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New Strategies for Multimodality Therapy in Treating Locally Advanced Cervix Cancer

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Cervical cancer is the fourth most common cause of cancer of women worldwide. In the developing world, it comprises 12% of all cancers of women. Since 1999, the mainstay of treatment for locally advanced cervical cancer (LACC) has been concurrent cisplatin-based chemoradiation. However, outcomes in this disease remain suboptimal, with long-term progression-free survival and overall survival rates of approximately 60%. There are several new strategies of combined modality treatment under evaluation in LACC, including chemotherapy before and after treatment as well as novel agents such as poly-adenosine diphosphate ribose polymerase inhibitors, antiangiogenic blockage, and immunotherapy. We provide a brief overview of these strategies and their potential in the treatment of women with LACC.
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Cervical cancer is the fourth most common cancer of women worldwide, with an estimated 528,000 new cases and 266,000 deaths in 2012. The vast majority of cases occur in less developed regions, where cervical cancer comprises nearly 12% of cancers of women.[1]

Concurrent chemoradiation (CCR) was established as the standard of care treatment for locally advanced cervical cancer (LACC), defined as International Federation of Gynecology and Obstetrics stages IB2-IVA, in 1999 after the publication of 5 large randomized trials that demonstrated a 30%-50% improvement in survival when compared with radiation alone.[2-6] Based on these studies, the National Cancer Institute issued an alert recommending that CCR should be considered the mainstay of treatment instead of radiotherapy (RT) alone in women with LACC.

A large meta-analysis of trials evaluating CCR vs RT alone confirmed a 6% benefit to overall survival (OS). However, despite this improvement, cisplatin-based chemoradiation only yielded progression-free survival (PFS) and OS rates of approximately 58% and 66%, respectively.[7] The suboptimal results have prompted investigators to explore other novel strategies of combined modality therapies, including modified chemotherapy (CT) schedules, targeted agents, and immunomodulation. The purpose of this article is to review these alternative approaches to combined modality therapies regarding LACC. The use of different techniques of delivering external beam RT and brachytherapy for LACC is beyond the scope of this article.

Cytotoxic CT

Platinum-based CT has shown the best results for cervical cancer.[7] However, other chemotherapeutic agents have also been studied (Table 1). Duenas-Gonzalez et al[8] reported a phase III randomized trial investigating the addition of concurrent gemcitabine and adjuvant cisplatin-gemcitabine CT to standard CCR in the treatment of LACC. Patients randomized to the experimental arm were treated with CCR and concurrent weekly cisplatin and gemcitabine, followed by 2 cycles of adjuvant cisplatin-gemcitabine. The authors reported that at 3 years, there was a 9% absolute improvement in PFS. There was a non-significant decrease in local-regional recurrence of 5.2% along with a statistically significant 8.3% decrease in rates of distant metastasis. These outcome improvements translated into an OS benefit. However, 86.5% of patients in the experimental group had grades 3 and 4 toxicities, which were mainly hematologic, compared with 46.3% of patients treated with standard CCR. It also was not clear if the survival benefit observed in this trial was because of the

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Table 1 Modified Chemotherapy Agents for Locally Advanced Cervical Cancer

Study	Type	Agents Studied	CCR Given
Duenas-Gonzalez et al[8]	Phase III	Gemcitabine/cisplatin	Yes
Wang et al[9]	Phase III	Gemcitabine/cisplatin	Yes
OUTBACK (NCT01414608)	Phase III	Adjuvant carboplatin/paclitaxel	Yes
INTERLACE (CRUK/11/024)	Phase III	Induction carboplatin/paclitaxel	Yes

Abbreviation: NCT, ClinicalTrial.gov Identifier.

addition of concurrent gemcitabine or the use of adjuvant CT added to standard treatment.[8]

A randomized trial by the Asian Gynecologic Oncology Group (GOG)[9] also evaluated standard CCR consisting of RT with concurrent cisplatin plus gemcitabine vs single-agent cisplatin. After an interim analysis of 74 women who were enrolled, the addition of concurrent gemcitabine was found to increase toxicities without increasing PFS or OS. Thus, the decision was made to close the trial early.

