

Gynecologic Oncology Group Trials of Chemotherapy for Metastatic and Recurrent Cervical Cancer

Krishnansu S. Tewari, MD and Bradley J. Monk, MD

Address

Division of Gynecologic Oncology, The Chao Family Comprehensive Cancer Center, University of California, Irvine Medical Center, 101 The City Drive, Building 56, Room 262, Orange, CA 92868-3298, USA.
E-mail: bjmonk@uci.edu

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Because only 16% of patients with metastatic cervical cancer are alive 5 years after diagnosis, the Gynecologic Oncology Group (GOG) has carefully designed and conducted many phase II studies to identify promising drugs. Cisplatin has emerged as the most active single agent with overall response rates of 19%. Recent phase III trials have documented response rates of 27% and 39% when cisplatin has been combined with either paclitaxel or topotecan, respectively. The comparison of cisplatin to cisplatin plus topotecan in GOG-179 has yielded the first study to show a statistically significant impact on the overall response rate, median progression-free survival, and median survival, with all outcome measures favoring the two-drug regimen. Despite these encouraging results, however, most of the responses are partial and of short duration. The need for novel combinations and the implementation of active biologic agents is implicit. The accumulated data in this disease setting, as evidenced by the experience of the GOG, are presented in this review.

Introduction

In 2004, the American Cancer Society (ACS) estimated 10,520 new cases of cervical cancer, with approximately 3900 deaths from cervical cancer [1]. For 2005, the ACS predicts 10,370 new diagnoses, with 3710 deaths among American women [2]. It is expected that the vast majority of women who die from cervical cancer will have received some form of cytotoxic therapy. Women with persistent or recurrent tumors (*ie*, chemoradiotherapy failures) constitute the largest referral population for systemic therapy, with a smaller group presenting with metastatic (*ie*, International Federation of Gynecology and Obstetrics [FIGO] IVB) disease [3].

The response rate is significantly lower in patients with disease confined to an irradiated pelvis due to disruption of the pelvic blood supply, which precludes the achievement of high local levels of antineoplastic drugs. The emergence of resistant cell clones within and beyond the radiation field is also of concern in light of the relatively recent adoption of concurrent chemoradiotherapy for locally advanced disease and for high risk postsurgical disease [4••-8••,9] Time to recurrence, performance status, and possibly, age, are also of prognostic significance.

Response rates to systemic therapy for metastatic cervical cancer are typically short-lived and therefore do not affect progression-free and overall survival to a great extent. Thus, chemotherapy has a palliative role in these patients. This article reviews the methodology and application of cytotoxic therapy in this disease, focusing primarily on a comprehensive evaluation of the phase II and III experiences of the Gynecologic Oncology Group (GOG).

Summary of Phase II Studies Introduction of cisplatin

In the 1970s, the GOG conducted a series of phase II trials (the protocol 26 series) to identify active agents in multiple sites, from which site-specific studies could then be designed employing highly active drugs that might be logically combined. Cisplatin was originally selected for phase II trials in cervical cancer because of its demonstrated activity in squamous cell cancers. Additionally, because it produced minimal myelosuppression and no mucositis, cisplatin was an attractive agent for patients who were likely to have been irradiated upfront.

Results from GOG-26 were reported by Thigpen *et al.* [10•] in 1981. Cisplatin was administered intravenously at 50 mg/m² on a 21-day schedule and yielded an impressive overall response rate of 38%. Responses were observed in cervical cancer patients with extra-pelvic disease and in patients with disease confined to an irradiated pelvis. Importantly, an objective response rate of 50% (three complete and eight partial responses) was observed among the 22 women who had received no prior chemotherapy, as compared with an objective response rate of 17% (two partial responses) among 12 patients who had been pre-

treated. The full implications of this would be realized nearly two decades later when the data from GOG-179 was analyzed (see Summary of Phase III Studies). Although the regimen was tolerable, a significant number of patients experienced leukopenia, thrombocytopenia, nausea and vomiting, and azotemia.

Enthusiasm for cisplatin prompted the GOG to evaluate the efficacy and toxicity profiles of the platinum analogs, iproplatin and carboplatin, in previously untreated patients with measurable advanced gynecologic malignancies, including cervical cancer. Investigators within the trialist group designed two phase II trials in parallel, without randomization or interdrug comparisons, and observed strikingly different toxicity profiles from that of the parent drug [11,12]. To gain experience with cisplatin-based combined regimens, the Southwest Oncology Group (SWOG) initiated a phase II randomized trial of cisplatin versus mitomycin-C plus cisplatin versus mitomycin-C (MC), vincristine, bleomycin plus cisplatin (MVBC) in 114 evaluable patients with advanced squamous cell carcinoma of the cervix and no prior chemotherapy exposure [13]. The overall objective response rates for cisplatin, MC, and MVBC were 33%, 25%, and 22%, respectively, and the median survival durations were 17.0 months, 7.0 months, and 6.9 months, respectively. Severe or life-threatening leukopenia and thrombocytopenia were observed in 18% to 24% of patients treated with MVBC and MC but in none of those receiving cisplatin alone. The SWOG trial would become the template upon which the GOG would design their own phase II series and phase III studies in this disease.

The 76 series and other phase II studies

When the 76 series was initiated, the concept proposed by the GOG was to study selected agents in a phase II setting at designated centers in chemotherapy-naïve women with advanced, persistent, and/or recurrent squamous cell carcinoma of the cervix. To this day, these limited-access trials follow a two-stage accrual methodology, and those that have been completed or are currently accruing patients appear in Table 1 [14–31]. Because these studies compete with phase III trials, they are open only at a small number of sites. Single agents tested in this series with decent performance include ifosfamide (GOG-76I, overall response rate 15.7%) [19], paclitaxel (GOG-76S, overall response rate 17.3%) [24], topotecan (GOG-76U, overall response rate 18.6%) [26], and dibromodulcitol (GOG-76D, overall response rate 29%) [15]. Promising combinations include cisplatin and vinorelbine (GOG-76Z, overall response rate 30%) [30], and cisplatin and paclitaxel (GOG-76X, overall response rate 46.3%) [28].

Launched in the 1990s, the 127 series was designed with a broader scope and enrolled advanced patients with squamous cell carcinoma of the cervix who had not received more than one prior regimen for recurrent disease (Table 2) [32–41]. Beginning with GOG-127Q, one prior regimen became part of the eligibility criteria. The highest overall

response rates have been reported for topotecan (GOG-127F, overall response rate 12.5%) [35] and for vinorelbine (GOG-127L, overall response rate 13.7%) [38].

The 128 series was established by the GOG to study the response of advanced, persistent, and recurrent endocervical adenocarcinomas to systemic therapy in a phase II setting (Table 3) [42,43]. Paclitaxel has yielded an impressive overall response rate of 31% in a study group that included 42 subjects (GOG-128B) [42].

