Introduction

Cervical cancer is the most common gynecologic malignancy worldwide. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are the three major histologic types, and this cancer develops slowly and locally. Radical hysterectomy plus pelvic lymph node dissection or concurrent chemoradiation therapy (CCRT) is the standard treatment when the disease is at an early stage. CCRT remains the standard for locally advanced disease, and systemic chemotherapy plays a major role in disease with distant metastases. In recent decades, some new trends in treating this cancer have been discussed and applied. A series of clinical trials and retrospective studies support a more conservative surgical treatment in early-stage disease. Sentinel lymph node mapping is used to decrease the morbidities after nodal dissection. Some new concurrent chemotherapeutic agents and schedules have been developed to replace the traditional cisplatin-base agents in order to decrease the toxicity during CCRT. Consolidation chemotherapy after CCRT can help improve the outcome. Neoadjuvant chemotherapy plus radiotherapy has revealed itself as the potential application as part of a new therapeutic trend in treating locally advanced cervical cancer patients. In the Gynecologic Oncology Group (GOG) phase III trial (GOG-179), cisplatin plus topotecan was proved to prolong the patients’ survival time. Vaccines, both prophylactic and therapeutic, will be the trend in the future. This article intends to review recent reports and update the available information relating to the current trends in the management of cervical cancer. [International Journal of Gerontology 2007; 1(2): 98–102]

Key Words: cervical cancer, chemotherapy, concurrent chemoradiation therapy (CCRT), surgery, vaccine

Trend 1: More Conservative Treatment in Early Stage Disease

The early stage of cervical cancer is defined as FIGO clinical stages IA1 to IIA, where the lesion is confined
within the cervical portion to the upper vagina without parametrial involvement. There are 3 main histologic types of cervical cancer: squamous cell carcinoma (SCC), adenocarcinoma, and adenosquamous cell carcinoma. SCC offers a better prognosis and allows for more conservative modalities than the other two types. Stage IA1 SCC cervical cancer can be treated by conization with the intention of preserving the uterus if fertility is desired, because the possibility of pelvic lymph node metastases is < 1%. Simple hysterectomy without pelvic lymph node dissection is acceptable if fertility is no longer a concern. On the other hand, the management of adenocarcinoma and adenosquamous cell carcinoma remains as conization followed by hysterectomy, for fear of a skip lesion in the cervical portion.

The traditional treatment of stage IA2 cervical cancer is class 2 radical hysterectomy (modified radical hysterectomy) with pelvic lymph node dissection. Alternatively, unlike adenocarcinoma or adenosquamous carcinoma, radical trachelectomy with pelvic node dissection is acceptable for SCC cervical cancer if fertility preservation is desired, because the probability of a nodal metastasis averages 7.3%.

The conventional treatment of stage IB1 or IIA tumors (4 cm or less in diameter) requires class III Wertheim’s radical hysterectomy plus bilateral pelvic lymph node dissection. Yang et al. suggested a more conservative modality, which employed class II radical hysterectomy (modified radical hysterectomy) and yielded results comparable to the traditional surgical method with low voiding or defecation dysfunction. The local failure rate was not increased and the complication rate was decreased if postoperative radiotherapy was required. The local recurrence in one adenocarcinoma patient revealed that conservative modalities were unsuitable for histologic types other than SCC.

Patients with stage IB2 or IIA tumors (4 cm or more in diameter) were favorably treated with concurrent chemoradiation therapy (CCRT) than those receiving large-scale surgeries. There was a 30–40% possibility of pelvic lymph node metastases, and postoperative radiotherapy was eventually unavoidable. The morbidity of surgery plus CCRT was higher than surgery or CCRT alone. The quality of life became worse in the combination group. It has been suggested that pelvic lymph node dissection will not increase the complication during consecutive CCRT and that the excision of existing bulky nodes is beneficial.

Trend 2: CCRT

Ever since 1988, CCRT has replaced the traditional radiotherapy and become the standard primary treatment of locally advanced cervical cancer (stages IIB–IVA). When a combination of cisplatin and 5-fluorouracil (5-FU) was used as radiosensitizers during pelvic radiation and brachytherapy, the local control rate, progressive-free survival, and overall survival were improved. Although the cisplatin–5-FU combination incurred other treatment morbidities such as severe bone marrow suppression, this morbidity had been shown to be acceptable in a recent literature.

