The Rationale for the Use of Non-platinum Chemotherapy Doublets for Metastatic and Recurrent Cervical Carcinoma

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Abstract: Ongoing drug discovery and synergy in cytotoxic combinations have served as the dominant theme for clinical research in women with metastatic and recurrent cervical cancer. The results of the most recent phase III randomized clinical trials conducted by the Gynecologic Oncology Group in this population evaluated the tolerability and efficacy of cisplatin-based chemotherapy doublets. Possibly as a consequence of the increasing use of radiosensitizing cisplatin with concurrent pelvic radiotherapy for treatment of locally advanced disease prior to recurrence, the response rates obtained with platinum-based regimens have decreased with each successive trial. There is clearly a need for a re-appraisal of therapeutic options for women with recurrent and metastatic cervical cancer, many of whom may harbor platinum-resistant clones. In this article we will provide a rationale for the use of non-platinum–based chemotherapy doublets for this patient population.

Keywords
Cervical cancer, platinum resistance, nonplatinum doublets

Introduction

Although invasive cervical cancer remains a worldwide epidemic—with more than 500,000 new cases diagnosed annually, resulting in 250,000 deaths each year—the incidence of the disease in developed countries has decreased dramatically during the previous 60 years as a result of successful screening programs employing cervical cytology.[1] In the United States in 2009, it is estimated that there were 11,270 new cases of invasive cervical cancer and approximately 4,070 deaths.[2] The vast majority of these deaths occurred among patients with untreated locally advanced (ie, Federation of Gynaecology and Obstetrics [FIGO] stages IB2-IVA) and metastatic disease (ie, FIGO stage IVB), as well as in patients who had a recurrence of disease following definitive therapy for locally advanced tumors.

Radiation therapy has been the primary treatment modality for locally advanced cervical cancer and can often result in durable, long-term remissions and cures. However, high FIGO stage (eg,

stages III-IVA vs stage II), periaortic nodal metastases as well as other subclinical metastases, treatment interruption, and treatment delays have all been recognized as adverse prognostic factors that limit the efficacy of pelvic irradiation alone.[1] Ten years ago, several pivotal trials of concomitant systemic cisplatin-based chemotherapy and pelvic radiotherapy demonstrated a 50% reduction in local failure and improvements in overall survival (OS).[3-8] As cisplatin-based chemoradiation has now been readily adopted as the standard of care for locally advanced disease, it follows that for those patients in whom disease ultimately recurs; palliative therapy with cisplatin-based regimens may be less effective due to prior platinum exposure with resulting acquired drug resistance.

In this article, a rationale will be proposed for exploring non-platinum chemotherapy doublets for metastatic and recurrent cervical cancer. A careful examination of the chemoradiation trials for locally advanced disease and the phase II and randomized phase III experiences of cisplatin-based systemic therapy for metastatic disease is essential in order to critically understand the need for active, non-platinum alternatives for this population.

Concurrent Chemoradiation for Locally Advanced Cervical Cancer

Radiation therapy alone fails to control the progression of cervical cancer in 35–90% of women with locally advanced disease. Concurrent chemoradiation has been employed in the treatment of many cancers in an attempt to improve local control and eradicate distant metastases, and has been successfully integrated into the therapeutic program of not only cervical carcinomas but also those of the head and neck and of the anal canal. Mechanisms of drug-radiation interaction leading to enhanced radiation kill may include modification of the slope of the dose-response curve, inhibition of sublethal damage repair, inhibition of recovery from potentially lethal damage, alterations in cellular kinetics, decrements in tumor volume leading to improved blood supply and tissue oxygenation, and increased radiosensitivity.[3]

Five phase III trials of concurrent chemoradiation performed by the Gynecologic Oncology Group (GOG), the Radiation Therapy Oncology Group (RTOG), and the Southwestern Oncology Group (SWOG) have demonstrated a reduction in the risk of recurrence by up to 50% in patients with locally confined bulky or advanced stage cervical cancer, regional spread, or high-risk features after hysterectomy.[4-8] Three studies compared radiotherapy alone with radiotherapy plus cisplatin-based chemotherapy,[4-6] 1 of which addressed the prescription of adjuvant therapy following radical surgery for early stage tumors.[4] Excluding patients with nodal involvement by computed tomography scan, Keys and colleagues evaluated the benefit of pre-operative chemoradiation therapy (weekly cisplatin 40 mg/m^2, maximal weekly dose of 70 mg) versus radiation therapy alone in patients with locally advanced disease confined to the cervix (ie, stage IB_2).[5] All patients underwent adjuvant hysterectomy. In this landmark study, the rates of both progression-free survival (PFS; $P<.001$) and OS ($P=.008$) were significantly higher in the combined therapy group at 4 years.[5] Patients receiving radiosensitizing chemotherapy experienced higher frequencies of grade 3 and grade 4 adverse hematologic effects and adverse gastrointestinal effects.[5]

