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Debate: Cisplatin Plus Paclitaxel in the Treatment of Patients With Metastatic/Recurrent Cervical Cancer

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PRO: Patients With Metastatic/Recurrent Cervical Cancer Should be Treated With Cisplatin Plus Paclitaxel

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Background

Invasive cervical cancer was once one of the most common malignancies to affect women in the United States. Although it remains a worldwide epidemic with greater than 500,000 new cases diagnosed annually, resulting in 250,000 deaths each year, the incidence of the disease in developed countries has decreased over the preceding 60 years.¹ In 2009, it was estimated that there were 11,270 new cases of invasive cervical cancer and approximately 4070 deaths.² The vast majority of these deaths occur among patients with untreated locally advanced and metastatic disease as well as those whose disease recurs after definitive therapy for locally advanced lesions.

The reasons for the decreased incidence of invasive cervical cancer in developed nations can be attributed primarily to screening programs using cervical cytology (ie, Papanicolaou testing). Because screening is available mainly to women who have health care coverage or who are able to pay out of pocket, advanced cases of disease now occur predominantly among poor women in developed countries and throughout impoverished regions of the world. Women diagnosed with invasive disease through screening programs are most likely to be found to have early-stage, and hence, curable lesions. Although algorithms exist that incorporate high-risk human papillomavirus DNA co-testing into screening programs that use cervical cytology,³ the degree of impact of dual modality of screening on mortality rates from cervical cancer is unclear at the present time. Similarly, vaccines that have been licensed by the United States Food

and Drug Administration to prevent cervical cancer (eg, Gardasil, Merck & Co., Inc.; and Cervarix, GlaxoSmithKline)^{4,5} will ultimately decrease the incidence of invasive disease further but have not yet reached large numbers of the populations through the existing vaccination programs.

Unlike other gynecologic malignancies such as ovarian, endometrial, and vulvar carcinomas, cervical cancers are staged clinically. Appropriate tools used to assign International Federation of Gynecology and Obstetrics (FIGO) stage include history and physical examination, pelvic examination under anesthesia, cervical biopsies (including endocervical curettage), urethrocytostomy, proctoscopy, intravenous pyelogram, and chest radiograph.¹ Other imaging modalities, including computed tomography, magnetic resonance imaging, and/or positron emission tomography, may be used to evaluate for sites of metastatic disease (including pelvic and para-aortic lymph node involvement) and for treatment planning purposes. The vast majority of cervical carcinomas are of squamous histology; however, in recent decades, there has been a relative increase in the proportion and absolute incidence of adenocarcinomas, presumably because of the high success rate screening programs have had in identifying precursor squamous lesions that can be treated before invasion results.¹ Adenocarcinomas arising in the endocervical canal may not be as accessible to standard screening modalities using a wooden spatula and a Cytobrush.

Evidence-based practice for management of early and locally advanced disease in the United States has evolved through the cooperative group clinical trial programs of the Gynecologic Oncology Group (GOG), the Southwestern Oncology Group (SWOG), and the Radiation Therapy Oncology Group (RTOG). Although radical hysterectomy with pelvic lymphadenectomy can be curative for many patients with early-stage disease (ie, FIGO stage I), random-

Authors were asked to defend the position they have taken for this debate.

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ized phase III trials have demonstrated a decrease in local recurrence and improvements in survival through the use of postoperative adjuvant therapy. Specifically, patients with early-stage tumors who are found to have ≥ 2 high-intermediate risk surgicopathologic factors (ie, large tumor diameter, deep stromal invasion, lymphovascular invasion) are often treated with adjuvant pelvic irradiation in accordance with findings reported by Sedlis et al in GOG protocol 92.⁶ Patients treated with radical hysterectomy and lymphadenectomy who are found to have lymph node metastases or vaginal margin involvement or microscopic parametrial extension are advised to undergo treatment with adjuvant chemoradiation as a consequence of findings by Peters et al on behalf of the Intergroup trial (GOG/SWOG/RTOG) that compared adjuvant radiation with or without radiosensitizing chemotherapy in patients with these high-risk surgicopathologic findings.⁷ An evidence-based therapeutic program for patients with locally advanced disease (FIGO IB2-IVA) may include definitive treatment with primary multimodality therapy using pelvic irradiation (with or without extended-field radiation therapy) with concurrent radiosensitizing chemotherapy (eg, cisplatin plus 5-fluorouracil) followed by brachytherapy.⁸ The addition of radiosensitizing chemotherapy to pelvic irradiation for locally advanced disease was shown to result in a 50% decrease in locoregional failure in 5 cooperative group trials, prompting a rare National Cancer Institute Clinical Announcement in 1999.⁷⁻¹²