Fiorica *et al.* [44] evaluated topotecan and cisplatin in the phase II setting in women with both squamous and non-squamous cell carcinomas of the cervix. Unlike the 5-day infusion schedules employed by the GOG in protocols 76U and 127F, to balance the added toxicity of cisplatin, the dose of topotecan was decreased from 1.5 mg/m² to 0.75 mg/m² and administered over 3 days. The overall response rate was 28%, with three complete and six partial responses. The median duration of response was 5 months (range, 2 to 15+ months), with a median survival of 10 months and three patients in lasting remission. This schedule for topotecan would eventually be incorporated into phase III studies by the GOG using the cisplatin plus topotecan combined regimen.

Other non-GOG phase II trials in cervical cancer that are of considerable interest include that of Buxton *et al.* [45], in which a combination of bleomycin, ifosfamide, and cisplatin yielded 34 objective responses (69%), including 10 complete responses, in a study group of 49 subjects. The regimen containing methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been the subject of two reports examining its role in advanced/recurrent cervical carcinoma: an overall response rate of 66% (including 21% complete responses) was observed in the study by Long *et al.* [46], whereas objective responses were observed in 52% (including 11% complete responses) of subjects reported by Papadimitriou *et al.* [47]. Clearly, a select patient population without obstructive uropathy and without renal or cardiac disease is preferred for such a regimen.

The papers by Fiorica *et al.* [44], Buxton *et al.* [45], and Long *et al.* [46], together with the GOG-76 trials [14–31], laid the foundation for the phase III GOG experience in metastatic cervical carcinoma.

Summary of Phase III Studies

Cisplatin dose intensity, infusion times, and analogs

A limited number of phase III chemotherapy trials have been conducted in advanced cervical cancer. In 1978, Wallace *et al.* [48] compared doxorubicin with or without vincristine and doxorubicin plus cyclophosphamide in 174 subjects, with no differences observed in response rate, progression-free interval or survival. Seven randomized phase III investigations by the GOG are summarized in Table 4 [49•–54•,55••,56]. The strategic sequence in designing randomized trials for advanced cervical cancer is fascinating and is presented in Figure 1.

Table 1. The limited-access GOG-76 phase II series for advanced, persistent, and/or recurrent squamous cell carcinoma of the cervix (no prior therapy)

GOG protocol	Study	Year	Agent(s)	Dosage	Patients, n	Response rates			
						PR, %	CR% Overall, %	95% Exact CI	
76C	Roberts et al. [14]	1987	Dichloromethotrexate	350–550 mg/m ² IV every 7 days	36	8.8	0	8.8	Not given
76D	Stehman et al. [15]	1989	Dibromodulcitol	180 mg/m ² orally x 10 days	55	27	2	29	18.8%–42.1%
76F	Malfetano et al. [16]	1991	Gallium nitrate	750 mg/m ² IV every 3 weeks	24	8.3	0	8.3	24% upper bound
76G	Bonomi et al. [17]	1989	Cisplatin + 5-fluorouracil	50 mg/m ² IV day 1; 1000 mg/m ² 24-hour infusion days 1–5	55	9.1	12.7	21.8	12.9%–34.4%
76H	Muss et al. [18]	1992	Echinomycin	1500 µg/m ² IV every 4 weeks	19	5	0	5	0%–26%
76I	Sutton et al. [19]	1993	Ifosfamide/mesna	1.2–1.5 g/m ² IV x 5 days	51	11.5	3.9	15.7	7.02%–28.59%
76J	Thigpen et al. [20]	1995	Mitomycin-C	20 mg/m ² IV every 6 weeks	52	6	6	12	21.5% upper bound
76K	Sutton et al. [21]	1994	Menogril	200 mg/m ² IV every 4 weeks	22	0	0	0	—
76P	Malfetano et al. [22]	1996	Didemnin B	6.3 mg/m ² IV every 4 weeks	22	0	4.5	4.5	Not given
76Q	Feun et al. [23]	1993	Tricyclic nucleoside-P	35 mg/m ² IV x 5 days every 6 weeks	21	5	5	10	Not given
76S	McGuire et al. [24]	1996	Paclitaxel	135–170 mg/m ² 24-hour infusion every 3 weeks	52	13.5	3.8	17.3	8.2%–30.3%
76T	Lincoln et al. [25]	1997	Piroxantrone	160 mg/m ² IV every 3 weeks	18	0	0	0	—
76U	Muderspach et al. [26]	2001	Topotecan	1.5 mg/m ² IV x 5 days every 4 weeks	43	11.6	7	18.6	8.4%–33.4%
76W	Look et al. [27]	1998	Irinotecan	125 mg/m ² IV every week x 4 weeks	45	11.1	2.2	13.3	5.1%–26.8%
76X	Rose et al. [28]	1999	Paclitaxel + cisplatin	135 mg/m ² 24-hour infusion; 75 mg/m ² IV every 21 days	41	34.1	12.2	46.3	30.7%–62.6%
767Y	Plaxe et al. [29]	2001	Pyrazoloacridine	750 mg/m ² IV every 21 days	21	4.2	0	4.2	Not given
76Z	Morris et al. [30]	2004	Cisplatin + vinorelbine	75 mg/m ² IV every 4 weeks; 30 mg/m ² IV every week	67	22	8	30	19.3%–42.3%
76BB	Muggia et al. (unpublished data)*	2004	Cisplatin + irinotecan	25 mg/m ² IV; 65 mg/m ² IV every week x 3 weeks	27	9.7	6.5	16.2	Not given
76CC	Garcia et al. (unpublished data)*	—	Capecitabine	1800 mg/m ² orally x 14 days	—	—	—	—	—
76DD	Farley et al. (unpublished data)*	—	Cetuximab + cisplatin	250 mg/m ² IV days 1, 8, 15; 30 mg/m ² IV days 1, 8	—	—	—	—	—

*Data not mature or study currently accruing.

CR—complete response; GOG—Gynecologic Oncology Group; IV—intravenously; PR—partial response.

Table 2. The GOG-127 phase II series for advanced, persistent, and/or recurrent squamous cell carcinoma of the cervix (one prior treatment)

