Adjuvant Therapy in Cervical Cancer Patients with High Risk Factors

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Neoadjuvant and adjuvant chemotherapies are used adjunctively with surgery or radiation and are among the treatment options that are now employed for reducing treatment failure in early-stage cervical cancers with high-risk prognostic factors. Adjuvant therapies have been reported to significantly improve survival than would otherwise be possible with surgery or radiotherapy alone. However, for advanced cervical cancers, sequential or concurrent chemoradiotherapy does not appear to significantly increase survival. The combination of radiotherapy with IFN-a2a and RA in the treatment of patients with locally advanced cervical cancer showed high response rates, however this should be confirmed in larger studies. Recent reports show that postoperative adjuvant radiotherapy has no benefit in survival, but that postoperative adjuvant chemotherapy has improved survival. Toxicities and the optimum number of cycles of neoadjuvant and adjuvant chemotherapy, as well as biologic therapy, will follow along with individualized treatment based on high-risk prognostic factors. Although more comprehensive studies and longer follow up will be required for complete evaluation of these adjuvant therapies, preliminary results are promising.

Key Words: Cervical cancer, high risk factors, adjuvant therapy

Cervical cancer is the most common female malignancy in Korea with an age-adjusted incidence rate of 29.9 per 100,000 women in Seoul, Korea. (International agency for research on cancer, 1992; Korean cancer research foundation, 1993) In developing countries, cervical cancer is a leading cause of cancer mortality in women. Therefore it is a significant world health-care problem.

It is generally accepted that radiotherapy and surgery are both effective techniques in the management of carcinoma of the cervix with small lesions. However, disease control for groups with risk factors such as advanced stage (Perez et al. 1983), bulky disease (Piver and Chung, 1975; Sardi et al. 1990), lymph node metastasis (Piver and Chung, 1975), or small-cell carcinoma (Van Nagell et al. 1977) is difficult even with the use of modern megavoltage equipment and optimal fractionation schemes or improved extensive surgery. The high treatment failure rate and poor survival with conventional treatment have spurred the development of new treatment modalities. With the advent of newer chemotherapeutic agents, chemotherapy has emerged as an additional mode of therapy in these patients. As a result, many investigators have studied the
combined modalities of chemotherapy and radiotherapy. It has been hypothesized that chemical debulking attained with cytotoxic drugs may induce better oxygenation of previously-hypoxic tumor cells, thereby facilitating the response to subsequent radiation and perhaps the control of micrometastasis. (Vermund and Gollin, 1968; Guthrie, 1985)

Numerous reports of locally-advanced cervical cancer comparing the concurrent and the sequential combination of chemotherapy and radiotherapy have been published with conflicting outcomes. Although some studies have shown promising results with the use of radiotherapy in combination with sequential chemotherapy in advanced disease (Symonds et al. 1989; Deppe et al. 1991; Park et al. 1991), there are also some negative reports. (Withers et al. 1988; Souhami et al. 1991; Tseng et al. 1997) Although several studies have documented 90% response rates using radiotherapy with concurrent chemotherapy in poor prognostic cervical cancer patients, this combination can also produce severe synergistic toxic effects. (Cummings, 1982; Thomas et al. 1987; Malviya et al. 1989) Roverts et al. reported a clinical CR rate of 85% among 67 cases of advanced disease treated in this manner. However, survival did not improve due to local recurrence. (Roberts et al. 1991) Further prospective randomized trials of concurrent chemotherapy and radiotherapy are currently in progress.

In recent years, the use of 13-cis-retinoic acid (RA) and interferon-α2a (IFN-α2a) in cancer therapy has stimulated significant interest. Both IFN-α2a and RA are known to possess antiproliferative, immunomodulatory and antineoplastic properties. IFN-α2a has two main mechanisms of action against neoplasia; first, it is directly cytotoxic and second, it is indirectly cytotoxic by immunomodulation. The combination of IFN-α and RA has produced high response rates in patients with cervical squamous-cell carcinoma. (Lippman et al. 1993) These compounds may also potentiate radiation cytotoxicity and act as a radiosensitizer.

