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Concurrent Chemoradiotherapy in Cervical Cancer (A New Paradigm in Cervical Cancer Treatment)

Hee-Sug Ryu

Department of Obstetrics & Gynecology, Ajou University School of Medicine, Suwon, Korea.

During the last century, the mainstay for the treatment of uterine cervix cancer has been via two main primary treatment modalities, these being radical surgery (radical hysterectomy and regional lymph nodes dissection) and radiotherapy. Generally, radical surgery is restricted to stages I and IIa of FIGO (the International Federation of Gynecology and Obstetrics) Classification, while radiotherapy may be applied to all stages of cervical cancer. In 1999 the National Cancer Institute Clinical Announcement established concurrent chemoradiotherapy as a new primary treatment modality, which is the focus of this review.

Key Words: Concurrent chemoradiotherapy, cervical cancer

INTRODUCTION

Recently, the combination of radiotherapy coupled with chemotherapy (concurrent chemoradiotherapy) has been shown to reduce treatment failure rates compared to radiotherapy alone, and thus improve cervical cancer survival by approximately 40%.[1-5]

The 5-year survival rate for cervical cancer stages Ib-IIa after radiotherapy is 74 - 91%, which is similar to the 83 - 91% rate for radical surgery.[6-8] Even for bulky tumors of more than 7 cm, radiotherapy alone results in more than 50% complete resolution.[9] The reason for the relatively high cure rate of radiotherapy for cervical cancer when compared to epithelial malignancies of other organs is that regional metastasis in cervical cancer begins at the parametrium, and progresses sequentially to the pelvic lymph nodes, common iliac lymph nodes, and then to the paraaortic lymph nodes. Also, the distant metastasis rate at the time of diagnosis is very low. Another reason is that this type of loco-regional disease is surrounded by the relatively radioresistant uterus and vagina, which acts to protect the local organs and tissues from radiation, and therefore a comparatively high dose of radiation can be delivered to the tumor. However, even with these advantages, the problem of treatment failure due to local tumor recurrence after radiotherapy remains. This is demonstrated by the fact that 40 - 50% of patients who die from cervical cancer show residual tumors in the pelvis.[10]

Many efforts have been made to overcome the problems of radiotherapy including the use of hyperfractionation of radiation, hypoxic cell radiation sensitizers, hyperbaric oxygen treatment, neutron therapy, and neoadjuvant chemotherapy prior to irradiation. However, concurrent chemoradiotherapy remains the only modality of clinical significance at this time.

The efficacy of chemotherapy for irradiated cervical cancer has been restricted due to the following reasons; resistant clones develop in the irradiated tumor after radiotherapy, tumor cell repopulation occurs after radiotherapy, and decreased blood flow at the irradiated site. Consequently, chemotherapy after radiotherapy has mainly been employed as a salvage therapy method in metastatic or recurrent cervical cancer patients, with single chemotherapeutic agents (5-fluoruracil, bleomycin, mitomycin C). However, the response rate was an extremely low, 10%, and only cisplatin showed an encouraging 20 - 40% response rate.[11]

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Reprint address: requests to Dr. Hee-Sug Ryu, Department of Obstetrics & Gynecology, Ajou University School of Medicine, 5 Wonchon-Dong, Paldal-Gu, Suwon 442-721, Korea. Tel: 82-31-219-5252, Fax: 82-31-219-5245, E-mail: hsryu@ajou.ac.kr

In order to maximize the efficacy of chemotherapy, the concept of chemotherapy before surgery or irradiation - neoadjuvant chemotherapy or induction chemotherapy was initiated in the 1980's.[12-14] The results showed that the response rate for neoadjuvant chemotherapy before surgery in reducing tumor volume was 67 - 100%, with a complete response rate of approximately 20%. Although neoadjuvant chemotherapy was able to shift non-operable patients to an operable status, there was no definite increase in the 5 year survival rate,[15-18] and thus, the use of this modality has recently declined. With the induction of chemotherapy before radiotherapy, the initiation of radiotherapy becomes delayed, resultings in worse survival rates.[19,20]

