modification of chemotherapy dose or schedule are important. Our review focused on the role of adjuvant or consolidation chemotherapy after the standard concurrent chemoradiation therapy (CCRT) in LACC. From the studies reviewed, additional chemotherapy appeared to yield a higher response rate and increased toxicities than simply CCRT. However, survival benefit from consolidation or adjuvant chemotherapy was still inconsistent. We explored each study in detail and discuss their findings to point out some important data which will be helpful in clinical management of these LACC patients.

Keywords: locally advanced cervical cancer, consolidation chemotherapy, adjuvant chemotherapy

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บทคัดย่อ

การให้ยาเคมีบำบัดเพิ่มเติมในมะเร็งปากมดลูกระยะลุกลามเฉพาะที่

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มะเร็งปากมดลูกเป็นปัญหาสุขภาพที่สำคัญของสตรีทั่วโลก ส่วนใหญ่ของสตรีที่เป็นมะเร็งปากมดลูกและเสียชีวิตจากโรคมะเร็งมักพบในประเทศที่กำลังพัฒนา เช่น ประเทศไทย ประเทศจีน และประเทศอินเดีย เป็นต้น ทั้งนี้อาจเป็นเพราะการคัดกรองยังไม่ครอบคลุม สมบูรณ์ทำให้ส่วนใหญ่ของผู้ป่วยเหล่านี้มักจะมีโรคอยู่ในระยะลุกลามหรือลุกลามเฉพาะที่ ทำให้การพยากรณ์โรคโดยรวมไม่ดี การให้ยาเคมีบำบัดร่วมกับการให้รังสีรักษา เป็นการรักษามาตรฐานสำหรับมะเร็งปากมดลูกระยะลุกลามเฉพาะที่ อย่างไรก็ตาม ผู้ป่วยเหล่านี้ก็ยังคงมีปัญหาของการกลับเป็นซ้ำของโรคได้สูงทั้งการกลับเป็นซ้ำเฉพาะที่และการแพร่กระจายไปที่อื่น ๆ การพัฒนาหาวิธีการรักษาใหม่ ๆ เช่น ยาเคมีบำบัดชนิดใหม่ ๆ การใช้ยาเคมีบำบัดร่วมกับ targeted therapy หรือการปรับเปลี่ยนขนาดหรือช่วงเวลาการให้ยาเคมีบำบัดแบบใหม่ ๆ จึงมีความสำคัญ บทความนี้มุ่งทบทวนบทบาทของการให้ยาเคมีบำบัดเพิ่มเติม หลังการรักษามาตรฐานด้วยยาเคมีบำบัดร่วมกับการให้รังสีรักษาในมะเร็งปากมดลูกระยะลุกลามเฉพาะที่ จากการทบทวนวรรณกรรม พบว่า การให้ยาเคมีบำบัดเพิ่มเติมทำให้มะเร็งมีการตอบสนองดีขึ้นแต่ในขณะเดียวกันก็ทำให้มีอาการข้างเคียงมากขึ้นด้วย ส่วนข้อมูลในด้านประโยชน์ เช่น อัตราการรอดชีวิตจากรายงานต่าง ๆ ยังไม่สอดคล้องกัน บทความนี้ได้บรรยายถึงการศึกษาต่าง ๆ โดยละเอียดเพื่อชี้ให้เห็นข้อมูลที่สำคัญเพื่อจะได้เป็นประโยชน์กับการดูแลรักษาผู้ป่วยมะเร็งปากมดลูกระยะลุกลามเฉพาะที่ต่อไป

Cervical cancer is still a global health problem as it is the third most common cancer and the fourth leading cause of cancer death in women all over the world, accounting for 9% (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females in 2008.[1] More than 85% of these cases and deaths occurred in developing countries. Cervical cancer is the second most common female cancer with an average age standardized incidence rate of 29.2 per 100,000 women in Thailand[2] and the eighth common female cancer in China with an average age standardized incidence rate of 11.7 per 100,000 women.[3] In developing countries, a higher proportion of locally advanced (stage IB2–IVA) or advanced stages (stage IVB) were found in comparison to those found in developed countries.[4] A high proportion of advanced or locally advanced stage cervical cancer (LACC) at diagnosis may be mainly due to a suboptimal cancer screening, leading to an ultimate poorer survival outcome. Thus, any means to improve treatment outcomes in advanced or locally advanced cervical cancer (LACC) are important.

