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Review Articles

The ideal strategies of chemotherapy for the treatment of cervical cancer

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Historically, the standard treatment for early-stage cervical cancer has been radical surgery in patients with operable disease. Patients with locally advanced disease (defined as FIGO stage IB2 and usually with tumors greater than 4 cm, IIB, III and IVA) are usually treated with radical radiotherapy, which consists of external beam radiotherapy and internal brachytherapy. However, the discovery that cervical cancer tumors are sensitive to chemotherapy led to the initiation of studies looking at adding chemotherapy to both radiotherapy and surgery. Following a National Cancer Institute (NCI) alert in 1999 (NCI 1999), chemoradiotherapy became the standard of care for women with locally advanced cervical cancer.[1]

Key Words: Cervical cancer, Chemotherapy

Around the world, cervical cancer is the third most common female reproductive system cancer with over 500,000 new cases diagnosed every year (WHO 2006 Jemal 2011). More than 85% of these cases and deaths occur in economically developing and medically under-served countries, largely in sub-Saharan Africa, South America and South-Central Asia where it is often the second most common female reproductive system cancer.[2]

Cases where the cancer has not spread outside the cervix (early-stage disease), women may have to undergo an operation to remove it via resection of the cervix, uterus, the fallopian tubes, and maybe other nearby tissues (radical surgery),[3] or they might have to undergo treatment with radical radiotherapy. Both of these treatments have been found to be equally good. If the tumor is bigger, or it has spread to tissues around the cervix (locally advanced disease), women may also receive chemotherapy at the same time as radiotherapy (chemoradiation).[4]

Administering chemotherapy before radical surgery (neoadjuvant chemotherapy) might cause shrinkage of the tumor. This may make surgery easier and help to remove any tiny tumors that cannot be easily seen. A previous review found that women receiving chemotherapy before radi-

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cal surgery lived longer than those who received radical radiotherapy. However, we do not know whether administering chemotherapy before radical surgery is better than radical surgery alone.[5,6]

The primary treatment for bulky, macroscopic stage IB-IIA cervical cancer and stage IIB-IVA cervical cancer patients is platinum-based chemotherapy combined with radiotherapy plus intracavitary brachytherapy, which has been shown to result in improved overall survival compared to radiotherapy alone. This multimodality approach is also indicated in patients who have high-risk features after primary surgery, such as metastatic disease in the pelvic lymph nodes, parametrial spread of disease, or positive surgical margins.

In a published phase II trial in stage IB2 to IVA patients (Lissoni 2009), the authors concluded that three neoadjuvant cycles of paclitaxel, ifosfamide and cisplatin (TIP) at three-week intervals followed by surgery was a valid alternative to chemoradiation, but whilst the pathological response was favourable when compared to that fater paclitaxel and cisplatin (TP), grade 3 or 4 hematological toxicity was considerable (TIP 78% vs TP 29%). It is also noteworthy that women in this trial were younger (median age 45 years for TIP and 42 years for TP) and had a better performance status than the general population of women with cervical cancer, and therefore, this regimen may not be tolerated by older, less fit women.[7]

Although chemoradiation is the current standard treatment, potential delays in definitive treatment or lack of access to radiotherapy, especially in the developing world, indicate that there is continued interest in the use of neoadjuvant chemotherapy.

A number of other phase II trials are also looking at alternative neoadjuvant chemotherapy regimens for locally advanced cervical cancer. Carboplatin is considered to have similar effectiveness to cisplatin but is associated with easier administration and less accompanying toxicity, and it is being evaluated in combination with paclitaxel as a dose-dense, weekly neoadjuvant regimen prior to chemoradiation.[8]

Results obtained from this trial, presented at the American Society of Clinical Oncology, show a high response rate with limited grade 3 or 4 toxicity (13%). Also, because raised levels of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) are considered to be independent prognostic factors, there is also increasing interest in the use of newer biological agents that act as EGFR and VEGF inhibitors. Thus, two further phase II trials were initiated, which looked at administering either cetuximab as single-agent neoadjuvant chemotherapy prior to chemoradiation (NCT00292955) or carboplatin in combination with bevacizumab (NCT00600210). The former trial is still ongoing but the latter trial has been terminated early due to poor accrual, with the accrual status being currently unknown. It remains to be seen whether the results will provide a feasible alternative to current neoadjuvant chemotherapy regimens in the surgical setting. In addition to these phase

II studies, in 2002, a large multi-centre phase III trial was initiated by the European Organization for the Research and Treatment of Cancer (EORTC), comparing cisplatin-based neoadjuvant chemotherapy, prior to surgery, with the current standard cisplatin-based chemoradiotherapy (EORTC 55994). Another two trials comparing standard platinum-based chemoradiation with neoadjuvant chemotherapy regimens comprising of either paclitaxel plus carboplatin (NCT00193739) or gemcitabine plus cisplatin (NCT01000415), followed by surgery are also ongoing in India and Thailand, respectively. The results of these three trials are anticipated, and they will be important in determining whether neoadjuvant chemotherapy prior to surgery is a valid alternative to chemoradiation.