INDICATION OF ADJUVANT THERAPY

Neo-adjuvant, adjuvant chemotherapy & biologic therapy

The current staging classification of cervical carcinoma by the International Federation of Gynecologists and Obstetricians (FIGO) does not address cell-type or lymph-node status of the cancer being staged. It is likely that stage I and II diseases with bulky tumor (or barrel-shaped lesion) may have a poorer prognosis than the comparable stage diseases with less bulky tumor and that higher-stage diseases harbor metastatic disease foci outside the traditional radiation field used for cervical cancer.

Indeed, this is likely when cervical cancer is associated with any of the following factors. (Park, 1986; Park et al. 1991)
- Stage III-IV
- Lesion size ≥ 4 cm
- Stage I-II with lesion ≥ 4 cm
- Adeno-squamous or small-cell carcinoma
- Evidence of lymph-node metastasis on lymphography

These high-risk cases deserve adjuvant therapy. Other authors have discussed similar risk factors. (Jampolis et al. 1975; Piver and Chung, 1975; Van Nagell et al. 1977)

Postoperative adjuvant chemotherapy

Some cervical cancers are apparently understaged. Pretreatment cancer staging, which forms the basis of primary treatment strategy in cervical cancer, does not always account for the entire cancer, which is usually more accurately delineated by surgery. Postoperative adjuvant chemotherapy is suitable for cases associated with any of the following factors documented postoperatively. (Park, 1986)
- Lymph node metastasis
- Lymph vascular space invasion
- Depth of invasion more than 10 mm
- Parametrial invasion

Traditionally, patients with cervical cancer thought
to have been less than adequately treated with surgery have been treated with postoperative radiotherapy. My criteria for postoperative adjuvant chemotherapy are cervical cancers with any one or more of these risk factors.

**TYPES OF NEOADJUVANT, ADJUVANT CHEMOTHERAPY & BIOLOGIC THERAPY**

Neoadjuvant chemotherapy may be administered sequentially preceding radiotherapy or surgery, or concurrently with radiotherapy. The sequential mode first delivers an average of three courses of chemotherapy at an interval of about three weeks before radiotherapy or surgery. The concurrent mode is the one in which radiotherapy is initiated during the first course of chemotherapy. Biologic therapy was administered with concurrent radiotherapy.

The sequential mode has merits by taking advantage of vascularity remaining undisturbed by radiation, tumor-cell radiosensitization brought about by the decrease in the hypoxic-cell fraction, and the earlier treatment of occult micrometastasis. Chemotherapy in this fashion often allows radical surgery by tumor reduction in inoperable cases.

The concurrent mode has the advantages of:
- not delaying radiotherapy by several courses of chemotherapy;
- shortening the total treatment duration;
- enhancing tumor control by possible synergistic effects of chemotherapeutic drugs with radiation (e.g. radiosensitization of the tumor mass by 5-FU)

Adjuvant chemotherapy, instituted after surgery in cases associated with at least one of the postoperatively documented high-risk factors described, is delivered in the same way as sequential chemotherapy before proceeding on to radiotherapy.

The biologic drugs (IFN-α2a, RA) may also potentiate radiation cytotoxicity by acting as a radiosensitizer. (Chang and Keng, 1987)

**REGIMENS AND ADMINISTRATION**

Quite a few regimens are being employed for neoadjuvant or adjuvant chemotherapy for cervical cancer. The most effective regimens, evaluated in the form of shrinkage of the tumor mass, are cisplatin-based. (Thigpen et al. 1981)

Cisplatin is present in almost all drug regimens currently being used in this mode of chemotherapy.

I have been using the cisplatin and 5-FU combination in patients associated with any of the high-risk prognostic factors described above. Cisplatin, 100 mg/m² IV, is followed by 5-FU 1000 mg/m² as a 24-hour IV infusion for five days. Carboplatin, a drug similar to cisplatin but with lower bone marrow toxicity, in a dose of 400 mg/m² may be used instead of cisplatin. A different regimen is used for adenocarcinoma. Interested readers are referred to regimens used by other authors. (Thigpen et al. 1981; Drescher et al. 1989; Zanetta et al. 1993) All patients are prehydrated for about 10 hours before receiving cisplatin or carboplatin and premedicated with metoclopramide and lorazepam.