Morris and coworkers compared pelvic radiation plus concurrent cisplatin and 5-fluorouracil (5-FU) with pelvic radiation plus extended field radiation therapy.[6] This trial was the only one to include chemotherapy during low-dose-rate brachytherapy. Eligibility requirements for this study differed from the previous GOG studies, with the inclusion of patients with FIGO stage IB_2–IIA tumors. The estimated 5-year survival rates were 73% and 58%, respectively, for patients treated with chemoradiation therapy versus radiation therapy alone.[6] A significant difference in disease-free survival was also seen in favor of the chemotherapy arm. The addition of chemotherapy to radiation therapy was effective in reducing both the frequency of local recurrences and distant metastases, with the latter observation refuting those detractors who claim that the benefit conferred by radiosensitizing chemotherapy is strictly a function of increasing the relative dose-intensity of the radiation that can be delivered to the pelvis.

Two additional phase III trials have confirmed the superiority of cisplatin-based chemoradiation for the treatment of locally advanced cervical cancer.[7,8] Whitney and associates published the results of concurrent cisplatin plus 5-FU and pelvic radiation therapy versus hydroxyurea plus pelvic radiation therapy in women with FIGO stage IIB-IVA disease who had undergone surgical staging and were found to have negative common iliac and aortocaval lymph nodes.[7] Among 368 eligible patients, the median follow-up time among survivors was 8.7 years.[7] Disease progression occurred in 43% of patients randomized to cisplatin plus 5-FU versus 53% of patients randomized to hydroxyurea.[7] PFS was significantly better among patients treated with the combined chemotherapy regimen ($P=.033$), with 3-year survival rates of 67% (cisplatin-5-FU arm) versus 57% (hydroxyurea).[7]

Rose and co-authors reported the results from the 3-arm GOG trial of pelvic radiation therapy plus concurrent single-agent cisplatin versus cisplatin plus 5-FU plus hydroxyurea versus hydroxyurea alone.[8] All patients had FIGO stage IIB-IVA cervical cancer with surgically confirmed negative common iliac and aortocaval lymph

nodes. The median duration of follow-up was 35 months for 526 women included in the final analysis. Significant improvements in PFS and OS were observed in patients randomized to either cisplatin-containing arm.[8] Effectively, the results from Morris and associates[7] and from Rose and co-authors[8] were critical in supplanting hydroxyurea as the radiosensitizer of choice.

Because the combination of cisplatin plus 5-FU results in added toxicity, weekly, single-agent cisplatin dosed at 40 mg/m^2 has emerged as the standard radiosensitizer in locally advanced cervical cancer.[3] At present, radiosensitizing chemotherapy is recommended during that part of the treatment program in which external beam pelvic radiotherapy is administered.[1] These pivotal phase III trials not only identified a significant survival advantage associated with the addition of concurrent chemotherapy, but were noteworthy in that the degree of benefit achieved with chemotherapy was remarkably similar for each of the 4 trials that studied chemoradiation for primary therapy. The results changed the standard of care for the treatment of locally advanced cervical cancer and formed the basis for the 1999 National Cancer Institute (NCI) Clinical Announcement (Practice Alert) in cervical cancer.[3] In 2005, a Cochrane Collaboration review of 24 randomized controlled trials comparing concomitant chemoradiation with radiotherapy was published. This analysis included a total of 4,921 patients and strongly suggested that chemoradiation improves OS and PFS, whether or not platinum is used.[9]

Cisplatin-based Chemotherapy for Metastatic and Recurrent Disease

Single-agent cisplatin chemotherapy has been used for nearly 3 decades to treat recurrent and metastatic cervical cancer, with a relative risk of approximately 20%.[1] Unfortunately, a significant impact of single-agent cisplatin on survival or quality of life among these incurable patients is unproven. The GOG and other investigators have studied the efficacy and tolerability of many cytotoxic regimens for metastatic and recurrent cervical cancer.[10] The GOG in particular has designed and completed a total of 8 randomized phase III trials using cisplatin-based regimens in this population.[11-18] The first 5 trials have been discussed in detail by the authors in an earlier review.[10] In this section, we will be concerned with the 3 most recently completed randomized trials by the GOG and select phase II experiences.

