

Chemotherapy in Endometrial Cancer

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Abstract: Endometrial cancer is a highly curable malignancy when it presents as uterine-confined disease, but the prognosis for metastatic or recurrent endometrial cancer is poor. The median survival of women enrolled in trials for recurrent or metastatic endometrial cancer is only approximately 12 months. Hormonal therapy, most commonly with progestins, benefits a small group of patients. Cytotoxic chemotherapy is indicated as frontline treatment for the majority of women with metastatic or recurrent disease. Anthracyclines, platinum compounds, and taxanes consistently achieve response rates greater than 20% in single-agent trials of chemotherapy-naïve patients. Combination chemotherapy typically produces higher response rates, although combination regimens have not always improved survival historically. Doxorubicin plus cisplatin has been accepted as the Gynecologic Oncology Group (GOG) standard regimen based on phase III data. Recently, a GOG randomized trial compared doxorubicin plus cisplatin to the triplet of doxorubicin, cisplatin, and paclitaxel, and it was found that the addition of paclitaxel significantly improved response rate, progression-free survival, and overall survival. Moreover, chemotherapy has been reported to improve survival when used in the adjuvant setting.

In the United States, endometrial cancer is the most common gynecologic pelvic malignancy, accounting for 6% of all cancers in women, and the eighth most common cause of cancer-related death.¹ According to the American Cancer Society, 40,880 new cases of endometrial cancer were diagnosed and 7,310 women died of the disease in 2005.

Endometrial cancer is usually diagnosed at an early stage because most women quickly report abnormal vaginal bleeding to their physicians. Approximately 80% of patients present with stage I disease and 13% present with stage II disease. Patients with disease confined to the uterine corpus are usually cured with hysterectomy and bilateral salpingo-oophorectomy. Five-year overall survival (OS) is as high as 88% for women with surgically staged stage I disease (all grades combined).² Surgery may be combined with adjuvant radiation therapy (RT) when high-risk features such as high-grade and/or deep myometrial invasion are present.

The majority of endometrial cancers are adenocarcinomas. The most common histology, endometrioid carcinoma, comprises 80%

Keywords

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of endometrial cancers.³ These tumors typically present with a low stage and grade, are often estrogen-related, and tend to arise on a background of endometrial hyperplasia. The most common nonendometrioid histology, serous carcinoma, most frequently arises in a background of endometrial atrophy and presents with stage IV disease.

Therapy for recurrent or metastatic endometrial cancer is palliative. Unfortunately, the 5-year survival of patients with recurrent or metastatic endometrial cancer remains poor, with median survival times of less than a year in most Gynecologic Oncology Group (GOG) trials. Although reported response rates (RRs) of the most active systemic chemotherapy have been as high as 70% in this setting, the median duration of such responses remains short, from 4 to 8 months.

Chemotherapy and hormonal therapy are the mainstays of treatment for advanced disease, except for rare cases amenable to surgery or RT such as isolated vaginal recurrences or solitary pulmonary metastases. Hormonal therapy with progestins may be effective for patients whose tumors are estrogen and progesterone receptor-positive (more common with low-grade tumors), but it is relatively ineffective for receptor-poor tumors.⁴ Among patients with advanced endometrial cancer treated with medroxyprogesterone acetate on a GOG trial (GOG-81), 37% of patients whose tumors were progesterone receptor-positive responded compared with 8% of women whose cancers were progesterone receptor-negative.⁵ Women whose tumors have low levels of progesterone-receptor expression tend to have higher-grade histology.⁶⁻⁸ Chemotherapy then becomes the cornerstone of treatment.

Prior pelvic irradiation, older age, and medical comorbidities place many patients with endometrial cancer at risk for complications from chemotherapy. Advances in supportive care, particularly the use of granulocyte colony-stimulating factors (G-CSFs), have allowed more intensive regimens. New agents and combinations prompted a series of phase II and III trials showing promising response rates and, recently, improved survival. This review focuses on chemotherapy as adjuvant treatment of high-risk disease and on the treatment of recurrent or metastatic disease.