For patients who present with metastatic disease (ie, FIGO stage IVB) and for patients whose disease recurs or who demonstrate evidence of persistent disease after definitive primary therapy, treatment options are limited and include total pelvic exenteration for a central, isolated pelvic recurrence; palliative intestinal and/or urinary diversion; palliative radiation therapy to control vaginal bleeding or alleviate bone pain due to metastases; and/or palliative systemic intravenous chemotherapy.¹ Importantly, the GOG has conducted 8 prospective, randomized phase III clinical trials in this patient population. Drug discovery for the most part has fed into these phase III trial designs through the GOG's phase II series dedicated to exploring the activity and tolerability of cytotoxic compounds in cervical cancer.¹³

The early trials of the GOG for recurrent and metastatic cervical carcinoma were designed to evaluate cisplatin dosing,¹⁴ schedules,¹⁵ and analogues.¹⁶ The next 2 trials evaluated the addition of ifosfamide, bleomycin, and mitolactol to cisplatin-based therapies.^{17,18} Among some of the lessons learned during the 1980s and 1990s governing chemotherapy for recurrent cervical cancer were that platinum-based therapies were most effective, and that cisplatin was more active than carboplatin (response rates [RRs], 19% vs. 15%, respectively).¹⁹ Two ways through which the RR could be increased without prolongation in survival included increasing the platinum dose and/or adding ifosfamide to cisplatin. As a consequence of these first 5 randomized phase III clinical trials, single-agent cisplatin 50 mg/m² emerged as the standard for recurrent disease.¹⁹

Things started to become interesting with the next 2 trials. In GOG 169, Moore et al studied cisplatin with or without paclitaxel (135 mg/m² over 24 hours) in 259 patients and reported an impressive 36% RR for the doublet, without an overall survival (OS) benefit.²⁰ Moving ahead, in GOG 179 Long et al studied cisplatin alongside the cisplatin-topotecan doublet and methotrexate, vinblastine,

doxorubicin, and cisplatin (MVAC).²¹ The MVAC arm was closed early by the Data Safety Monitoring Board after 4 treatment-related deaths due to sepsis.²² Importantly, the comparison of cisplatin to cisplatin plus topotecan (cisplatin 50 mg/m² plus topotecan 0.75 mg/m² days 1-3 every 21 days) was the first study in which a statistically significant impact on overall RR, median progression-free survival (PFS), and median OS was demonstrated, with all outcome measures favoring the doublet.²¹ Because the survival curves demonstrated a separation of 2 months that was sustained until 18 months from study entry, the observed 2.9-month improvement in median survival, although short, is taken to reflect a durable benefit of the combined regimen on long-term survival in the population studied.^{13,19,21} Important predictors of response to chemotherapy in this population that have emerged from these trials include African-American ethnicity, performance status, pelvic disease, previous radiosensitizers, and time interval from diagnosis to first recurrence less than one year.²³

In the GOG's eighth randomized trial in this population (protocol 204), Monk et al tested 4 cisplatin-based doublets.²⁴ Because of the high RR reported by Moore et al, cisplatin plus paclitaxel was selected as the reference arm and was studied alongside doublets containing topotecan, gemcitabine (1000 mg/m² days 1 and 8), and vinorelbine (30 mg/m² days 1 and 8) on 21-days schedules. On April 24, 2007, results of a scheduled interim analysis of 513 evaluable patients were presented to the Data Monitoring Committee (DMC) indicating that all of the experimental arms in the clinical trial were unlikely to demonstrate improved survival over cisplatin plus paclitaxel by the end of the study. Based on this analysis, the DMC recommended early closure of the study.