McGuire and colleagues reported a 17% overall response rate (ORR) for single-agent paclitaxel in advanced squamous cell carcinoma of the cervix.[19] When paclitaxel was combined with cisplatin as part of a feasibility study, Rose and coworkers documented an impressive ORR of 46.3%.[20] This study was followed by a phase III trial of cisplatin 50 mg/m^2 versus cisplatin 50 mg/m^2 plus paclitaxel 135 mg/m^2, 24-hour infusion every 21 days, in which Moore and associates reported superior response rates (36% vs 19%) and PFS (4.8 vs 2.8 months) with the combined regimen; there were, however, no significant differences demonstrated in an analysis of OS.[16]

Moving ahead, the GOG considered the report by Long and co-authors, in which the MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin) generated a 66% overall RR (including 21% complete response [CR]) in patients with advanced cervical carcinoma.[21] Similarly, the phase II study by Fiorica's team employing cisplatin plus a 3-day infusion of topotecan was noteworthy for its associated 28% ORR in advanced cervical cancer.[22] These regimens were prospectively evaluated alongside cisplatin alone in the GOG.[17] The MVAC arm was closed on July 23, 2001 by the Data Safety Monitoring Board of the GOG after 4 treatment-related deaths due to sepsis.[23] Long and co-authors reported that the comparison of cisplatin to cisplatin plus topotecan (cisplatin 50 mg/m^2 plus topotecan 0.75 mg/m^2 on days 1–3 every 21 days) was the first analysis to demonstrate a statistically significant impact on the ORR, median PFS, and median OS, all outcome measures favoring the 2-drug regimen.[17]

Because the survival curve by treatment demonstrated a separation of 2 months that was sustained until 18 months from study entry, the demonstrated 2.9 month improvement in median survival, although short, is taken to reflect a durable benefit of cisplatin plus topotecan on long-term survival in the population studied.[17] In this study, the survival benefit observed with topotecan and cisplatin may reflect reduced activity of single-agent cisplatin as a consequence of the increasing use of radiosensitizing chemotherapy for upfront treatment. In contrast to the GOG trial by Moore and associates (cisplatin vs cisplatin plus paclitaxel),[16] the phase III trial by Long and co-authors was completed after concurrent chemoradiation became standard treatment in the upfront management of advanced disease (Table 1).[17] Only 27% of patients treated in the earlier trial received prior radiosensitizing chemotherapy,[16] as compared with 57% of patients treated by Long and co-authors.[17] Stated differently, chemotherapy for patients in the latter trial was, for the most part, "second-line" chemotherapy rather than the "first-line" chemotherapy that patients in the former trial typically received. The implication is that if tumors have developed acquired resistance to cisplatin at the time of relapse, then the benefit observed in the second study lies primarily with topotecan. Further testament to this hypothesis is the observation that in the cisplatin

Table 1. The Impact of Prior Platinum Exposure on Response Rates in Patients Treated in Two Randomized Phase III Studies of the Gynecologic Oncology Group

Long et al[17]	Response rate with no prior cisplatin	Response rate with prior cisplatin (57% of patients)*
Cisplatin	20%	8%
Cisplatin/ topotecan	39%	15%
Moore et al[16]	**Response rate with no prior cisplatin**	**Response rate with prior cisplatin (27% of patients)***
Cisplatin	26%	5%
Cisplatin/ paclitaxel	37%	32%

*Platinum as part of cisplatin-based chemoradiation.

plus topotecan phase III trial, the response rate and PFS for the single-agent cisplatin arm were lower than those observed in previous randomized trials of the GOG in this population.[14-16] In the report by Long and co-authors, for patients who did not receive prior platinum therapy versus those who did receive prior platinum therapy, the hazard ratios for PFS were 0.50 and 0.87, respectively; the hazard ratios for OS were 0.63 and 0.78, respectively. These findings suggest a less beneficial effect in the latter (pretreated) group (homogeneity of risk test: P=.03 for PFS; P=.42 for OS).[17] These observations have important implications for the expected efficacies of various salvage and palliative regimens in which cisplatin is a key player. In fact, these ideas came into play in the next phase III trial by the GOG (Protocol 204).[18]