The leading guidelines recommend weekly cisplatin treatment or treatment with the combination of cisplatin plus 5-FU. These recommendations were first made in 1999 when the National Cancer Institute published a Clinical Announcement that strongly recommended concurrent platinum-based chemotherapy combined with radiotherapy for patients with locally advanced disease. This recommendation was based on the results of 5 randomized trials. However, in the historical GOG 85 and GOG 120 studies, cisplatin plus 5-FU-based doublet therapy was found to be superior to HU, but similar to weekly cisplatin treatment, in a 3-arm phase III trial led by Rose and colleagues. The aim of potentiating the systemic component of treatment with polychemotherapy was attempted successfully in 2011 by Duenas-Gonzalez and colleagues, who compared weekly cisplatin with cisplatin + gemcitabine. After this publication, no other randomized trial comparing single agent cisplatin with polychemotherapy has been published, and until now, no systematic reviews in the literature have evaluated polychemotherapy versus monochemotherapy with curative radiotherapy.[9]

In this meta-analysis, we showed that cisplatin-based polychemotherapy plus radiotherapy was associated with significantly better OS and PFS compared to weekly cisplatin plus radiotherapy as curative treatment for locally advanced squamous cell cervical cancer. The improved outcomes appear to be driven by a better LRR rate in the experimental arm versus the control arm. According to a 2008 meta-analysis of randomized trials, the absolute risk reduction in death, progression, and distant recurrence for cisplatin versus radiotherapy alone was 6%, 8%, and 7%, respectively. Similar absolute gains were observed in our analysis of polychemotherapy-based chemotherapy combined with radiotherapy versus single agent-based chemotherapy combined with radiotherapy (8%, 7%, and 3% gains, respectively). A subgroup analysis showed a significant benefit in OS, PFS, and LRR, in particular with schedules not including cisplatin and 5-FU but other cisplatin-containing doublets.[10-12]

The toxicities associated with combining 2 drugs are expected to be worse than those seen with use of a single agent, cisplatin. However, in-

formation on toxicities has been largely under-reported. An increase in grade 3 or 4 gastrointestinal toxicities (nausea or vomiting and diarrhea), thrombocytopenia, and neutropenia were observed as expected with use of some of the agents (mainly with 5-FU continuous infusion with high-dose 3-weekly cisplatin schedules).[13-15]

Even with the increased incidence of hematological and gastrointestinal toxicities, the completion rate of chemotherapy protocols tended to be higher in the combination chemotherapy arms, and the duration of radiotherapy was similar between the study arms.

Other agents have been used in clinical trials with a cisplatin plus radiotherapy backbone. Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, showed promising efficacy and acceptable safety when added to standard radiotherapy plus weekly cisplatin in a Radiation Therapy Oncology Group phase II study, without a comparator arm, but this study only had a median follow-up of 3.9 years. A recent phase III GOG study examined the effect of addition of tirapazamine, a hypoxic cell sensitizer, to standard weekly cisplatin plus radiotherapy compared to standard chemotherapy combined with radiotherapy alone. The addition of tirapazamine did not improve PFS or OS, although the number of events that occurred during the median follow-up period of 28 months was inadequate. Therefore, no new targeted agents have been added to create a new standard of care that can replace weekly cisplatin plus radiotherapy.[16-20]

In conclusion, platinum-based doublet therapy with concurrent curative radiotherapy is potentially the best regimen for stage IB-IVA cervical cancer. This regimen improves survival by enhancing locoregional control while minimally increasing the toxicity compared to single agent weekly cisplatin plus radiotherapy.

In cervical cancer, neoadjuvant chemotherapy prior to surgery is a valid alternative to chemoradiation, and if new neoadjuvant chemotherapy regimens and targeted biological agents perform well prior to chemoradiation, further trials of these agents in the surgical setting are warranted.

In locally advanced cervical cancer, platinum-based doublet chemotherapy plus concurrent radiotherapy was associated with improvements in the OS and PFS among 35% and 30% of the patients, respectively, compared to radiotherapy plus weekly cisplatin.

Therefore, cisplatinum-based doublet therapy with concurrent curative radiotherapy is potentially the best regimen for locally advanced cervical cancer. This regimen improves survival by enhancing locoregional control while minimally increasing the toxicity compared to single agent weekly cisplatin plus radiotherapy.

Also, bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, showed promising efficacy and acceptable safety when added to standard radiotherapy plus weekly cisplatin.

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