The Case for Cisplatin Plus Paclitaxel

The cervical cancer landscape in which we find ourselves treating patients has changed over the years. As described earlier, the incidence and mortality rates of cervical cancer have dramatically decreased in the United States and Western European countries because of successful screening programs and evidence-based practice guidelines for the management of early-stage and locally advanced disease. The vast majority of patients with early lesions can be cured with radical surgery, and for those with high-risk and intermediate-high-risk surgicopathologic features, careful attention to adjuvant therapy guidelines will also place most of these patients into durable remissions. Furthermore, with the addition of radiosensitizing chemotherapy to pelvic irradiation for locally advanced disease, pelvic control rates have increased significantly. As a consequence, very few patients with recurrent disease present with isolated central pelvic recurrences that would be amenable to pelvic exenteration. In fact, the performance of pelvic exenterative surgery for this indication has declined in most centers over the years. For all of these reasons, most patients with recurrent disease (or persistent disease following therapy) need to be treated with systemic chemotherapy, as do those who are initially diagnosed with metastatic disease (ie, FIGO stage IVB). For the most part, chemotherapy in this population is palliative. Cisplatin 50 mg/m² plus paclitaxel 135 mg/m² represents the treatment of choice for these patients.

Expert Panel: Cisplatin Plus Paclitaxel in Metastatic/Recurrent Cervical Cancer

First, the 36% RR with cisplatin plus paclitaxel as reported by Moore et al²⁰ has not been superseded by any other regimen, including that of cisplatin plus topotecan, which did confer a relatively short improvement in OS when compared with single-agent cisplatin in the report by Long et al.²¹ The survival benefit observed with cisplatin plus topotecan may reflect reduced activity of single-agent cisplatin as a consequence of the increasing use of radiosensitizing chemotherapy for first-line treatment.²¹ In contrast to the study by Moore et al, the trial of cisplatin with or without topotecan was completed after concurrent chemoradiation became standard in the first-line management of advanced disease.^{20,21} Only 27% of the patients treated in the former trial received previous radiosensitizing chemotherapy compared with 57% of the patients in the latter trial. In other words, chemotherapy for patients in the cisplatin/topotecan trial was for the most part “second-line” chemotherapy rather than the “first-line” chemotherapy patients in the cisplatin/paclitaxel trial typically received. The implication is that if tumors have developed acquired resistance to cisplatin at the time of relapse, then the benefit observed by Long et al lies primarily with topotecan. Further testament to this hypothesis is the observation that in this study, the RR and PFS for the single-agent cisplatin arm were lower than that observed in previous trials.^{17,18,20} Although the 4-arm study reported by Monk et al (described above) was designed while the cisplatin/topotecan study was ongoing, the combination of cisplatin plus paclitaxel was selected as the reference arm primarily because of its relatively high RR as reported by Moore et al.^{20,24} It was also deemed important to determine whether the activity of cisplatin plus paclitaxel would be sustained in the era of chemoradiation for locally advanced disease.

This brings us to the second argument supporting the hypothesis that cisplatin plus paclitaxel represents the therapy of choice for recurrent and metastatic disease. Monk et al recently reported results from the largest and most complex randomized, multicenter phase III clinical trial performed in this population.²⁴ In this 4-arm trial, none of the experimental regimens was found to be superior to the control arm of cisplatin plus paclitaxel. The RRs for the control, cisplatin plus vinorelbine, cisplatin plus gemcitabine, and cisplatin plus topotecan were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. 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. Therefore, even in the era of chemoradiation, not only was cisplatin plus paclitaxel associated with a higher RR than the other regimens, but in the survival analyses, none of the experimental regimens outperformed cisplatin plus paclitaxel in the largest randomized trial performed in this population.