Protocol 204 was opened within the GOG on May 27, 2003. Four different platinum-based intravenous doublets containing topotecan, paclitaxel, vinorelbine, or gemcitabine comprised the study arms.[18] Health-related quality of life analysis was conducted through 4 cycles of therapy and at 9 months follow-up. The cisplatin-paclitaxel doublet was assigned as the control arm in this trial based on the 36% response rate associated with this doublet observed by Moore and associates[16] (and also because Protocol 204 was developed before the discovery that the combination of cisplatin plus topotecan imparts a positive effect on median OS, as reported by Long and co-authors[17]).

By January 2007, 424 evaluable patients had been enrolled in this study.[24] On April 24, 2007, results of a scheduled interim analysis were presented to the Data Monitoring Committee (DMC), indicating that all of the experimental arms on the clinical trial were unlikely to demonstrate improved survival over the control (cisplatin plus paclitaxel) by the end of the study.[24] Based on this analysis, the DMC voted to close the study early, and effective April 30, 2007, the phase III trial was closed to patient entry.[24]

GOG 204 was the largest and most complex phase III, randomized, multicenter clinical trial performed in this population. In this 4-arm trial, none of the experimental regimens were found to be superior to the control arm of cisplatin plus paclitaxel.[18] Monk and colleagues have recently reported the response rates, which were 29.1% for the control, 25.9% for cisplatin plus vinorelbine, 22.3% for cisplatin plus gemcitabine, and 23.4% for cisplatin plus topotecan.[18] The experimental-to-control hazard ratios for death were 1.15 for cisplatin plus vinorelbine, 1.32 for cisplatin plus gemcitabine, and 1.26 for cisplatin plus topotecan, with all 95% confidence intervals crossing 1.0.[18] Although the RR for the control arm (cisplatin plus paclitaxel) was higher than that of the other regimens, in the survival analyses, none of the experimental regimens outperformed cisplatin plus paclitaxel.[24] As expected, more patients in GOG 204 had received prior cisplatin therapy in conjunction with radiation therapy than in the GOG phase III trials by Long and associates[17] and by Moore and associates,[16] which had immediately preceded it. Monk and colleagues reported that prior chemoradiation was associated with an increased risk of death.[18]

The Rationale in Support of Non-platinum Doublet Therapy for Metastatic and Recurrent Cervical Cancer

As discussed above, the formal adoption of platinum-based chemoradiation for locally advanced disease has important therapeutic implications when considering palliative therapy for those patients in whom disease ultimately recurs.[24] Indeed, the majority of patients treated for metastatic, persistent, and/or recurrent cervical carcinoma represent chemoradiation failures. These patients may be considered to harbor tumors that have acquired drug resistance to cisplatin. As observed progressively in the 3 most recently completed phase III GOG trials for metastatic disease, more patients in each succeeding trial had prior exposure to platinum for locally advanced disease.[24] In fact, the response to systemic platinum-based therapy at relapse was demonstrably inferior in each of these studies for those groups who had received platinum before.[24] There is a clear need for alternatives to standard cisplatin-based salvage therapy for this population. Although there has been some interest generated in

targeted therapy, for the purposes of this discussion, we will consider cytotoxic therapeutic strategies to overcome and/or circumvent platinum-resistance in women with recurrent disease. Potential options include the inclusion of non–cross-resistant platinum analogs, reversal of platinum resistance, and use of non-platinum chemotherapy doublets.