GOG protocol	Study	Year	Agent(s)	Dosage	Patients, n	Response rates			95% Exact CI
						PR, %	CR, %	Overall, %	
I27B	Look et al. [32]	1998	Isotretinoin + IFN alfa	1 mg/kg orally every day; 6,000,000 U/d SC	26	3.8	0	3.8	0.1%–19.6%
I27C	Mannel et al. [33]	2000	Cisplatin + pentoxifylline	75 mg/m ² IV every 21 days; 1600 mg orally every 8 hours x 9 doses	40	7.5	2.5	10	Not given
I27D	Rose et al. [34]	1996	Altretamine	260 mg/m ² /d orally x 21 days	26	0	0	0	—
I27F	Bookman et al. [35]	2000	Topotecan	1.5 mg/m ² IV x 5 days every 21 days	40	10	2.5	12.5	Not given
I27H	Rose et al. [36]	1998	Etoposide	40–50 mg/m ² /d orally x 21 days	17	5.9	5.9	11.8	Not given
I27K	Schilder et al. [37]	2000	Gemcitabine	800 mg/m ² IV/wk x 3 weeks	24	8	0	8	Not given
I27L	Muggia et al. [38]	2004	Vinorelbine	30 mg/m ² IV days 1, 8 every 21 days	44	11.4	2.3	13.7	5.2%–27.4%
I27M	Plaxe et al. [39]	2002	Pyrazoloacridine	560–760 mg/m ² IV every 21 days	24	0	4.2	4.2	Not given
I27N	Armstrong et al. [40]	2003	Bryostatatin-1	25 µg/m ² IV weekly x 3 wks	32	3.1	0	3.1	0.4%–10.7%
I27P	Fracasso et al. [41]	2003	Bryostatatin-1	120 µg/m ² 72-hour infusion every 2 weeks	33	3.2	0	3.2	—
I27Q	Brewer et al. (unpublished data)*	—	Oxaliplatin + gemcitabine	130 mg/m ² IV every 21 days; 30 mg/m ² IV days 1, 8; 800 mg/m ² IV days 1, 8, every 28 days	24	4.2	4.2	8.4	Not given
I27R	Rose et al. (unpublished data)*	—	Liposomal doxorubicin	40 mg/m ² IV every 28 days	—	—	—	—	—
I27S	Garcia et al. (unpublished data)*	—	Docetaxel	100 mg/m ² IV every 21 days	—	—	—	—	—
I27T	Miller et al. (unpublished data)*	—	Pemetrexed	900 mg/m ² IV every 21 days	—	—	—	—	—

*Data not mature or study currently accruing.

CR—complete response; GOG—Gynecologic Oncology Group; IFN—interferon; PR—partial response; SC—subcutaneously.

Table 3. The GOG-128 phase II series of advanced, persistent, and/or recurrent non-squamous cell cancers of the cervix

GOG protocol	Study	Year	Agent	Dosage	Patients, n	Response rates			
						PR, %	CR, %	Overall, %	95% Exact CI
I28B	Curtin et al. [42]	2001	Paclitaxel	135–170 mg/m ² IV over 24 hours every 21 days	42	21.4	9.5	31	18.1%–48.1%
I28D	Bigler et al. [43]	2004	Tamoxifen	10 mg orally twice a day	27	7.4	3.7	11.1	Not given
I28E	Muggia et al. (unpublished data)*	—	Vinorelbine	30 mg/m ² IV days 1, 8 every 21 days	—	—	—	—	—
I28F	Schilder et al. (unpublished data)	—	Gemcitabine	800 mg/m ² IV weekly x 3 weeks	—	—	—	—	—
I28G	Look et al. (unpublished data)*	—	Capecitabine	1800 mg/m ² orally x 14 days	—	—	—	—	—

*Data not mature or study currently accruing

CR—complete response; GOG—Gynecologic Oncology Group; PR—partial response.

Table 4. Phase III experience within the GOG in metastatic cervical cancer

GOG protocol	Study	Year	Arms	Patients, n	Objective response			Median duration of response, mo	Median PFS, mo
					PR, %	CR, %	Overall, %		
43	Bonomi et al. [49•]	1985	Cisplatin, 50 mg/m ² IV every 21 days	150	10.7	10	20.7	4.9	7.1
			Cisplatin, 100 mg/m ² IV every 21 days		18.7	12.7	31.4	4.1	7
			Cisplatin, 20 mg/m ² IV x 5 days every 21 days		16.4	8.6	25	4.8	6.1
64	Thigpen et al. [50•]	1989	Cisplatin, 50 mg/m ² 24-hour continuous infusion	156	12	6	18	5.5	Median survival, mo 6.4
			Cisplatin, 1 mg/min rapid infusion	164	11	6	17	4.5	6.2
77	McGuire et al. [51•]	1989	Carboplatin, 340–400 mg/m ² IV every 28 days	175	9.7	5.7	15.4	2.7	Median survival, mo 6.2
			Iproplatin, 230–270 mg/m ² IV every 28 days	177	6.8	4	10.8	3	5.5
110	Omura et al. [52•]	1997	Cisplatin, 50 mg/m ² IV every 21 days	140	11.4	6.4	17.8	3.2	Median survival, mo 8
			Cisplatin, 50 mg/m ² IV + mitolactol, 180 mg/m ² orally days 2, 6 every 21 days	147	11.6	9.5	21.1	3.3	7.3
			Cisplatin, 50 mg/m ² IV + ifosfamide, 5 g/m ² 24 hour infusion + mesna, 6 g/m ² every 21 days	151	18.5	12.6	31.1	4.6	8.3
149	Bloss et al. [53•]	2002	Cisplatin, 50 mg/m ² IV + ifosfamide, 5 g/m ² 24 hour infusion + mesna, 6 g/m ² every 21 days	146	NS	NS	32.2	4.6	Median survival, mo 8.5
			Bleomycin, 30 U 24-hour infusion, followed by cisplatin, 50 mg/m ² IV + ifosfamide, 5 g/m ² 24 hour infusion + mesna, 6 g/m ² every 21 days	141	NS	NS	32.1	5.1	8.4
			Cisplatin, 50 mg/m ² IV every 21 days	134	13	6	19	2.8	8.8
169*	Moore et al. [54•]	2004	Paclitaxel, 135 mg/m ² 24-hour infusion + cisplatin, 50 mg/m ² IV every 21 days	130	21	15	36	4.8	9.7
			Cisplatin, 50 mg m ² IV every 21 days	145	10	13	13	2.9	6.5
179*	Long et al. [55••]	2005	Topotecan, 0.75 mg/m ² IV, days 1–3 + cisplatin, 50 mg/m ² IV every 21 days	148	16	10	26	4.6	9.4
			MVAC every 4 weeks, analysis forthcoming	63	9	13	22	4.4	9.4

*Protocols 169 and 179 also measured median PFS and median survival, both in months.
 CR—complete response; GOG—Gynecologic Oncology Group; MVAC—methotrexate, vinblastine, doxorubicin, cisplatin (note that this arm was closed due to unacceptable mortality); NS—not specified; PFI—progression-free interval; PFS—progression-free survival; PR—partial response.

The phase III experience of the GOG in metastatic cervical carcinoma can be separated into distinct periods. The first era, containing the accumulated lore of protocols 43, 64, and 77, generated data on cisplatin dose intensity [49•], cisplatin infusion times [50•], and platinum analogs [51•], with the overriding conclusion that cisplatin at 50 mg/m² would remain the standard against which other agents would need to be compared. Closer examination of these early phase III studies is warranted.