Third, the regimen of cisplatin plus paclitaxel has demonstrated acceptable toxicity profiles in the 2 randomized trials in which it was studied.^{20,24} Moore et al reported that, with the exception of select hematologic toxicities (eg, grade 3/4 neutropenia and anemia), the doublet was well tolerated, with all nonhematologic grade 3/4 toxicities and grade 3/4 thrombocytopenia occurring in < 10% of the subjects.²⁰ Similarly, Monk et al observed that grade 3/4 hematologic toxicities occurred more frequently in patients receiving the cisplatin/topotecan doublet than among patients treated with cisplatin plus paclitaxel (anemia, 34.9% vs. 16.8%; neutropenia, 82.6%

vs. 78.2%; and thrombocytopenia, 34.9% vs. 6.9%, respectively).²⁴ Furthermore, nonhematologic grade 3/4 adverse events such as fatigue, nephrotoxicity, and peripheral neuropathy manifested in a higher percentage of patients receiving the cisplatin/topotecan doublet than in those treated with cisplatin plus paclitaxel. Finally, although not statistically significant, it may be clinically important that there were more treatment-related deaths in the cisplatin/topotecan arm than in the cisplatin/paclitaxel arm.

Fourth, because chemotherapy in this population is palliative in nature, it is important to recognize quality of life (QOL) as imparting prognostic significance. Moore et al noted that a disproportionate number of patients (cisplatin, $n = 50$; cisplatin plus paclitaxel, $n = 33$) dropped out of the QOL component, presumably because of progressing tumors, deteriorating health, and/or early death.²⁰ Although the difference in QOL scores were not statistically significant between the 2 treatment arms in this study, it is important to note that patients who completed the fourth QOL assessment were almost exclusively those who had achieved a better clinical response and reported stable or slightly improving QOL over time. The higher RR among patients treated with cisplatin plus paclitaxel (36% vs. 19%) is understood to have translated into less impairment and possibly even improved QOL as a result of palliation of distant symptomatic metastases and control of in-field pelvic failures. This QOL phenomenon was also observed by Monk et al, with scores among responders improving over time.²⁰ Patients whose cancers responded to chemotherapy felt better, and despite the 4-arm randomized study being conducted well into the era of first-line cisplatin-based chemoradiation for locally advanced disease, there were more RRs associated with the cisplatin/paclitaxel doublet, although admittedly the differences were not statistically significant.²⁴

Fifth, and perhaps most enlightening, has been the realization that not all cases of FIGO stage IVB cervical cancer are incurable. Although most patients who are part of the population under discussion have recurrent disease, there will be some who present with distant metastases at initial diagnosis. Aggressive multimodality therapy using intravenous systemic chemotherapy (eg, cisplatin plus paclitaxel) followed by definitive chemoradiation and brachytherapy may render some patients disease free.²⁵ This treatment program using cisplatin plus paclitaxel was used by Qui et al for 33 women with histologically confirmed supraclavicular lymph node metastases at primary diagnosis.²⁶ The 3- and 5-year survival rates of these patients were equivalent at 16.5%, indicating that 5 of these women with FIGO stage IVB disease were cured.

The last consideration supporting the dominant role of cisplatin plus paclitaxel in recurrent and metastatic cervical cancer is a practical and economic one. Although there has been great enthusiasm about targeted therapy for this disease, including anti-epidermal growth factor receptor and anti-vascular endothelial growth factor antibodies, neither of these novel agents can be provided outside of a clinical trial for this indication. The current randomized phase III trial of the GOG (protocol 240)²⁷ in this population is studying nonplatinum doublets and antivascular therapy, but this trial has not been designed to move forward as a registration trial for bevacizumab even if this agent is tolerable and demonstrates some activity.

Conclusion

Recurrent and metastatic cervical cancer remains a challenging problem, with the majority of patients having disease at distant sites as a result of superior pelvic control rates since the formal adoption of chemoradiation for locally advanced disease 10 years ago. Systemic chemotherapy, therefore, remains the treatment of choice, and from the available data, which include several prospective, randomized phase III clinical trials in this population, cisplatin plus paclitaxel provides a superior RR and is tolerable. Importantly, no other platinum-based doublets that have undergone rigorous investigation have demonstrated efficacy greater than that of the cisplatin/paclitaxel doublet. Furthermore, this doublet is associated with improved QOL over time, presumably because of its palliative effects on symptomatic metastatic deposits (eg, bone lesions) and control of in-field recurrent disease. Cisplatin plus paclitaxel is readily available to treat patients with recurrent cancer and has been associated with some cures in select patients who have presented with metastatic disease.

Disclosure

The author has no relevant relationships to disclose.

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