Concurrent chemoradiation therapy (CCRT) is currently the standard treatment for LACC. The combined treatment has been demonstrated to yield significantly higher survival rate than radiation therapy (RT) alone.[5–7] Despite an improvement in survival, the prognosis of patients with LACC is still poor with high rates of local and distant failures (17% and 18%, respectively).[8] Many treatment modifications have been attempted for examples: RT technique, combining chemotherapy with novel target agents, other chemotherapeutic regimens either alone or in combination with the stan-

dard drug of platinum compound, chemotherapy dose or schedule modifications, or additional chemotherapy after completion of CCRT. The role of giving additional chemotherapy after RT or radical surgery, so called adjuvant or consolidation chemotherapy has been explored in many studies involving early-stage cervical cancer[9,10] or LACC.[7,11-17] This review focuses on the studies evaluating the efficacy of additional chemotherapy in LACC which have been used in different ways: after RT[7] or after CCRT,[7,11-17] as a single arm phase II prospective study[13,14,16] or with comparative arms.[7,11,12,15,17] The terms adjuvant or consolidation chemotherapy will be used according to the primary report of each study.

Among the three single-arm studies, a report by Vrdoljak et al[13] included 62 patients with stages IB2 to IVA who received CCRT followed by consolidation chemotherapy. Concurrent chemotherapy of ifosfamide 2 g/m^2 (24 hour) plus cisplatin 75 mg/m^2 (1 hour) was given during the two applications of brachytherapy with additional four cycles of ifosfamide 2 g/m^2 (day 1-3) plus cisplatin 75 mg/m^2 (day 1) given every 21 days after completion of RT. A complete response rate (RR) of 100% was achieved at 3 months after completion of treatment. Approximately 90% overall survival (OS) was obtained. The excellent treatment outcomes regarding the complete RR and a high survival rate in this study may be because the two chemotherapeutic agents are both well recognized radiosensitizers. The authors proposed that this effect should be substantially higher with the drug administration during brachytherapy which yields a higher local dose than external radiation. Despite the excellent treatment outcomes, severe acute toxicities were encountered. Grade 3 and 4 hematologic toxicities occurred in 37% and 12% of the cycles, respectively; the most common of which was leucopenia: 25% grade 3 and 11% grade 4, with 11% incidence of febrile neutropenia. Although the authors did not separately report the timing of the acute toxicities in relation to either CCRT or consolidation chemotherapy, these unfavorable adverse effects were most likely due to the additional chemotherapy which was given for four cycles and especially the usage of ifosfamide which is notorious for its marrow suppression. Although the authors expected that the use of concurrent chemotherapy during the insertion of brachytherapy would decrease toxicity to normal surrounding organs, late urinary or gastrointestinal grade 2-4 toxicities were still encountered in 16%. Only if the dose modification of consolidation chemotherapy and the optimal survival benefit are carefully balanced, will this pattern of treatment be safer for clinical practice. Another single arm phase II study by Choi et al[14] reported the efficacy of CCRT and consolidation chemotherapy in 30 patients with cervical carcinoma stage IB2-IVA. Cisplatin 60 mg/m^2 (day 1) and 5-fluorouracil 1000 mg/m^2 (days 1-5) were given every 3 weeks concurrently with RT followed by 3 more cycles of the same chemotherapy as consolidation treatment. Complete RR was 67% after CCRT and increased to 87% at the completion of consolidation chemotherapy. The 3-year progression-free survival (PFS) and OS were 83% and 91% respectively. Toxicity was acceptable in that 94% of patients completed 3 cycles of consolidation treatment while grade 3-4 hematologic and non-hematologic toxicities were encountered in only 17% and 11% of consolidation chemotherapy cycles, respectively. Although the optimal number of cycles of additional chemotherapy after CCRT has not been settled, the 3-cycle consolidation chemotherapy used in this study appeared reasonable with high efficacy and limited toxicity. Nevertheless, a high percentage of stage IB-IIB patients in this study (56%) may account for this high RR and survival. Other studies with more stages III-IV cancer population may produce a different result.