Single-agent Chemotherapy

Numerous single-agent trials have been performed since the late 1970s in both the first- and second-line settings. Only a few agents—taxanes, anthracyclines, and platinum agents—produced RRs greater than 20% in chemotherapy-naïve patients. Alkylating agents (particularly ifosfamide), vinca alkaloids (vincristine), and hexamethylmelamine also have shown modest activity, but with more significant toxicities.⁹⁻¹³ Options remain limited

for patients who have failed first-line therapy. In women who have received prior cytotoxic therapy, only paclitaxel (Taxol, Bristol-Myers Squibb) has consistently produced RRs greater than 20%.^{14,15} Results of single-agent trials in chemotherapy-naïve and previously treated patients are presented in Tables 1 and 2, respectively.

Doxorubicin has formed the backbone of modern combination regimens, as it was among the earliest active agents discovered, with RRs of 20–37%.^{16,17} Likewise, epirubicin produced an RR of 26% in one small phase II study.¹⁸ Pegylated liposomal doxorubicin proved disappointing in first-line treatment, producing a RR of 11.5%, and is unlikely to replace doxorubicin in combination regimens, based on these results.¹⁹ In the first-line treatment of metastatic breast cancer, liposomal doxorubicin appears as effective as doxorubicin, with reduced adverse events.²⁰ In studies of pretreated women, anthracyclines were less effective; RRs decreased to approximately 10%.^{17,21}

The activity of cisplatin in other gynecologic malignancies prompted phase II trials in endometrial cancer. Investigators observed RRs of 20–42% when cisplatin at a dose of 50–60 mg/m² was administered to chemotherapy-naïve patients.²²⁻²⁵ In contrast, cisplatin had limited activity in patients who received prior chemotherapy.^{26,27} A GOG study of cisplatin in previously treated women reported only a 4% RR.²⁸ Carboplatin, which is generally less neurotoxic and nephrotoxic than cisplatin, produces RRs similar to those of cisplatin in both the first-²⁹⁻³⁰ and second-line settings.^{29,30}

The first GOG trial evaluating paclitaxel in chemotherapy-naïve endometrial cancer patients used a continuous 24-hour infusion of paclitaxel 250 mg/m² every 21 days and G-CSF.³¹ The authors reported an RR of 36% (complete response, 14%) and median OS of 9.5 months. Subsequent trials in pretreated patients used a 3-hour infusion at lower doses and continued to demonstrate impressive RRs of 27–37%.^{14,15} Two phase II studies reported in 2005 evaluated the efficacy of docetaxel and showed encouraging activity (RR, 21–37% in chemotherapy-naïve patients, 23% in those previously treated).^{32,33}

Topotecan appears to have limited activity as a single agent for the treatment of endometrial cancer, but the optimal dose and schedule are unclear. A study of topotecan administered at 1.5 mg/m² for 5 days every 3 weeks to endometrial cancer patients with no prior therapy produced an unacceptable rate of severe adverse events, primarily sepsis and bleeding.³⁴ There were five toxic deaths among the first 28 subjects. The study was suspended but later reopened at a lower starting dose of 1.0 mg/m². At the modified dose, clinical activity was preserved and toxicities were acceptable. Likewise, a GOG study of topotecan as second-line therapy demonstrated