Employing non–cross-resistant platinum analogs to circumvent platinum resistance in this population is enticing only in theory. Unlike cisplatin and carboplatin, oxaliplatin substitutes a 1,2-diamiocyclohexane in place of the 2 ammonia ligands. Oxaliplatin also contains a bidentate oxalate group. Oxaliplatin not only has a favorable toxicity profile but is widely regarded as active in cisplatin-resistant solid tumors. In a systematic review of the literature, Stordal and coworkers carefully evaluated the preclinical and clinical evidence concerning the use of oxaliplatin in patients with platinum-resistant cancer.[25] The investigators identified 25 preclinical cellular models of platinum resistance and 24 clinical trials reporting oxaliplatin-based salvage therapy. Importantly, in the clinical trials, there was a much lower response rate in patients with platinum-refractory or -resistant cancers (ie, prior exposure to either cisplatin and/or carboplatin) compared to patients with platinum-sensitive cancers, suggesting that cross-resistance between cisplatin and oxaliplatin may exist. Additionally, in the studies under scrutiny, single-agent oxaliplatin had a poor response rate in cisplatin resistant/refractory cancer but performed better in combination with other agents in this setting. It would appear that the benefit of oxaliplatin does not lie in its underlying activity in cisplatin-resistant disease, but in its more favorable toxicity profile, which allows it to be combined with other, more active agents. For example, when used in combination with gemcitabine as part of induction therapy for locally advanced cervical cancer, Duenas-Gonzalez and associates reported an ORR of 80% among 10 patients. Three women (30%) had a CR, and 7 (70%) ultimately underwent surgery.[26] Unfortunately, evidence for oxaliplatin activity in previously treated metastatic/recurrent cervical cancer is lacking. Among 22 evaluable patients reported by Fracasso and co-authors in a phase II trial by the GOG, there were only 2 responses (8.3%) using the single agent at 130 mg/m^2 every 21 days.[27]

A second potential strategy involves overcoming or reversing platinum resistance. Acquired drug resistance may be a multifactorial phenomenon due to failure of drug uptake or activation, alterations in target enzymes including topoisomerase, activation of enzymatic systems involved in the repair of damage to DNA, enhanced expression of detoxifying enzymes including glutathione-S-transferase, and/or increased drug efflux.[28] The acquisition of the multidrug resistance (MDR) phenotype is often discussed in reference to the expression of the drug efflux protein MDR1 (P-glycoprotein) encoded by the MDR1 gene, and its related proteins, including multidrug resistance-associated protein 1 (MRP1), multidrug resistance-associated protein 2 (MRP2), and breast cancer resistance protein (BCRP).[28] These efflux proteins actively expel structurally and functionally antineoplastic drugs from cells, decreasing their intracellular accumulation to noncytotoxic levels. Takara and colleagues evaluated the effects of 27 cytotoxic agents in immortalized cervical cancer cell lines (ie, HeLa) and MDR1-overexpressing derivative cell lines. Interestingly, cyclosporin A was able to reverse the high level of resistance exhibited by MDR1-overexpressing cell lines to several antineoplastic drugs. These effects of cyclosporin A on cytotoxicity suggest that the efficacy of chemotherapy could be improved by co-administration with other drugs that are substrates of MDR1. Enthusiasm for this strategy to reverse platinum resistance has waned, as it has become increasingly recognized that P-glycoprotein is not usually overexpressed in cisplatin-resistant tumors. Indeed it is now generally accepted that reduced platinum accumulation is due to reduced drug uptake rather than to increased drug efflux. The precise mechanism of cellular uptake of cisplatin remains unclear. However, it appears that passive diffusion plays a predominant role, although some evidence supports the involvement of facilitated or active transport mechanism(s).[29]

In clinical trials among patients with relapsed breast and/or ovarian carcinoma, Nagourney and associates and Rose and coworkers have separately reported the ability of gemcitabine to alter established platinum resistance and also synergize with platinum.[30-32] Cisplatin-resistant cells upregulate nucleotide excision repair enzyme complexes ERCC1, ERCC2, and XPA and provide a potential target for gemcitabine. "Masked" chain termination occurs when gemcitabine is directly incorporated into DNA as a triphosphate. The diphosphate inhibits ribonucleotide reductase and concurrently depletes cells of necessary deoxynucleoside pools. For metastatic, previously treated squamous cell carcinoma of the cervix, Brewer and colleagues conducted a phase II trial of cisplatin 30 mg/m^2 plus gemcitabine 800 mg/m^2 (days 1 and 8) every 28 days.[33] Among 32 eligible patients, there were 7 partial responses (PRs; 21.9%), and 12 women (37.5%) had stable disease.[33] The median time to progression was 3.5 months. The modest activity of this doublet was comparable to that of other active agents and combinations tested in this population, with primarily hematologic toxicities that were generally manageable with dose reductions. However, as discussed earlier, when the cisplatin-gemcitabine doublet was advanced to the phase III arena in the GOG's recently

completed 4-arm trial of cisplatin doublets, it did not outperform the control arm of cisplatin plus paclitaxel.[18]