The third single arm phase II study by Zhang et al[16] included 34 patients of stages IIB to IIIB receiving CCRT followed by consolidation chemotherapy. Concurrent chemotherapy of paclitaxel 35 mg/m^2 plus nedaplatin 20 mg/m^2 was given weekly for 6 weeks followed by paclitaxel 135 mg/m^2 and nedaplatin 60 mg/m^2 every 3 weeks for 4 more cycles as consolidation

chemotherapy. A complete RR of 79% was reported at one month after CCRT and increased to 88% at the end of consolidation chemotherapy. After a median follow-up of 23 months, estimated 2-year PFS and 2-year OS were 82% and 93% respectively. Local recurrence occurred in 12%, distant metastasis alone and local with distant failure were found in another 6% of patients. Grade 3-4 hematologic toxicities were experienced in 22% of consolidation chemotherapy cycles despite the fact that 85% of patients had G-CSF supporting therapy. Grade 3-4 non-hematologic toxicity was negligible. Several observations could be made from this study: the use of nedaplatin which was reported to have equivalent or superior anti-tumor activity, less renal and gastrointestinal toxicities in comparison to cisplatin; dose-dense chemotherapy during CCRT might improve the RR; and consolidation chemotherapy might result in an improved RR with higher PFS and OS than CCRT alone. One problem regarding the clinical use of this chemotherapy regimen in developing countries is the increased cost of chemotherapeutic drugs and G-CSF support.

Among the comparative studies or trials of consolidation or adjuvant chemotherapy, RT alone was used as a standard comparative arm in early years[7,11,12] while CCRT was used as a comparator in recent years.[7,15,17] One of the three trials which used RT alone as a comparator was reported by Wong et al[11] in 1999. The authors randomized 220 bulky stage I, II, and III cervical cancer patients to receive standard pelvic RT alone or RT in concurrently with epirubicin 60 mg/m^2 (number of cycles not stated) followed by five additional cycles of epirubicin 90 mg/m^2 at 4-week intervals. Although the benefit of long term local control was not found, significant reduction in distant failure rates and improvement in PFS and OS were observed in the study arm. This trial was interesting for its positive results and the use of single agent chemotherapy. However, the treatment in the control arm was only radiation. We cannot presume that the results would be the same if a current standard treatment of CCRT was used as a benchmark. Furthermore, epirubicin is rarely used for cervical cancer nowadays due to its low efficacy and its cumulative dose-toxicity on cardiac function. In this trial, seven patients in the combined therapy arm developed impaired ventricular function confirmed by echocardiogram.