CCRT was also shown to be applicable in early-stage cervical cancer patients who were not suitable for radical surgery or had major risk factors after radical surgery. The schedule of chemotherapy during radiotherapy is cisplatin plus 5-FU for three courses with a 21-day interval between the courses, or a single-agent cisplatin (40 mg/m²) given weekly for six courses. Ikushima et al. reported that the reduction of the weekly cisplatin dose to 30 mg/m² significantly reduced hematologic toxicity. A new chemotherapeutic schedule of daily cisplatin (20 mg/m²/d for 5 consecutive days) for a total of two courses during radiotherapy has been developed, and it was reported to have a better outcome. Other chemotherapeutic agents, such as gemcitabine, oxaliplatin, etoposide, liposomal doxorubicin, carboplatin and tagafur, or paclitaxel, and carboplatin, were tested as radiosensitizers, but cisplatin remains the most effective agent in treating cervical cancer.

Trend 3: Sentinel Lymph Node-Mapping

Sentinel lymph node mapping is well developed for the surgery of breast cancer, for the reduction of morbidity after total axillary lymph node dissection. Similarly, this procedure is currently applied during radical surgery of cervical cancer to reduce the lower-extremity lymphedema, lymphagitis or pelvic lymphocyst after pelvic lymph node dissection and is often coupled with postoperative pelvic radiotherapy. Metastable technetium-99 (Tc-99m) lymphoscintigraphy and blue dye injection are used to investigate the sentinel lymph node distribution during pelvic node dissection. A recent study by Wydra et al. reported the sensitivity (86.4%), negative predictive value (95.5%), and specificity (100%) using a
combination of these two methods in 100 patients with early cervical cancer.

**Trend 4: Consolidation Chemotherapy After CCRT in Locally Advanced Cervical Cancer**

CCRT is the standard treatment in locally advanced cervical cancer. Although CCRT improves the survival rate by 30–50%, the 5-year survival rate in these patients remains <65%. Local failure and distant metastases often happen after treatment. The concept of post-radiotherapy consolidation chemotherapy originates from maintenance chemotherapy of advanced ovarian cancer, which can either suppress the microscopic circulating cancer cells in the systemic circulation or achieve the anti-angiogenesis effects (metronomic therapy) by maintaining the blood concentration of the chemotherapeutic agent. Vrdoljak et al. reported a clinical trial in which locally advanced cervical cancer patients who received external beam pelvic radiation therapy without chemotherapeutic agent concurrently. A combination of ifosfamide (2 g/m²) and cisplatin (75 mg/m²) was used concurrently during two low-dose rate brachytherapy applications. After completing concomitant chemoradiation therapy, four courses of systemic chemotherapy with the same two-drug regimen were given as consolidation therapy. The results showed a high response rate (nearly 100%) and high recurrence-free rate (88.7%) during a follow-up of 49 months. The trial also demonstrated acceptable morbidity rate (25% grade 3, 11% grade 4 hematologic toxicities). Only 16% of the patients developed delayed major complications. This protocol may become more promising than the traditional CCRT schedule.

**Trend 5: Neoadjuvant Chemotherapy (NACT)**

NACT plus surgery have demonstrated itself on phase II trials to be feasible as a valid replacement for conventional radiotherapy or surgery. However, most phase III trials of NACT plus radiotherapy have failed to show further benefit than those of radiotherapy alone. In contrast, a recent meta-analysis by Medical Research Council (UK) showed the benefit of a more intensive chemotherapy at shorter cycle length or higher dose intensity for the NACT plus radiotherapy treatment. This meta-analysis included 2,074 patients from 18 different trials with a median follow-up analysis of 5.7 years. Sardi et al., in a recent review article, drew attention to the significance of this meta-analysis and highlighted the potential application of NACT plus radiotherapy as part of a new therapeutic trend in treating locally advanced cervical cancer patients. Further research is required to verify and conclude this finding.