The biologic therapy consisted of a IFN-α2a subcutaneous injection of 6 million units (MU) per day for the first 3 days, followed by 3 MU per day for 81 days and then RA orally 1mg/kg/day in 2 divided doses for 84 days with concurrent radiotherapy.

It is important that patients should be maintained to have at least 12 g/dl of hemoglobin level and the absence of other intercurrent diseases which may contraindicate chemotherapy. A guideline like ‘Common Toxicity Criteria of Gynaecologic Oncology Group (October 1988)’ may be followed for monitoring the toxicity of chemotherapy and biologic therapy during and after adjuvant therapy.

**OUTCOME**

Neoadjuvant, adjuvant chemotherapy & biologic therapy

Many authors including myself have reported favorable results of neoadjuvant chemotherapy administered to invasive cervical cancer patients. (Friedlander et al. 1984; Kim et al. 1989; Sardi et al. 1990; Panici et al. 1991; Park et al. 1991) In
my series (Park et al. 1991), the survival of patients with high-risk factors was significantly better after neoadjuvant chemotherapy followed by surgery or radiotherapy than it was after surgery or radiotherapy alone. For example, with a lesion of more than 4cm, the five-year survival was 67% after sequential chemoradiotherapy, significantly higher than the 53% obtained after radiotherapy alone.

After sequential chemoradiotherapy, stage III-IV diseases, adeno-squamous or small-cell carcinomas, stage I-II diseases having lesions greater than 4cm, and diseases with evidence of lymph-node metastasis on lymphography all showed significantly higher five-year survivals of 69, 68, 78, and 80%, respectively when compared to the radiotherapy-alone group, which showed survival rate of 57, 55, 48, and 49%, respectively.

Concurrent chemoradiotherapy did not appear to be superior to sequential chemoradiotherapy in the patients we treated. (Park et al. 1993) In bulky tumors of more than 4cm, however, its effects may be better than the sequential mode. (Kersh et al. 1990; Thomas et al. 1990)

IFN-α2a, RA and radiotherapy resulted in a 47% response rate (33% complete response) while concurrent chemoradiotherapy resulted in a 42% response rate (17% complete response) in locally advanced squamous carcinoma of the cervix. (Park et al. in press)

Postoperative adjuvant chemotherapy

This mode of chemotherapy followed by radiotherapy may improve the survival of patients showing postoperatively documented high-risk factors (Park, 1986) compared with postoperative radiotherapy, which according to many previous studies did not benefit the overall survival outcome.

TOXICITY OF ADJUVANT CHEMOTHERAPY & BIOLOGIC THERAPY

As is the case with chemotherapy of other malignancies, nausea and vomiting, elevation of liver transaminases, decreased creatinine clearance, and neutropenia were the frequently encountered drug toxicities from neoadjuvant and adjuvant chemotherapy.

Neutropenia occurred in 36% of all drug cycles administered in our series. (Park et al. 1991; Park et al. 1993) Neutropenia usually causes no serious infection when patients are carefully monitored, since many patients with neutropenia of less than 1000/μl will remain afebrile. Thus, unless fever is associated with neutropenia, antibiotics were not always administered. However, it should be remembered that once fever of even a mild degree occurs in the neutropenic patient, combination antibiotic therapy should be initiated. Hepatotoxicity, though demonstrated by increased transaminases, was rarely symptomatic and was short-lived without any treatment. In the face of decreased creatinine clearance, doses of cisplatin or carboplatin, the drugs chiefly cleared through the kidney, are usually reduced to diminish the potential nephrotoxicity.

The major toxicity of IFN-α2a, RA and radiotherapy was fever (60%). There was no grade 3 or 4 toxicity. (Park et al. in press)

CONCLUSION

Neoadjuvant and adjuvant chemotherapy in cervical cancer is a method of treatment aimed at increasing the chance for longer survival in a set of patients with high risk factors for treatment failure after conventional surgery or radiotherapy alone. It is a form of treatment that is one step closer to achieving individualized treatment. As more experience with this mode of therapy is gained, it will become clearer what regimens and how many drug courses are the optimum for patients. The combination of systemic IFN-α2a, RA and radiotherapy is an active, well-tolerated therapy for locally-advanced cervical cancer. Further studies are required to define its role in the treatment of advanced cervical cancer.

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