Due to an impressive response rate of 38%, the original report by Thigpen *et al.* [10•] generated a great deal of interest in cisplatin for advanced squamous cell carcinoma of the cervix. However, with the larger phase III trial, protocol 43, the response rate was more accurately revised to 20% to 30%, among which 10% of the 500 patients treated experienced a complete response. GOG-43 was designed to compare the efficacy and toxicity of cisplatin given at a dose of 50 mg/m² with the results obtained at a dose of 100 mg/m² given on two schedules: a single intravenous infusion at the rate of 1 mg/min versus 20 mg/m² at the rate of 1 mg/min daily for five consecutive days [49•]. Although the higher doses of cisplatin were associated with higher overall response rates, because there was no appreciable difference in complete response rates, response duration, progression-free interval, or survival, protocol 43 provided no convincing argument to use cisplatin at doses higher than 50 mg/m². The implication is that the dose-response curve for cisplatin in cervical cancer is not steep, thus lending credence to the hypothesis proposed for solid tumors with low to intermediate chemosensitivity.

As interest developed in the use of a continuous infusion schedule of cisplatin to ameliorate its emetogenic potential, the GOG designed protocol 64 to determine if prolonged infusion would also have a therapeutic advantage. Although prolonged infusion appeared to enhance the killing effect of cisplatin *in vitro*, in GOG-64 the response rates were nearly identical (17% to 18%) for the prolonged infusion and pulse administration arms [50•]. Gastrointestinal toxicity was diminished in the prolonged infusion arm, with 34% of subjects experiencing no nausea and vomiting as compared with 18% ($P=0.002$). Therapeutic efficacy was maintained, but labor intensity with prolonged infusion time was increased. This demonstrated improvement in therapeutic index supports prolonged infusion only in those patients with refractory cisplatin-related nausea and vomiting.

Emetogenicity was not the sole plague upon cisplatin. Frequent underlying renal dysfunction and peripheral neuropathy as a consequence of tumor-associated ureteral obstruction and pelvic nerve entrapment, respectively, prompted a search for less toxic platinum analogs. Furthermore, because of the need for adequate hydration, outpatient cisplatin administration was both labor- and time-intensive. Protocol 77 was designed to test the efficacy and tolerability of the platinum analogs, iproplatin and carboplatin, both of which were devoid of any significant neph-

rotoxicity or neurotoxicity and were easily administered in the outpatient setting without prior hydration. Although GOG-77 was not designed to compare either analog with the parent, cisplatin, as can be seen in Table 4, the overall (10% to 15%) and complete (4% to 5%) response rates for the analogs were not superior to those previously reported for cisplatin. In point of fact, the response rates were possibly inferior to that of cisplatin [51•], and were certainly lower than what had been prematurely reported by the GOG during phase II testing of the analogs [11,12].

The finding that hematologic toxicity was dose-limiting with both analogs, together with the observed lack of significant nephrotoxicity and neurotoxicity, verified earlier, smaller reports that the analogs had a different spectrum of end-organ toxicities. Certainly, patients with marginal renal function or severe antecedent peripheral neuropathy could receive one of the analogs with some expectation of response, but the data did not support replacing cisplatin with either analog.

Perhaps the most interesting information to be gleaned from GOG-77 involved a subset of patients who had failed treatment with the assigned analog and went on to receive cisplatin as second-line therapy. Four responses were documented (two complete and two partial responses) among 22 subjects for whom this information was available [51•]. This apparent secondary response rate of 18% to cisplatin as a salvage agent was not only equivalent to (and actually rather better) than the primary response rate with either iproplatin or carboplatin, but it verified that there was not total cross resistance between cisplatin and its analogs.

Thus, the first three phase III trials by the GOG, specifically a comparison of cisplatin dose intensity ($n=444$) [49•], a study of cisplatin infusion time ($n=320$) [50•], and a comparison of carboplatin versus iproplatin ($n=352$) [51•], did not manifest any differences in response rate, progression-free interval, or survival, and certainly did not provide any convincing evidence to abandon cisplatin as the agent of choice for advanced squamous cell carcinoma of the cervix.

Cisplatin versus cisplatin-based combinations: response rates and survival

The second period of the GOG phase III experience in metastatic cervical cancer is where interesting things begin to happen. Encompassing protocols 110, 149, 169, and 179, the GOG compared single-agent cisplatin with an array of anti-neoplastic agents, including ifosfamide (with and without bleomycin) [52•,53•], mitolactol [52•], paclitaxel [54•], topotecan [55••], and the MVAC regimen [55••]. This era was noteworthy for dispelling the phase II myth that bleomycin had anything significant or worthwhile to contribute in this disease, for emphasizing the hazards of using MVAC in this patient population, and for substantiating the activity of platinum-based combined regimens containing paclitaxel or topotecan. Data from these trials underscored an improvement in progression-free survival (GOG-110, -169, and -179)