**Trend 6: Improvement of Systemic Chemotherapy**

Single-agent cisplatin (50 mg/m²) administered every 3 weeks apart has been the standard systemic chemotherapeutic agent for the treatment of advanced/recurrent and metastatic SCC of the uterine cervix. It demonstrated a 50% objective response rate in previously untreated patients. Several new single agents with antineoplastic activity were trialed in combination with cisplatin, including ifosfamide, oxaliplatin, paclitaxel, and gemcitabine. Ifosfamide plus cisplatin demonstrated a significant improvement in response rate and progressive-free survival but failed to improve the overall survival. The combination of ifosfamide and cisplatin showed limited improvement on the progressive-free survival (1.4 months). A recent Gynecologic Oncology Group (GOG)-169 study demonstrated that a combination of paclitaxel and cisplatin also showed limited improvement in progressive-free survival without any improvement in overall survival. The aforementioned trials once again reinforce the role of single-agent cisplatin as the current standard systemic therapy for cervical cancer. There have been two new trends in multiple chemotherapeutic agent combinations recently, the first is the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), and the other is cisplatin plus topotecan (GOG-179). The three-arm clinical trial involving the MVAC regimen was forced to close prematurely because of many treatment-related deaths. In the comparison between cisplatin plus topotecan and single-agent cisplatin, the combination group showed a statistically significant improvement in response rate (27% vs. 13%), progressive-free survival (4.6 months vs. 2.9 months) and overall survival (9.4 months vs. 6.5 months). The combination of cisplatin plus topotecan has now replaced the single-agent cisplatin to become the most effective systemic chemotherapeutic combination agents.
Trend 7: Prophylactic and Therapeutic Vaccines

Oncogenic HPV are epitheliotropic and detectable in over 99% of cervical cancers. The vaccines of HPV are classified into two major groups: prophylactic and therapeutic vaccines. The prophylactic vaccine protects against HPV infection, and the therapeutic vaccine kills previously infected or transformed keratinocytes. Prophylactic vaccines can induce a high titer of blood antibodies against oncogenic HPV 16 and 18. They can retard the progression of cervical cancer or prevent the cancer from occurring. Two types of prophylactic vaccines are recently under investigation. However, the quadrivalent vaccine (Gardasil) has already been approved for marketing, while the bi-valent HPV vaccine (Cervarix) is still pending approval. On the other hand, therapeutic vaccines are currently being developed in order to increase anti-HPV natural CD4+ and CD8+ T-cell immunity in women infected during their sexual activity. Researchers have designed these vaccines to target the activity of the E6 and E7 oncoproteins. These therapeutic vaccines can be divided into several subgroups, such as viral-vector, bacterial-vector, peptide, protein, DNA, dendrite cell-based, and tumor cell-based. A number of approaches have shown significant therapeutic benefit in preclinical papillomavirus models. Although the therapeutic vaccines might have efficiency similar to surgical treatment of CIN, the current therapeutic vaccine trials are still less mature with respect to disease clearance. Further testing in patient populations is required to determine the most effective curative strategy.

Trend 8: Molecular/target Drugs

Advances in molecular biology have led to the discovery of a number of cancer pathways. Having gained substantial understanding of the mechanisms of cell proliferation, cell cycle regulation, apoptosis, angiogenesis and inflammation, pharmaceutical companies have developed several kinds of molecular or protein drugs to target the key enzymes, growth factors or receptors in order to block these pathways. For example, erlotinib (OSI-774) is an endothelial growth factor receptor tyrosine kinase inhibitor, which has been used to treat cervical cancer. Although only limited drugs are clinically useful in the treatment of breast cancer, lung cancer or other solid tumors, many newly developed drugs are now undergoing further experiments. Target therapy can play either a major or an assistant role in the future treatments of cancers, including cervical cancer and other gynecologic malignancies.

Conclusion

This review summarizes the current trends in the management of cervical cancer. Although the results of some clinical trials are still inconclusive, many clinical improvements have been observed in recent years. It is the author’s belief that the investigation of alternate treatment modalities that are more conservative, less toxic, less harmful, and more effective is an ongoing objective in the field of gynecologic oncology.

References