The subject of adjuvant CT is currently being addressed by the OUTBACK trial, National Cancer Institute-sponsored NRG Oncology Group (ANZGOG-0902/GOG-0274/RTOG-1174/ClinicalTrials.gov Identifier: NCT01414608), which is randomizing eligible patients with LACC to standard CCR with or without f4 cycles of adjuvant carboplatin and paclitaxel. A trial being conducted in the UK, the INTERLACE trial (Cancer Research UK 11/024), has been designed to evaluate the potential benefit of neoadjuvant CT in LACC. In this trial, which has begun accrual, patients are being randomized to carboplatin and paclitaxel followed by standard chemoradiotherapy (CRT), or standard CRT alone.

These trials will take several more years to accrue enough evaluable subjects with adequate follow-up. Therefore, considerable time will be required before any meaningful analyses can be performed on this patient population.

Angiogenic Blockade

Tumor angiogenesis is associated with poor prognosis in cervical cancer.[10-12] Vascular endothelial growth factor, a key mediator in angiogenesis, is overexpressed in patients with high-grade dysplasia and invasive carcinoma. Inhibition of angiogenesis (Table 2) may also restore oxygen supply to tumors that may make them more sensitive to CT and RT.[13]

Bevacizumab (Avastin, Genentech, South San Francisco, CA), a humanized antivascular endothelial growth factor monoclonal antibody, has been found to have activity in cervical cancer. In the legacy Gynecologic Oncology Group protocol 227C,[14] a phase II trial in the treatment of persistent or recurrent cervical cancer, single-agent bevacizumab resulted in a 24% PFS rate at 6 months which compared favorably with historical phase II trials in this pretreated patient population. Bevacizumab was subsequently evaluated in a large randomized phase III trial in patients with recurrent, persistent, or metastatic cervical cancer. In this study, the legacy GOG 0240 protocol, patients were randomized using a 2-by-2 factorial design to CT with or without bevacizumab.[15] The CT was a combination of either cisplatin plus paclitaxel or topotecan (Hycamtin, GlaxoSmithKline, UK) plus paclitaxel. The authors found that the addition of bevacizumab resulted in a statistically significant improvements in OS (17.0 vs 13.3 months; hazard ratio = 0.71; $P = 0.004$) and PFS (8.2 vs 5.9 months; hazard ratio = 0.67; $P = 0.008$). Based on this aforementioned trial, in 2014 the Food and Drug Administration approved bevacizumab in combination with paclitaxel and either cisplatin or topotecan in the treatment of recurrent, persistent, or metastatic cervical cancer.

The addition of bevacizumab to CCR for LACC cancer was addressed by the legacy Radiation Therapy Oncology Group (RTOG) 0417 clinical trial.[16] In this completed phase II study, eligible patients with bulky stage IB to IIIB cervical cancer were

Table 2 Molecular Agents for Cervical Cancer

Study	Stage	Type	Agents Studied	CCR Given
Angiogenesis inhibitors				
Monk et al[14]	Persistent/recurrent/metastatic	Phase II	Bevacizumab	No
Schefter et al[16]	IB-IIIB	Phase II	Bevacizumab	Yes
Tewari et al[15]	Persistent/recurrent/metastatic	Phase III	Bevacizumab/cisplatin/paclitaxel	No
PARP inhibitors				
NCT01237067	Persistent/recurrent/metastatic	Phase I	Olaparib/carboplatin	No
Legacy GOG-0076HH	Persistent/recurrent/metastatic	Phase I/II	Veliparib/cisplatin/paclitaxel	No
Ribonucleotide reductase inhibitors				
Whitney et al[21]	IIB-IVA	Phase III	Hydroxyurea	Yes
Kunos et al[22]	IB2-IIIB	Phase I	Triapine	Yes
Kunos and Sherertz[23]	IB2-IIIB	Phase II	Triapine	Yes
NCT01835171	IB2-IVA	Phase II	Triapine	Yes

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