The second trial reported by Kantardzic et al,[12] in 2004, randomized 80 stage IIB-III patients to RT alone against CCRT with cisplatin 40 mg/m^2 and bleomycin 15 mg/m^2 followed by additional cycles of the same chemotherapy regimen. This study demonstrated better outcomes in LACC patients treated with CCRT and adjuvant chemotherapy than RT alone. However, there is a question whether the benefit was simply due to the effect of concurrent chemotherapy or from the effect of adjuvant chemotherapy. Unfortunately, this trial was reported in a non-English language so we could only retrieve information from a systematic review and meta-analysis on CCRT trials utilizing individual patient data.[18] Data from this trial was incorporated with data from another trial which involved patients with early-stage high-risk cervical carcinoma who had CCRT and two additional cycles of cisplatin and fluorouracil.[8] The subgroup meta-analysis based on these two trials demonstrated more significant benefit from consolidation chemotherapy after CCRT compared with RT alone. The consolidation chemotherapy arm 54% reduced risk of death (hazard ratio HR: 0.46, 95% confidence interval (CI) of 0.32 - 0.66, p-value < 0.001) and represented 19% 5-year survival benefit.[18] The third trial was from Thailand by Lorvidhaya et al[7] who aimed to study the efficacy of CCRT and the role of adjuvant chemotherapy in LACC. This study randomized 926 patients with stage IIB-IVA LACC into four treatment arms: RT alone as a standard arm and the three study arms of RT with adjuvant chemotherapy, and CCRT with or without adjuvant chemotherapy. Chemotherapy used in the concurrent setting were intravenous mitomycin C at 10 mg/m^2 (days 1 and 29) plus oral 5-FU at 300 mg/day (days 1-14 and 29-42), while that in the adjuvant setting was oral 5-FU at 200 mg/day for 4 weeks with a 2-week

rest for three cycles. This trial demonstrated the benefit of CCRT, but not the adjuvant chemotherapy. The 5-year DFS of the patients who had CCRT was significantly improved comparing with those who had RT alone (65% vs 48%, p-value < 0.001). The corresponding 5-year DFS of the patients who had adjuvant chemotherapy after CCRT or after RT alone was not different from those who did not have additional chemotherapy (60% and 54%). A significant decrease in locoregional (but not distant) recurrence was demonstrated in the patients who had CCRT as compared to radiation alone, with or without adjuvant chemotherapy: 14% vs 26%. There was no significant difference in both local recurrence and distant metastasis between the patients with or without adjuvant chemotherapy. The negative effect of adjuvant chemotherapy in this trial might be partly due to the unpredictable bioavailability and absorption of oral 5-FU which was used as a single agent as adjuvant chemotherapy.

CCRT has been recommended as a standard treatment of LACC since 1999 and studies in later years have compared some innovative treatments with CCRT.[15,17] A small matched case-comparison study evaluating the efficacy and toxicity of consolidation chemotherapy after CCRT or CCRT alone in 78 LACC patients was recently reported by Choi et al[15] in 2010. The chemotherapy regimen used in the concurrent setting were either 6 cycles of weekly cisplatin or 3 cycles of cisplatin 60 mg/m^2 (day 1) plus 5-fluorouracil 1,000 mg/m^2 (days 1-5) given every 3 weeks. Additional 3 cycles of consolidation chemotherapy was given after the CCRT in the intervention group with the same regimen as that in the concurrent setting. The complete RRs of these two groups were not significantly different either at the completion of RT or at 3 months later. After a median follow-up period of 35 months (range, 8-96 months), 41% of patients who had only CCRT had progressive disease compared to 26% in those who had additional chemotherapy (p-value not given). Distant/ hematogenous failure tended to be significantly higher in those who had only CCRT (p-value = 0.06), but no differences in locoregional or lymphogenous failures was observed. Better systemic control of the disease was probably translated into a significantly improved OS in the consolidation chemotherapy group (HR: 0.20, 95% CI, 0.04 - 0.95, p-value = 0.043). Although neutropenia was more common in the consolidation treatment group (10.9% vs. 4.7%, p-value = 0.07), no significant difference in grade 3-4 toxicities in other systems was found. Unfortunately, this study did not report the efficacy and toxicities of combined cisplatin plus 5-FU and those of single cisplatin separately.