A third strategy directed against the problem of prior platinum exposure in this population involves the identification of active and tolerable non-platinum chemotherapy doublets. At the 2007 Annual Meeting of the American Society of Clinical Oncology, Symonds and associates reported their results of a Scottish phase II trial of docetaxel (75 mg/m^2 day 1) plus gemcitabine (1,000 mg/m^2 days 1 and 8) as second-line chemotherapy in cervical cancer (SCOTCERV study).[34] Among 24 evaluable patients, 23 had prior chemoradiotherapy. The principal toxicity was neutropenia (grade 3 in 8 patients, grade 4 in 8 patients), with 4 patients experiencing grade 3 febrile neutropenia.[34] Dose reductions occurred in 29% of patients receiving docetaxel and in 25% of patients receiving gemcitabine.[34] Hematologic toxicity resulted in the day 8 gemcitabine dose being omitted in 41% of cycles.[34] Among 18 patients evaluable for response, there was 1 CR, 4 PRs, 6 stable disease, and 7 progressive disease.[34] The investigators acknowledged that although this combination exhibited some activity against "platinum-resistant" metastatic cervical cancer, the ability to deliver the day 8 gemcitabine dose was compromised.

The folic acid antimetabolite, pemetrexed, has demonstrated modest activity as a second-line agent in persistent and recurrent cervical carcinoma. Through inhibition of thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, pemetrexed prevents formation of precursor purine and pyrimidine nucleotides required for DNA and RNA synthesis. Miller and co-authors reported 4 PRs (15%) among 29 patients with recurrent cervical cancer who enrolled in a phase II second-line trial of the GOG.[35] In the CERVIX 1 study of the Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO) Group, Lorsso and coworkers recently reported 6 PRs (13.9%) among 43 patients with recurrent cervical carcinoma who received pemetrexed as second-line chemotherapy.[36] In both trials, grades 3 and 4 toxicities included leukopenia (28–30%) and neutropenia (26–30%).[35,36] Future work with this promising agent should be aimed at combining it with non-platinum agents.

The combination of topotecan plus paclitaxel is a non-platinum doublet for which preclinical data are available. Bahadori and associates demonstrated synergy between topotecan and microtubule-interfering agents such as paclitaxel and vinblastine.[37] Using the MTT assay on a colon cancer cell line, these investigators noted that incubation with paclitaxel increased the efficacy of subsequent treatment with topotecan. Specifically, the concentration of topotecan necessary to induce a 50% decrease in cell survival was reduced by 10- to 40-fold.[37] Immediately prior to the addition of topotecan, paclitaxel caused an increase in topoisomerase I protein levels (presumably through stabilization of topoisomerase I and RNA or through induced gene expression), fraction of S phase cells (possibly through higher transformation of topotecan-topoisomerase I-DNA complexes), and extent of Bcl-xL phosphorylation (thus decreasing anti-apoptotic activity).[37]

Both topotecan and paclitaxel have shown activity alone and in combination with cisplatin in metastatic cervical cancer (hence their inclusion in protocol 204). Tiersten and coworkers has piloted paclitaxel plus topotecan in 15 patients with recurrent, persistent, or metastatic cervical carcinoma.[38] Fourteen had received prior pelvic irradiation. Patients were treated with paclitaxel 175 mg/m^2 on day 1 and topotecan 1 mg/m^2 on days 1–5 of a 21-day cycle with growth factor support. Among 13 evaluable patients, there were 7 (54%) responses (1 CR, 6 PR), and 3 patients (23%) experienced stable disease.[38] The PFS and OS were 3.77 and 8.62 months, respectively.[38] Grade 3/4 toxicities included anemia (47%), leukopenia (27%), thrombocytopenia (13%), neurotoxicity (13%), and diarrhea (13%).[38] The non-platinum doublet of topotecan plus paclitaxel warrants further study in this population of potentially platinum-resistant patients.