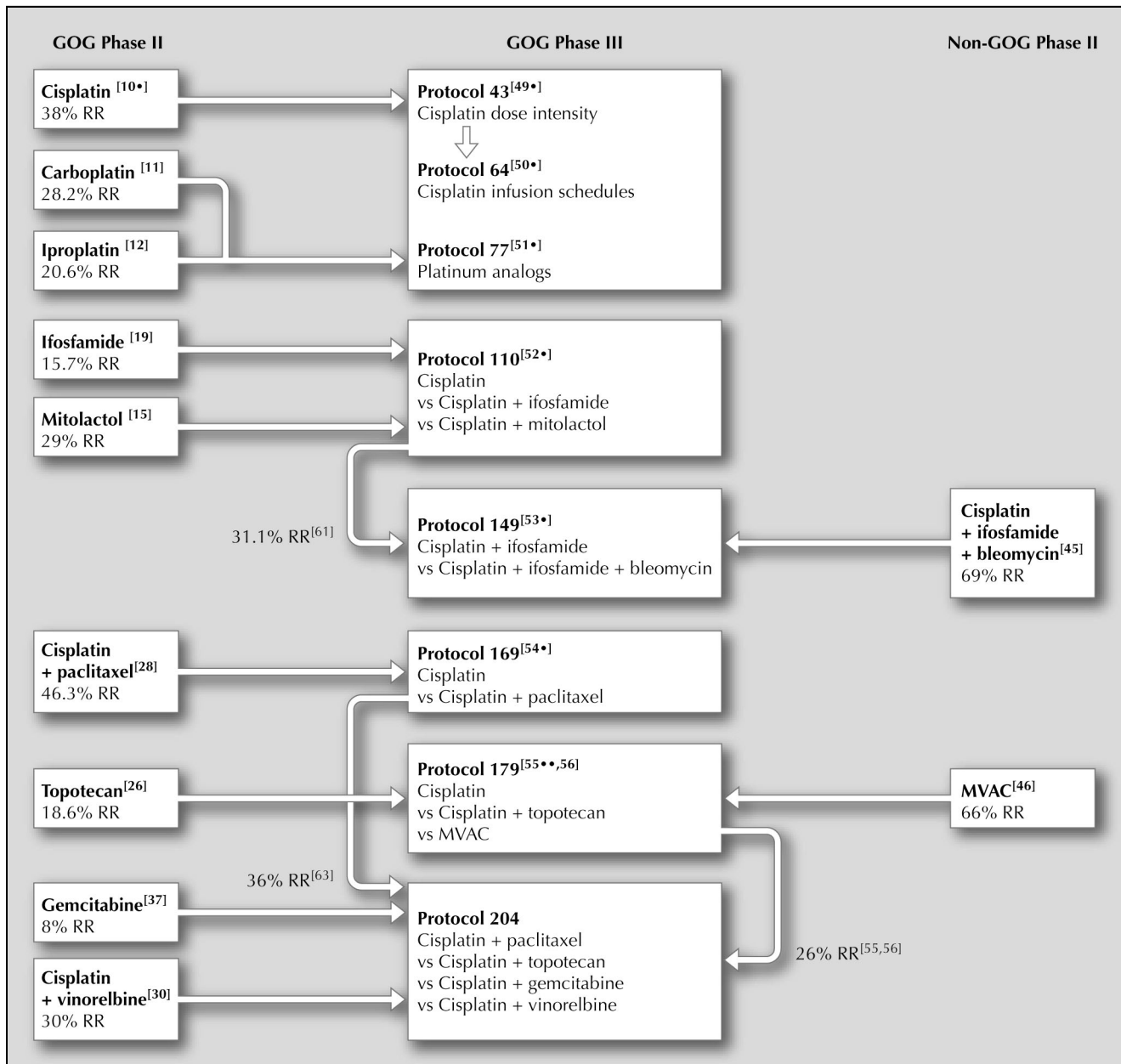


Figure 1. Evolution of the Gynecologic Oncology Group (GOG) phase III experience in metastatic cervical cancer. (RR—response rate).

and for the first time yielded a statistically significant (albeit short) enhancement in overall survivorship (GOG-179). Once again, a closer examination of these studies is required to fully appreciate the methodology that went into their design and the interpretations of critical data sets that were subsequently generated.

Mitolactol is a hexitol derivate that is converted to dianhydrogalactol (DAG) in human serum and functions as an alkylating agent. GOG-76D noted a 29% response rate when this drug was used as a single agent [15]. Because the principal toxicity for mitolactol was hematologic, it seemed reasonable to combine it with cisplatin. Ifosfamide was known to have less marrow toxicity but more bladder toxicity than cyclophosphamide, which required concomi-

tant use of the uroprotector, mesna. The series of 49 patients from Buxton *et al.* [45] treated with a combination of ifosfamide, cisplatin, and bleomycin yielded an impressive 69% response rate. The importance of bleomycin, however, was unclear, and because of its troublesome toxicity, which restricted its use to patients with good pulmonary function, it was excluded from protocol 110.

In 1997 Omura *et al.* [52•] reported the results from GOG-110, a randomized trial comparing cisplatin versus cisplatin and mitolactol (dibromodulcitol), versus cisplatin and ifosfamide in advanced squamous carcinoma of the cervix. No significant difference in overall survival was observed among the three arms, although the combination of cisplatin and ifosfamide induced a higher response rate

(31.1% vs 17.8%, $P=0.004$) (Table 4) and longer progression-free survival ($P=0.003$) compared with cisplatin alone. Increased nephrotoxicity, neurotoxicity, and myelotoxicity were observed in the arm with ifosfamide. These data are in agreement with a growing body of evidence concerning advanced solid tumors in that a higher response rate (not a higher complete response rate) can be achieved with combined therapy at the cost of more toxicity and no survival benefit. It remains unclear to what extent the improvement in progression-free survival benefited the patients in the absence of increased overall survival because the impact of progression-free survival on the patients' sense of well-being was not assessed in GOG-110. Nevertheless, protocol 110 will remain the first evidence of positive impact of a chemotherapy regimen on progression-free survival in advanced cervical cancer. The question for the GOG was whether this improvement in progression-free survival could be translated into a survival benefit by the addition of bleomycin.

Building on the success of the cisplatin plus ifosfamide base demonstrated in protocol 110, the GOG launched protocol 149 to assess the value of adding bleomycin to the therapeutic equation. Unfortunately, even when adjusted for age, performance status, and prior therapy, GOG-149 failed to demonstrate any benefit derived from the inclusion of bleomycin, with response rates, progression-free survival, and survival being virtually identical between the two groups [53•]. As anticipated, there was a higher degree of pulmonary toxicity in the arm containing bleomycin (18% vs 5%); however, only 5% of subjects required discontinuation of bleomycin due to severe or life-threatening lung damage.

Although GOG-149 was unable to substantiate the projected improved outcome measures that had been predicated on promising phase II data involving the cisplatin-based triplet containing bleomycin, the search for active regimens in the management of advanced cervical cancer continued with a randomized trial by the GOG comparing cisplatin with or without paclitaxel (protocol 169). In protocol 76S, the GOG had reported a 17% overall response rate for single-agent paclitaxel in advanced squamous cell carcinoma of the cervix [24], and when combined with cisplatin as part of a feasibility study (GOG-76X) [28], an impressive overall objective response rate of 46.3% had been documented (Table 1).

Although the combined regimen employed in GOG-169 exhibited superior response rates (36% vs 19%), there were no singular differences demonstrated in an analysis of overall survival [54•]. Similar to what had been seen in GOG-110, a statistically significant difference was observed in median progression-free survival favoring the combination of paclitaxel plus cisplatin (4.8 months vs 2.8 months). The quality-of-life component of protocol 169 is discussed later.

The GOG considered the report by Long *et al.* [46], in which the MVAC regimen generated a 66% overall

response rate (including 21% complete response rate) in patients with advanced cervical carcinoma. Similarly, the phase II study by Fiorica *et al.* [44] using cisplatin plus a 3-day infusion of topotecan was noteworthy for its associated 28% overall response rate in advanced cervical cancer. These regimens were prospectively evaluated alongside cisplatin alone in GOG-179 [55••,56].

The MVAC arm was closed on July 23, 2001 by the Data and Safety Monitoring Board of the GOG after four treatment-related deaths due to sepsis (Long *et al.*, manuscript in preparation). Among the 186 eligible patients who had been enrolled and randomized before this date, there were 173 reported deaths as of June 2004 in GOG-179. The overall response rate for the three regimens (Table 4) ranged from 18% to 22%, although the complete response rate was higher for MVAC (13%) as compared with cisplatin (5%) and cisplatin plus topotecan (8%). Despite the early closure of the MVAC arm, the previously reported high response rate with this regimen in advanced cervical cancer was not verified. Additionally, there was no demonstrable survival advantage for those patients receiving MVAC as compared with those treated with cisplatin plus topotecan. Moreover, treatment with the MVAC regimen resulted in excessive hematologic toxicity and unacceptable mortality.

The comparison of cisplatin to cisplatin plus topotecan in protocol 179 has yielded the first study that has shown a statistically significant impact on the overall response rate, median progression-free survival, and median survival (Table 4), with all outcome measures favoring the two-drug regimen [55••]. Because the survival curve by treatment (not shown) demonstrates 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 the combined regimen on long-term survival in the population studied.