To date, only one randomized controlled trial recently reported by Dueñas-González et al[17] specifically focuses on the efficacy of additional chemotherapy after CCRT compared to CCRT alone in LACC. The trial compared 259 stage IIB-IVA patients who had additional chemotherapy after CCRT to 256 patients who had chemotherapy concurrent with radiation. The chemotherapy used in the study arm was cisplatin 40 mg/m^2 plus gemcitabine 125 mg/m^2 weekly for 6 weeks concurrently with RT, followed by additional two cycles of cisplatin at 50 mg/m^2 (day 1) plus gemcitabine at 1,000 mg/m^2 (days 1 and 8) after CCRT. The chemotherapy used in the control arm was cisplatin 40 mg/m^2 weekly for 6 weeks in concurrent with RT. Significantly improved PFS and OS were found in those who had additional treatment: 3-year PFS was 74% vs 65% (HR of 0.68; 95% CI, 0.49 - 0.95, p-value = 0.023) while 3-year OS was 80% vs 69% (HR of 0.68; 95% CI, 0.49 - 0.95, p-value = 0.022). The rates of local failure were not significantly different (11% vs 16%). The outcome of this study should be interpreted with caution since the regimen of chemotherapy was not well balanced in the study design between the standard and study arms: a combination of cisplatin and gemcitabine in the study arm (CCRT plus adjuvant chemotherapy of the same regimen) vs single cisplatin in the standard arm (CCRT only).[17] This chemotherapy discrepancy might have overstated the benefit of adjuvant chemotherapy. Furthermore, together with the survival benefit, grade 3 and 4

Table 1 Studies evaluating adjuvant or consolidation chemotherapy for locally advanced cervical cancer

First author, year[ref]	N	Stage	Histology	Treatment	Chemotherapy in concurrent setting	Adjuvant or consolidation chemotherapy	Median follow up (range)	Outcomes
Prospective single arm study								
Vrdoljak, 2006[13]	62	IB2–IVA	SCC, ACA, or AS	CCRT/consolidation CT	ifosfamide 2 g/m^2 D1, cisplatin 75 mg/m^2 D1, during 2 brachytherapies	ifosfamide 2 g/m^2 D1–3, cisplatin 75 mg/m^2 D1 x 4 cycles	49 months (11–74 mos)	– CR 100% – approximated 4-yr DFS & OS, 90% (both) – acute gr 3 & 4 hemato toxicities, 49% – late urinary or GI tract toxicities, 16%
Choi, 2007[14]	30	IB2–IVA	SCC, ACA, or AS	CCRT/consolidation CT	cisplatin 60 mg/m^2 D1, 5-FU 1 g/m^2 D1–5 x 3 cycles	same drug & dosage x 3 cycles	27 mos (6–58 mos)	– CR 67% after CCRT and 87% after adj CT – 3-year PFS & OS, 83% & 91% – gr 3 & 4 hemato toxicities, 17%
Zhang, 2010[16]	34	IIB–IIIB	SCC	CCRT/ consolidation CT	paclitaxel 35 mg/m^2, nedaplatin 20 mg/m^2 wkly for 6 wks	paclitaxel 135 mg/m^2, nedaplatin 60 mg/m^2 q 3 wk x 4 cycles	23 mos (14–30 mos)	– CR 79% after CCRT and 88% after adj CT – 2-year PFS & OS, 82% & 93% – gr 3 & 4 hematotoxicities, 22%
Randomized controlled trial or matched-case comparison study								
Wong, 1999[11]	220	I bulky – III	NA	RT alone vs CCRT/adj CT	epirubicin 60 mg/m^2 q 4 wk x ?	epirubicin 90 mg/m^2 q 4 wk x 5 cycles	66 mos (8–113 mos) in arm 1 96 mos (16–130 mos) in arm 2	RT vs CCRT/ adj CT: – CR, 81% vs 100% (p=0.002) – distant recurrences, 24% vs 8% (p=0.01) – 5-yr PFS, 70% vs 83% (p=0.02) – 5-yr OS, 68% vs 80% (p=0.04)
*Kantardzic, 2004[12]	80	IIB–III	NA	RT alone vs CCRT/adj CT	cisplatin 40 mg/m^2, bleomycin 15 mg/m^2 x ?	same drug & dosage x ? cycles	NA	NA
Lorvidhaya, 2003[7]	926	IIB–IVA	SCC, ACA	RT alone vs RT/adj CT vs CCRT vs CCRT/adj CT	mitomycin C 10 mg/m^2 D1 & D29, oral 5-FU 300 mg/day D 1–14 & D 29–42	oral 5-FU 200 mg/day x 4 wks (2 wks break) x 3 cycles	89 mos	no benefit of adjuvant chemotherapy after RT or after CCRT (p=0.09 given for DFS between RT vs RT + adj CT arms only)
Choi, 2010[15]	78	IIB–IVA	SCC, ACA	CCRT vs CCRT/consolidation CT	cisplatin 60 mg/m^2 D1, 5-FU 1 g/m^2 D1–5 x 3 cycles, or wkly cisplatin 40 mg/m^2 for 6 wks	same drug, for 3 or 6 cycles	35 mos (8–96 mos)	CCRT vs CCRT/consolidation CT: – progressive diseases, 41% vs 26% – distant recurrences, 23% vs 8% (p=0.06) – PFS, 70% vs 55% (p=0.08) – OS, 93% vs 70% (p=0.04)
Dueñas-González, 2011[17]	515	IIB–IVA	SCC, AC, AS, poorly diff CA	CCRT vs CCRT/adj CT	cisplatin 40 mg/m^2 in CCRT arm cisplatin 40 mg/m^2, gemcitabine 125 mg/m^2 wkly x 6 wks in CCRT/ adj CT arm	cisplatin 50 mg/m^2 D1, gemcitabine 1,000 mg/m^2 D1,8 x 2 cycles	46.9 mos	– HRs for both PFS & OS in favor of CCRT/adj CT: 0.68 (p=0.02; 95% CI, 0.49–0.95)