Drugs

Concurrent chemoradiation is where the chemotherapeutic agent acts as a radiosensitizer, thus producing a synergistic effect between the radio and chemotherapies. The criteria for the type of chemotherapeutic agent to be used in such cases are as follows; no delay in the start of the definitive radiation, and no prolongation of the overall treatment time. In addition, there are possible interactions of the concurrent chemoradiation, through such mechanisms as inhibition of repair of radiation damage, cell cycle synchronization, recruitment of nonproliferating cells into the cell cycle, and reduction of the hypoxic fraction.[21] Drugs which meet the above criteria have been demonstrated to act as radiosensitizers in *in-vitro* and *in-vivo* studies, with the commonly used drugs being hydroxyurea, cisplatin, and 5-fluoruracil (5-FU).[10]

The reason for the synergistic effect of hydroxyurea and cisplatin with radiotherapy is due to the additional drug effect in the S-phase of the cell cycle following the effect of irradiation in the radiosensitive M-phase cell cycle, which produces sublethal cells. In the clinical setting, concurrent chemoradiotherapy, with hydroxyurea, for cervical cancer is administered once or twice a week during external irradiation. The main side effect is bone marrow depression.[22-24] Concurrent chemoradiotherapy with a cisplatin protocol is either, one dose of chemotherapy every five fractions, or daily administration during radiotherapy, both of which have been demonstrated to produce a similar synergistic effect *in-vitro*. Clinically, the cisplatin schedule is varied, and consists of either, one dose administration every 3-4 weeks, administration every week, administration every day, or continuous infusion. The main side effects of cisplatin are nephrotoxicity, upper GI tract toxicity, and bone marrow depression.[25]

5-FU acts synergistically by suppressing the repair of DNA damaged due to the irradiation. With long-term, continuous administration, it has been established as an effective drug in GI tract cancers, and in cervical cancers 5-FU is administered for 4 days a week, every 3 - 4 weeks. The main side effects of 5-FU are diarrhea and bone marrow depression.[26]

Development

Since the 1960's, concurrent chemoradiotherapy has been employed sporadically for cervical cancer. A report on its efficacy, by Piver et al.[27] in 1974, showed that hydroxyurea increased the response rate of cervical cancer, but had no effect on the overall survival. In a later study they attempted to remove several patient bias by selecting stage IIIb patients without a surgically proven extrapelvic disease by removing the paraaortic lymph nodes. These patients were divided into two groups, one being given hydroxyurea and the other a placebo. The study reported 94% and 53% 5-year survival rates, respectively.[28] This resulted in the possibility of concurrent chemoradiotherapy as a valid mode of therapy, and thereafter the Gynecologic Oncology Group (GOG) initiated a multi-institutional randomized trial, with hydroxyurea as an agent for concurrent chemoradiotherapy.

The next generation of chemoradiotherapy clinical trial drugs was the nitroimidazoles, a hypoxic cell sensitizer. The GOG conducted clinical trials for the combination of misonodazole and hydroxyurea with irradiation, and showed that the loco-regional treatment failure rates were 23.6% and 18%, with recurrence rates of 44% and 37%, respectively. Thus, hydroxyurea was shown to be superior.[29,30]

The next GOG clinical trial (GOG #85) was the

first trial comparing cisplatin + 5-FU with hydroxyurea for concurrent chemoradiotherapy. In patients with surgically evaluated paraaortic lymph nodes, to exclude extrapelvic tumor metastasis, it was shown that compared to hydroxyurea, the cisplatin and 5-FU concurrent chemoradiotherapy group had statistically significant increased treatment rates.[5]