Determinants of response in the salvage setting

Before moving on to the replacement for GOG-179, we must examine the information gathered from the completed studies concerning the ability to predict failure in the setting of metastatic cervix cancer. The use of concurrent platinum-based radiosensitizing chemotherapy, the disease-free interval (time to recurrence for relapsing disease in patients who have had objective complete responses to primary therapy), the site of recurrence, and finally, baseline quality of life at the time of relapse (or diagnosis of FIGO IVB disease) are likely to have some role in the equation for which durable response to salvage therapy can be solved.

As early as the original report by Thigpen *et al.* [10•] (GOG-26C), a disparity in response rates to cisplatin was observed between subjects who had been treated previously with chemotherapy and those who had not (see Summary of Phase II Studies). This phenomenon was also

observed in GOG-179, in which the response rates for cisplatin and for cisplatin plus topotecan among patients who did not receive prior chemotherapy were 20% and 39%, respectively, as compared with response rates of 8% and 15%, respectively, among patients who had received prior cisplatin [55••]. In GOG-179, 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 GOG-169, GOG-179 was completed after concurrent chemoradiotherapy became standard in the upfront management of advanced disease. Only 27% of patients treated on GOG-169 received prior radiosensitizing chemotherapy [54•] as compared with 57% of patients on GOG-179 [55••]. In other words, chemotherapy for patients on protocol 179 was for the most part “second-line” chemotherapy rather than the “first-line” chemotherapy patients on GOG-169 typically received. The implication is that if tumors have developed acquired resistance to cisplatin at the time of relapse, then the benefit observed in GOG-179 lies primarily with topotecan. Further testament to this hypothesis is the observation that, in GOG-179, the response rate and progression-free survival for the single-agent cisplatin arm were lower than those observed in previous trials (GOG-110, GOG-149, and GOG-169) (Table 4) [52•–54•,55••].

In GOG-179, for patients who did not versus those who did receive prior platinum therapy, the hazard ratios for progression-free survival were 0.50 and 0.87, respectively, and the hazard ratios for overall survival were 0.63 and 0.78, respectively, suggesting a less beneficial effect in the latter (*ie*, pretreated) group (homogeneity of risk test: $P=0.03$ for progression-free survival; $P=0.42$ for overall survival [55••]).

We also learned in GOG-179 that the time to recurrence is a powerful prognostic factor in this disease. When analyzing the time from diagnosis to study entry for patients with recurrent disease and accounting for performance status, age, and disease status at the time of study entry, it was noted that every 6-month increment was associated with a 19% reduction of risk of progression and a 21% reduction of risk of death, plateauing at 30 months [55••].

As discussed earlier, the site of recurrence must have prognostic significance for all previously irradiated patients. Among 110 patients with measurable disease in the pelvis in GOG-149, there were only 22 responders (40.2%), as compared with 69 responders among 177 patients with extrapelvic disease (78.2%, $P<0.001$) [53•].

Finally, patient-reported quality-of-life measures may become an important prognostic tool in advanced cervix cancer. When antineoplastic agents are combined, there is the potential for increased toxicity, and quality-of-life measures become critical endpoints. Psychosocial data, though subjective, do not lack scientific merit, and when evaluated correctly distills a worldview that is germane to discussions regarding “futile” therapy. It should be noted that GOG-169 was the first randomized controlled trial of palliative

chemotherapy in cervical carcinoma to obtain quality-of-life measures in addition to traditional clinical outcome measures. In protocol 169 there were no significant differences in quality-of-life scores between the two arms. Having stated this, the authors have cited a disproportionate number of dropouts from the quality-of-life portion of the study among patients randomly allocated to receive cisplatin alone (50 of 133 patients) compared with the combined regimen (33 of 128 patients, $P<0.05$) [54•]. The higher clinical response rate of the combined regimen was correlated with completion of the quality-of-life component, which in turn was correlated with stable rather than deteriorating quality of life.

The secondary endpoint of GOG-179 was to compare the impact of the treatment regimens on quality of life. When comparing cisplatin with cisplatin plus topotecan, the investigators noted that despite more hematologic toxicity in the combined regimen, a significant reduction in quality of life up to 9 months after randomization was not observed [56]. Not being strangers to lateral thinking, the investigators explored the hypothesis that baseline quality-of-life scores (qualified by the Functional Assessment of Cancer Therapy-Cervix [FACT-Cx]) may influence survival. By using a Cox proportional hazard model and adjusting for treatment effect, age, and baseline performance status, the baseline FACT-Cx was not found to be associated with progression-free survival but was significantly associated with overall survival ($P=0.002$) [56]. When the FACT-Cx score was separated into quaternary subgroups, it was found that the estimated hazard of death for patients in the highest quality-of-life quartile was 47% lower than for patients in the lowest quartile (95% CI, 0.38 to 0.78, $P=0.001$), 40% lower than for patients in the second lowest quartile (95% CI, 0.41 to 0.89, $P=0.001$), and 40% lower than in patients in the third lowest quartile (95% CI, 0.4 to 0.88, $P=0.001$) [56]. Thus, the degree of functional impairment at baseline had prognostic significance in this disease.

Baseline quality-of-life assessments were collected on 183 of 186 eligible patients before closure of the MVAC arm in GOG-179 [66]. Possibly because more patients on the MVAC arm (92%) had persistent or recurrent disease after treatment with radiosensitizing chemotherapy, baseline quality-of-life scores for these patients were lower than for those on the cisplatin arm (7.78 units less) and lower than those on the cisplatin plus topotecan arm (5.9 units less). Although the investigators could not identify a statistical relationship between quality-of-life scores and performance status or disease status at enrollment, it is interesting that the baseline quality-of-life scores did not deteriorate with subsequent MVAC therapy (manuscript in preparation).

Protocol 204

Protocol 204 was opened within the GOG on May 27, 2003. Constituting the first randomized trial of the GOG in advanced cervical cancer to include only cisplatin-based combined regimens, this study heralded the third period of