Conclusions

The non-platinum chemotherapy doublet of topotecan plus paclitaxel is currently being studied in 2 phase III randomized trials for women with metastatic, recurrent, and/or persistent cervical cancer. In December 2006, Germany's national trialist group, the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), launched a prospective, randomized phase III study of cisplatin (50 mg/m^2 on day 1) plus topotecan (0.75 mg/m^2 days 1–3) versus paclitaxel (70 mg/m^2 days 1, 8 and 15) plus topotecan (1.75 mg/m^2 days 1, 8 and 15) in patients with relapsed/persistent/metastatic cervical cancer (Zervix-1 trial).[39]

In April 2009, the NCI of the United States activated GOG protocol 240, which has been designed to study both non-platinum doublet therapy and anti-vascular therapy.[40] Although GOG 240 represents the first randomized trial of anti-angiogenesis agents in cervical cancer, it has not been developed as a registration trial for bevacizumab (Avastin, Genentech). GOG 240 uses a 2 × 2 factorial design to answer not only the question regarding targeted therapy, but also the important chemotherapy question concerning the efficacy and tolerability of non-platinum doublet therapy among relapsing patients initially treated for locally advanced disease in the era of chemoradiation.[40] The argument to assign the control arm to cisplatin

plus paclitaxel has been advanced by Tewari.[41] In this trial, cisplatin (50 mg/m^2 day 1 or day 2) plus paclitaxel (175 mg/m^2 or 135 mg/m^2 on day 1) with and without bevacizumab (15 mg/kg) is being studied alongside paclitaxel (175 mg/m^2 on day 1) plus topotecan (0.75 mg/m^2 days 1–3) with and without bevacizumab (15 mg/kg). A total of 450 patients will be enrolled. In addition to important translational science objectives, GOG 240 has also been designed to prospectively evaluate independent prognostic factors (eg, prior radiosensitizer and time from interval from diagnosis to recurrence) identified by Moore and associates in a post-hoc analysis of 3 GOG protocols.[42] Because it is unlikely that targeted therapy in this population outside of a clinical trial will be paid for by third party payers, much of the furor and genuine excitement surrounding bevacizumab must necessarily be curtailed,[43-45] with attention redirected to the potential for non-platinum chemotherapy doublets emerging as an acceptable therapeutic alternative for metastatic and recurrent cervical carcinoma.

References

1. Monk BJ, Tewari KS. Invasive cervical cancer, In DiSaia PJ, Creasmant WT, eds. *Clinical Gynecologic Oncology*. 7th ed. Philadelphia, PA: Mosby Publishers; 2007.
2. Jemal A, Siegel R, Ward E, Hao Yongping, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225-249.
3. Monk BJ, Tewari KS, Koh WJ. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. *J Clin Oncol.* 2007; 27:2952-2965.
4. Peters III WA, Liu PY, Barrett II RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*. 2000;18:1606-1613.
5. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999;340:1154-1161.
6. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med.* 1999;340:1137-1143.
7. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol.* 1999;17:1339-1348.
8. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999;340:1144-1153.
9. Green J, Kirwan J, Tierney J, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database Syst Rev.* 2005;3:CD002225.
10. Tewari KS, Monk BJ. Gynecologic Oncology Group trials of chemotherapy for metastatic and recurrent cervical cancer. *Curr Oncol Rep*. 2005;7:419-434.
11. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: A Gynecologic Oncology Group study. *J Clin Oncol.* 1985;3:1079-1085.
12. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr, Hatch KD. A randomized comparison of a rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1989;32:198-202.
13. McGuire WP III, Arseneau J, Blessing JA, et al. A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 1989;7:1462-1468.
14. Omura GA, Blessing JA, Vaccarello L, et al. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 1997;15:165-171.
15. Bloss JD, Blessing JA, Behrens BC, et al. Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2002;20:1832-1837.
16. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2004;22:3113-3119.
17. Long HJ 3rd, Bundy BN, Grendys EC, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2005;23:4626-4633.
18. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27:4649-4655.
19. McGuire WP, Blessing JA, Moore D, Lentz SS, Photopulos G. Paclitaxel has moderate activity in squamous cervix cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 1996;14:792-795.
20. Rose PG, Blessing JA, Gershenson DM, McGehee R. Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 1999;17:2676-2680.
21. Long HJ 3rd, Cross WG, Wieand HS, et al. Phase II trial of methotrexate, vinblastine, doxorubicin, and cisplatin in advanced/recurrent carcinoma of the uterine cervix and vagina. *Gynecol Oncol*. 1995;57:235-239.
22. Fiorica J, Holloway R, Ndubisi B, et al. Phase II trial of topotecan and cisplatin in persistent or recurrent squamous and nonsquamous carcinomas of the cervix. *Gynecol Oncol*. 2002;85:89-94.
23. Long HJ 3rd, Monk BJ, Huang H. Clinical results and quality of life analysis for the MVAC combination (methotrexate, vinblastine, doxorubicin, and cisplatin) in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006;100:537-543.
24. Tewari KS, Monk BJ. Recent achievements and future developments in advanced and recurrent cervical cancer: trials of the Gynecologic Oncology Group. *Semin Oncol.* 2009;36:170-180.
25. Stordal B, Pavlakis N, Davey R. Oxaliplatin for the treatment of cisplatin-resistant cancer: a systematic review. *Cancer Treatment Reviews.* 2007;33:347-357.
26. Duenas-Gonzalez A, Lopez-Graniel C, Gonzalez A, et al. Induction chemotherapy with gemcitabine and oxaliplatin for locally advanced cervical carcinoma. *Am J Clin Oncol.* 2003;26:22-25.
27. Fracasso PM, Blessing JA, Wolf J, Rocereto TF, Berek JS, Waggoner S. Phase II evaluation of oxaliplatin in previously treated squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003;90:177-180.
28. Takara K, Sakaeda T, Yagami T, et al. Cytotoxic effects of 27 anticancer drugs in HeLa and MDR1-overexpressing derivative cell lines. *Biol Pharm Bull.* 2002;25:771-778.
29. Ohmichi M, Hayakawa J, Tasaka K, Kurachi H, Murata Y. Mechanisms of platinum drug resistance. *Trends Pharmacol Sciences*. 2005;26:113-116.
30. Nagourney RA, Link JS, Blitzer JB, Forsthoff C, Evans SS. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. *J Clin Oncol.* 2000;18:2245-2249.
31. Nagourney RA, Brewer CA, Radecki S, Disaia P. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer subjects. *Gynecol Oncol*. 2003;88:35-39.
32. Rose PG, Mossbruger K, Fusco N, Smrekar M, Eaton S, Rodriguez M. Gemcitabine reverses cisplatin resistance: demonstration of activity in platinum and multidrug-resistant ovarian and peritoneal carcinoma. *Gynecol Oncol.* 2003;88: 17-21.
33. Brewer CA, Blessing JA, Nagourney RA, McMeekin DS, Lele S, Zweizig SL. Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 2006;100:385-388.
34. Symonds R, Davidson S, Chan S, Reed N, McMahon T, Paul J. SCOTCERV: a phase II trial of docetaxel and gemcitabine as second-line chemotherapy in cervical cancer. *J Clin Oncol (ASCO Annual Meeting Abstracts)*. 2007;25:Abstract 5548.
35. Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, Schorge JO. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 2008;110:65-70.