Three other phase III trials have confirmed the value of cisplatin-based chemoradiation for the treatment of loco-regionally advanced cervical cancer. The Radiation Therapy Oncology Group (RTOG) protocol, RTOG #90-01, compared the effect of the cisplatin + 5-FU concurrent chemoradiotherapy with extended field radiotherapy in loco-regionally advanced cervical cancer, and concluded that the cisplatin + 5-FU concurrent chemoradiotherapy demonstrated significantly increased survival, disease free survival, resolution rates, and decreased distant metastasis rates, over the extended field radiotherapy.[2] There was a slightly increased incidence of acute toxicity in the cisplatin + 5-FU group, but there was no difference in the incidence of chronic toxicity. As reported by Keys et al.,[1] the GOG #123 showed that there was significantly decreased recurrence rates in bulky stage I disease patients administered with cisplatin in the concurrent chemoradiotherapy regimen prior to surgery. In another study (GOG #120), Rose et al.[4] reported that a weekly regimen was optimal in reducing cisplatin toxicity. We also demonstrated that compared to monthly cisplatin + 5 FU regimens, weekly cisplatin showed a significantly lower incidence of toxicity.[31]

Therefore in 1999, encouraging results regarding cisplatin + 5-FU as chemotherapeutic agents for concurrent chemoradiotherapy in cervical cancer emerged. For cervical cancer patients, the superiority of cisplatin based concurrent chemoradiotherapy lead to it replacing radiotherapy, and many studies are being undertaken to ascertain the optimal dose schedule in order to minimize its toxicity. With the monthly cisplatin protocol, the optimal dose is 70 mg/m^2/cycle every 3 - 4 weeks, and in the weekly protocol, 40 mg/m^2/week is the most commonly used regimen. There are continuous efforts to decrease the total dose of cisplatin administered. Mitomycin C has been shown to produce similar results as cisplatin, but the frequency of late bowel complications has restricted its use.[32] Other agents, such as taxanes, gemcitabine, and oral 5-FU analogs are presently being studied, but their superiority over cisplatin have not yet been clearly demonstrated. It has yet to be proven that carboplatin, which is used in ovarian cancers with fewer systemic side effects compared to cisplatin, has the same radiosensitizer properties, and its use is limited to patients with markedly impaired renal function.

Adjuvant radiotherapy in high-risk treatment failure patients, after surgery for stage I cervical cancer, had been a standard treatment modality, and although it improves local control rates it has no effect on survival.[33] Therefore, the Southwest Oncology Group (SWOG) conducted clinical trials, SWOG #87-97 (GOG #109), and reported that adjuvant concurrent chemoradiotherapy with cisplatin + 5-FU for the treatment of high-risk failure patients after surgery (pelvic lymph nodes metastasis, positive margin, parametrial invasion) significantly improved survival rates.[3] Pedulla et al.[34] and ourselves[35] obtained results similar to those of the SWOG #87-97 trial.

Conclusion

There is a present, worldwide trend to apply multimodality therapy in all cancers, where specialists from respective fields of medicine apply several treatment modalities to maximize treatment success. As a result of the 1999 clinical trials, the National Cancer Institute Clinical Announcement established concurrent chemoradiotherapy as the primary mode of therapy, instead of radiotherapy in regionally advanced (stage IIb - IVa), and the adjuvant treatment modality for high-risk patients following surgery or locally advanced (stage I) cervical cancers.

With stage Ib2, i. e., a bulky tumor of more than 4 cm, the three mainstay treatment modalities remain controversial. These are, firstly, concurrent chemoradiotherapy followed by extrafascial hysterectomy,[1] secondly, in institutions where surgical skill is competent, radical surgery followed by adjuvant treatment is conducted, on the basis of high-risk factors for recurrence,[36] and thirdly,

neoadjuvant chemotherapy, followed by radical surgery and elective postoperative radiotherapy.[37] The modality is selected according to the bias of the institution, therefore a randomized prospective comparative study is necessary.

In conclusion, concurrent chemoradiotherapy is a new paradigm for loco-regionally advanced cervical cancer patients as an alternative to radiotherapy, but it is only recommended for patients in whom the benefits have been proven objectively in multiple studies. Concurrent chemoradiotherapy should also be conducted with the optimal dose of cisplatin. There exists, however, potential adverse acute toxicities with concurrent chemoradiotherapy, with an increase in the cost of treatment compared to classical radiotherapy. Care should be taken in selecting patients for such treatment.

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