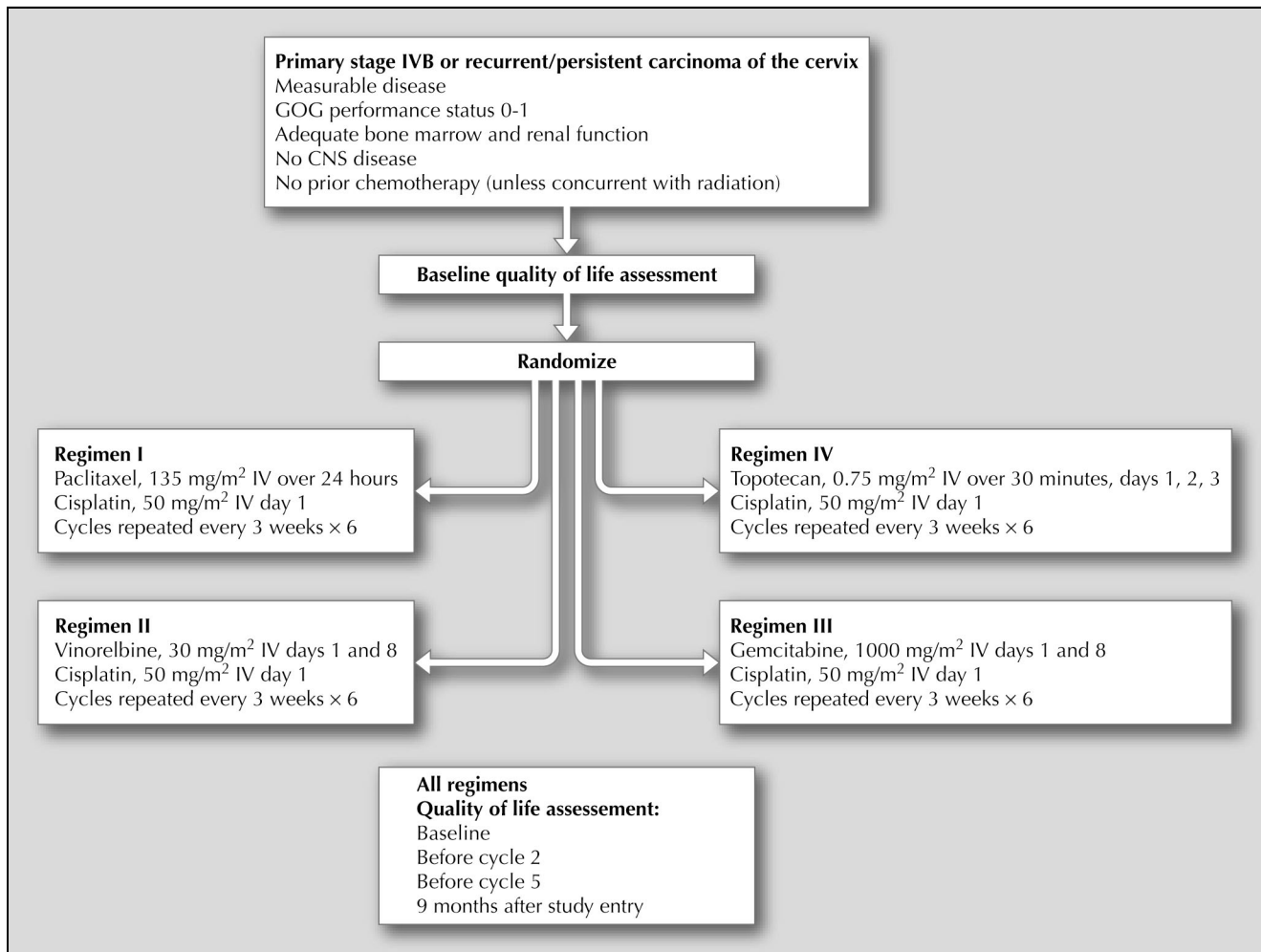


Figure 2. Treatment and assessment scheme for Gynecologic Oncology Group (GOG) protocol 204.

their phase III experience with this patient population. As seen in Figure 2, the trial includes four different platinum-based intravenous doublets containing topotecan, paclitaxel, vinorelbine, or gemcitabine. The study has been designed with a health-related quality-of-life analysis across the four treatment regimens through four cycles of therapy and at 9-month follow-up.

The importance of studying paclitaxel in combination with cisplatin against other novel platinum doublets is underscored by the observation that GOG-169 was conducted before concurrent chemoradiotherapy had become the standard of care for upfront therapy of locally advanced disease. It is necessary to study this regimen during present times to determine whether the favorable response rates are sustained and whether there is any survival impact over that of the presumably more toxic regimen containing cisplatin plus topotecan, which thus far has been the only regimen studied to generate a significant survival advantage over single-agent cisplatin (GOG-179).

Vinorelbine is a semi-synthetic vinca alkaloid that differs from other vinca alkaloids by a modification of the catharanthine moiety. The drug has been studied as a sin-

gle agent and in combination with cisplatin in patients with advanced cervical cancer outside of the GOG, with response rates of 17% and 46.7%, respectively [57,58]. Morris *et al.* [30] documented a 30% overall response rate in a phase II trial of cisplatin with vinorelbine (GOG-76Z), with only mild toxicity (Table 1). In this study, vinorelbine was administered at a dosage of 30 mg/m² weekly, but a more tolerable combination has been proposed for GOG-204 by elimination of the day-15 dose.

Gemcitabine is an analogue of the nucleoside deoxycytidine (dCTP), which inhibits DNA synthesis through masked chain termination, leaving a fraudulent base relatively resistant to excision repair by DNA repair enzymes. This attribute may overcome a key mechanism for the development of drug resistance. In addition, gemcitabine has self-potentiating mechanisms that lead to prolonged high intracellular concentrations of the active metabolites [59]. Although the GOG piloted a study of single-agent gemcitabine in advanced cervical cancer (GOG-127K), which yielded a poor overall response rate of 8% (Table 2) [37], in vitro [60] and in vivo studies in patients with advanced ovarian cancer [61] and advanced pancreatic can-

cer [62] have demonstrated synergy between gemcitabine and cisplatin.

Scientific exploration of the synergy between gemcitabine and platinum allows for extrapolation to the clinical arena of acquired resistance, generating a hypothesis that perhaps gemcitabine can reverse platinum resistance, making this an important combination to study in persistent and recurrent cervical cancer treated upfront with platinum-based radiosensitizing concurrent chemoradiation. The responses recorded by Villella *et al.* [63] in their advanced ovarian cancer study in women with platinum-resistant disease adds further support to the hypothesis that gemcitabine both potentiates cisplatin cytotoxicity and reverses platinum resistance, thus permitting re-introduction of platinum compounds in the salvage setting. The need to study this combination against other platinum-based doublets is implicit.

Looking Ahead Beyond 204

Although GOG-204 is well-designed and has the potential to generate interesting data sets, it cannot be expected to identify a regimen that will have a substantial impact on overall survival. Several factors influence the durable response of recurrent disease, and it is possible that protocol 204 may allow for a more precise description of how these factors interplay and if some are more important than others.

It is therefore imperative that well thought out, limited-access phase II trials (*ie*, the 76 series) run concurrently with GOG-204 so that, when the time comes, appropriate regimens for the replacement trial will be readily available. Some studies outside of the GOG have investigated cisplatin-based triplets. The TIP scheme (cisplatin, paclitaxel, and ifosfamide) generated objective response rates in the salvage setting ranging from 46% to 66.6%, with Zanetta *et al.* [64] reporting a 33% rate of complete clinical responses, of which 15% were documented pathologically. Ninety-one percent of patients experienced grade 3 and 4 myelotoxicity in the Italian study, whereas the Hellenic Cooperative Oncology Group reported neurotoxicity in 44% of patients treated with TIP [65]. Another cisplatin-based triplet (cisplatin, paclitaxel, and doxorubicin with granulocyte colony-stimulating factor [G-CSF] support) was reported by Fleming *et al.* [66] to have induced a 50% response rate with 10% grade 3 neutropenia and 10% grade 3 peripheral neuropathy.