36. Lorusso D, Ferrandina G, Pignata S, et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. *Ann Oncol.* 2010;21:61-66.
37. Bahadori HR, Green MR, Catapano CV. Synergistic interaction between topotecan and microtubule-interfering agents. *Cancer Chemother Pharmacol.* 2001;48:188-196.
38. Tiersten AD, Selleck MJ, Hershman DL, et al. Phase II study of topotecan and paclitaxel for recurrent, persistent, or metastatic cervical carcinoma. *Gynecol Oncol.* 2004;92:635-638.
39. Thiel F (study chair). AGO protocol IFG-01-0106. A prospective, randomized phase III study to compare the effects of paclitaxel and topotecan to those of cisplatin and topotecan for treatment of patients with recurrent or persistent cervical cancer.
40. Tewari KS (study chair). Protocol GOG-0240. A randomized phase 3 trial of cisplatin plus paclitaxel with and without NCI-supplied bevacizumab (NSC #704865 IND #7921) versus the non-platinum doublet, topotecan plus paclitaxel, with and without NCI supplied bevacizumab, in stage IVB, recurrent or persistent carcinoma of the cervix. www.gog.org. Accessed April 2009.
41. Tewari KS. Expert panel: Patients with metastatic/recurrent cervical cancer should be treated with cisplatin plus paclitaxel. *Clinical Ovarian Cancer.* 2010 (in press).
42. Moore DH, Tian C, Monk BJ, Long HJ, Omura GA, Bloss JD. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010;116:44-49.
43. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009;27:1069-1074.
44. Takano M, Kikuchi Y, Kita T, et al. Complete remission of metastatic and relapsed uterine cervical cancers using weekly administration of bevacizumab and paclitaxel/carboplatin. *Onkologie.* 2009;32:595-597.
45. Tewari KS, Monk BJ. Beyond platinum for metastatic and recurrent carcinoma of the cervix. *Onkologie*. 2009;32:552-554.