Abbreviations: ACA, adenocarcinoma; adj, adjuvant; AS, adenosquamous cell carcinoma; CCRT, concurrent chemoradiation therapy; CR, complete response rate; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; NA, not available; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SCC, squamous cell carcinoma

* Data from this study was obtained from the systematic review and meta-analysis

toxicities were also significantly higher in the patient having additional CT treatment (87% vs 46%, p-value < 0.001). Two deaths were attributed to the additional chemotherapy after CCRT. This finding probably precludes its clinical use outside a research setting.

Details of the studies using consolidation chemotherapy in LACC are summarized in Table 1. The role of consolidation chemotherapy for LACC is still in the early stage of development. There were many differences among the previously mentioned studies: stages of disease; concurrent or additional chemotherapy administration regarding the chemotherapeutic drugs, dosages, schedules, and number of chemotherapy cycles; toxicity; and the outcomes of treatment. Although a few studies including one RCT has demonstrated the benefit of additional chemotherapy,[12,15,17] many criticisms could be made concerning methodology. Furthermore, additional chemotherapy resulted in a high degree of toxicity which will certainly lead to an increased cost for management schedules of this toxicity. This is of particular concern especially in developing countries. Trials which use an effective chemotherapy regimen, preferably single agent e.g. cisplatin, to improve treatment outcome in LACC are warranted, as this can be more easily applied in clinical practice.

Before consolidation chemotherapy is widely used in clinical practice, more high level evidence is needed. Well designed, large, randomized control studies should be performed to objectively evaluate the benefit and the adverse effects of such therapy. Currently, the Australia New Zealand Gynaecological Oncology Group (ANZGOG)[19] is recruiting LACC patients and randomizing them to have standard cisplatin-based chemotherapy concurrently with radiation as a primary treatment or CCRT followed by adjuvant chemotherapy (type and cycles of chemotherapy not stated). The target primary outcome is OS and the result is awaited with anticipation.

Conclusion

Consolidation chemotherapy after standard concurrent chemoradiation therapy (CCRT) for locally advanced cervical cancer appeared to yield a higher response rate but with increased toxicities than simply CCRT. However; survival benefit from consolidation chemotherapy was still inconsistent.

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