Non-platinum doublets are a novel therapeutic strategy through which acquired resistance to platinum (following upfront concurrent cisplatin-based chemoradiotherapy) may be overcome by increasing the platinum-free interval (*ie*, theoretical platinum sensitivity). Tiersten *et al.* [67] conducted a phase II study of topotecan and paclitaxel in 15 women with advanced cervical cancer. Among 13 evaluable patients there were one complete and six partial responses for an overall response rate of 54%. Grade 3 and

4 toxicities included anemia (47%), leukopenia (27%), neurotoxicity (13%), thrombocytopenia (13%), and diarrhea (13%).

In three phase II studies involving patients with carcinoma of unknown primary site [68], advanced urothelial carcinoma [69], and advanced pancreatic cancer [70], the doublet gemcitabine and docetaxel produced objective response rates ranging from 27% to 40%. In all three studies, the regimen was well tolerated and toxicity was manageable. Furthermore, in a phase II evaluation of docetaxel and gemcitabine plus G-CSF in the treatment of recurrent or persistent leiomyosarcoma of the uterus [71] grade 3 and 4 hematologic toxicity occurred in less than 15% of patients (see also GOG-131G) [72]. The present authors (Tewari and Monk) have collaborated with Hensley to study this non-platinum doublet (gemcitabine, 675 mg/m² intravenously [IV], days 1 and 8; docetaxel, 75 mg/m² IV, day 8; pegfilgrastim, 6 mg subcutaneously, day 9) given every 21 days in this patient population through the limited-access GOG-76 series (*ie*, GOG-76FF). The potential specificity of topotecan in advanced cervical cancer needs to be exploited through an exploration of dose intensity, infusion schedules, and analogs, similar to the way the GOG studied cisplatin during the first period of their phase III experience with this disease. For example, in protocols 179 and 204, the dose of topotecan, 0.75 mg/m²/d over 72 hours, is lower than that used in the GOG phase II study, (protocol 76U), and the higher dose given over 5 days needs to be investigated in a phase III trial. Furthermore, weekly topotecan [73] may result in lower hematologic toxicity, and a weekly regimen containing both topotecan and cisplatin should be considered. Finally, Gimatecan (Novartis, East Hanover, NJ) is a newly developed topoisomerase I inhibitor analog of topotecan that can be administered orally, suggesting that pharmacokinetic and bioavailability data in this patient population would be of substantial merit to study.

Because the objective responses are finite, all patients will progress, most often after only a few months following systemic antineoplastic therapy. The inability of conventional cytotoxic agents to enhance long-term survival is likely multifactorial. Women suffering from metastatic cervical cancer typically have been previously irradiated (and therefore harbor radioresistant and chemoresistant tumor cell populations when the mechanisms of drug resistance overlap). Furthermore, such patients often have nephropathy as a consequence of a blocked kidney, limiting their ability to clear cytotoxic compounds from the bloodstream. Finally, recurrent tumors within the irradiated and therefore devascularized fields are difficult to bathe in chemotherapy. For these reasons, unlike their counterparts with ovarian cancer, who typically have longer sustained responses to systemic treatment, these patients are not suited to receive multiple lines of chemotherapy. Clearly, this disease is ideal for the critical study of immunotherapy, gene therapy, and other novel biologic stratagems.

Biologic agents can be channeled in three directions, specifically as mediators of angiogenesis, modulators of oncogene products (*ie*, indirect mediators of apoptosis and necrocytosis), and finally as support for tumor suppressor gene product cell cycle regulation. As inhibitors of angiogenesis, biologic therapy may be useful in retarding tumor growth and progression and even eliminating small volume residual disease. Evidence that angiogenesis plays an important role in locally advanced cervical cancer has accumulated in recent years [74•,75,76]. In one study of 111 patients, Cooper *et al.* [76] identified tumor angiogenesis (as reflected by the tumor microvessel density) as a significant prognostic factor within a Cox multivariate analysis, where it was associated with poor locoregional control and overall survival. Neutralizing anti-vascular endothelial growth factor (VEGF) monoclonal antibodies have demonstrated therapeutic activity in a variety of preclinical solid tumor models [77,78]. Bevacizumab (rhUMAb VEGF) is a recombinant humanized version of a murine antihuman VEGF monoclonal antibody that has been advanced into clinical development by Genentech (South San Francisco, CA) to induce tumor growth inhibition in patients with solid tumors and for use in combination with cytotoxic chemotherapy to delay the time to progression in patients with metastatic solid tumors. In a recent study comparing carboplatin and paclitaxel with and without bevacizumab, the addition of bevacizumab prolonged survival by 20% in patients with advanced or metastatic non-small-cell lung cancer [79•]. Because such patients may share a similar treatment paradigm with women with cervical cancer, one of the current authors (BJM) is conducting a phase II evaluation of bevacizumab within the GOG (protocol 227C). This immunologic molecule is being administered at a dosage of 15 mg/kg IV on a 21-day cycle.

The importance of oncogenes and tumor suppressor genes and their protein products as they pertain to cervical carcinogenesis must be considered as well [80]. The epidermal growth factor (EGFR) receptor is a 170-kD transmembrane glycoprotein that, when activated, promotes cell growth in a variety of normal and transformed tissues [81]. EGFR is expressed in 75% of squamous cell cervical cancers and plays a key role in the HPV-16-mediated transformation of normal keratinocytes [82,83]. Inhibition of tumor-associated EGFR with monoclonal antibodies leads to growth arrest [84].

In 2004, Sheppard *et al.* [85] presented data from a randomized placebo controlled trial of the EGFR inhibitor, Tarceva (erlotinib, OSI-774; Genentech) in patients with advanced non-small-cell lung cancer following failure of first-line or second-line chemotherapy and documented statistically significant and clinically relevant differences for overall and progression-free survival. Schilder (study chair for GOG-227D) is currently evaluating OSI-774, an orally active, potent, selective inhibitor of the EGFR tyrosine kinase, in patients with persistent or recurrent squamous cell cervical cancer. Farley (study chair for GOG-

76DD) is investigating the combination of cisplatin and cetuximab (an antibody that targets EGFR-expressing tumors) in this disease [86].

Therapeutic vaccines specific for oncolytic strains of the human papillomavirus [87,88] and gene therapy [89] to reintroduce wild-type tumor suppressor that is resistant to degradation by virulent HPV E6 gene product are two lines of attack currently in development. The application of technologic advancements in proteomics and in vitro drug resistance assays [90] should also be of significant benefit in the future.

Conclusions

The next era in the randomized phase III setting for the GOG in this disease will need to be one for studying conventional chemotherapeutic agents in tandem with important biologic agents, such as bevacizumab, cetuximab, and OSI-774. Without the addition of active biologics, metastatic cervical cancer will remain a disease suitable only for palliative therapy.

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