Table 1. Single-Agent Trials: No Prior Chemotherapy

Lead Author	Year	Agent	Dose	N	RR, %
<i>Anthracyclines</i>					
Horton ¹⁷	1978	Doxorubicin	50 mg/m ² q 3 wk	21	19
Thigpen ¹⁶	1979	Doxorubicin	60 mg/m ² q 3 wk	43	37
Calero ¹⁸	1991	Epirubicin	80 mg/m ² q 3 wk	27	26
Homesley ¹⁹	2005	Liposomal doxorubicin	40 mg/m ² q 4 wk	52	11.5
<i>Taxanes</i>					
Ball ³¹	1996	Paclitaxel	250 mg/m ² /24 hr + G-CSF q 21 d	28	36
Hirai ⁸⁰	2004	Paclitaxel	210 mg/m ² q 3 wk	10	60
Günther ³³	2005	Docetaxel	35 mg/m ² q wk	34	21
Katsumata ³²	2005	Docetaxel	70 mg/m ² q 3 wk	19	31
<i>Platinum</i>					
Trope ²²	1980	Cisplatin	50 mg/m ² q 3 wk	11	36
Seski ²³	1982	Cisplatin	50–100 mg/m ² q 4 wk	26	42
Edmonson ²⁴	1987	Cisplatin	60 mg/m ² q 21 d	14	21
Thigpen ²⁵	1989	Cisplatin	50 mg/m ² q 21 d	49	20
Green ²⁸	1990	Carboplatin	400 mg/m ² q 28 d	23	33
Burke ²⁹	1993	Carboplatin	360 mg/m ² q 28 d	27	32
van Wijk ³⁰	2003	Carboplatin	400 mg/m ² q 28 d	33	24
<i>Alkylating agents</i>					
Horton ¹⁷	1978	Cyclophosphamide	660 mg/m ² q 3 wk	19	0
Seski ¹¹	1981	Hexamethylmelamine	8 mg/kg/d	20	30
Thigpen ¹²	1988	Hexamethylmelamine	280 mg/m ² /d × 14 d q 28 d	34	9
Barton ⁹	1990	Ifosfamide	5 g/m ² /24 hr q 21 d	16	12.5
Sutton ¹⁰	1996	Ifosfamide	1.2 g/m ² /d × 5 d q 4 wk	33	24
Pawinski ⁴⁵	1999	Ifosfamide	5 g/m ² /24 hr q 3 wk	16	25
Pawinski ⁴⁵	1999	Cyclophosphamide	1,200 mg/m ² /24 hr q 3 wk	14	14
<i>Vinca alkaloids</i>					
Thigpen ⁴⁰	1987	Vinblastine	1.5 mg/m ² /24 hr × 5 d q 3 wk	34	12
Broun ¹³	1993	Vincristine	1.4 mg/m ² q wk × 4 then q 2 wk	33	18
<i>Other</i>					
Muss ⁴⁰	1990	Methotrexate	40 mg/m ² /wk	33	6
Poplin ³⁶	1999	Oral etoposide	50 mg/d × 21 d q 28 d	44	14
Wadler ³⁴	2003	Topotecan	0.8–1.5 mg/m ² × 5 days q 21 d	40	20

G-CSF = granulocyte colony-stimulating factor; RR = response rate.

Table 2. Single-Agent Trials: Prior Chemotherapy

Lead Author	Year	Agent	Dose	N	RR, %
<i>Anthracyclines</i>					
Horton ¹⁷	1978	Doxorubicin	50 mg/m ²	9	11
Hilgers ³⁹	1985	Mitoxantrone	10–12 mg/m ²	15	0
Muggia ²¹	2002	Liposomal doxorubicin	50 mg/m ² q 4 wk	42	9.5
<i>Taxanes</i>					
Lissoni ¹⁴	1996	Paclitaxel	175 mg/m ² q 3 wk	19	37
Woo ⁸¹	1996	Paclitaxel	170 mg/m ² q 3 wk	7	43
Lincoln ¹⁵	2003	Paclitaxel	200 mg/m ² q 3 wk	44	27
Hirai ⁸⁰	2004	Paclitaxel	210 mg/m ² q 3 wk	13	7.7
Katsumata ³²	2005	Docetaxel	70 mg/m ² q 3 wk	13	23
<i>Platinum</i>					
Deppe ²⁶	1980	Cisplatin	3 mg/kg q 3 wk	13	31
Thigpen ²⁷	1984	Cisplatin	50 mg/m ² q 3 wk	25	4
van Wijk ³⁰	2003	Carboplatin	300 mg/m ² q 4 wk	17	0
<i>Alkylating agents</i>					
Sutton ¹⁰	1994	Ifosfamide	1.2 g/m ² /d × 5 q 4 wk	40	15
Pawinski ⁴⁵	1999	Ifosfamide	5 g/m ² /24 hr q 3 wk	16	0
Pawinski ⁴⁵	1999	Cyclophosphamide	1,200 mg/m ² /24 hr q 3 wk	15	0
<i>Epidodophyllotoxins</i>					
Slayton ⁸²	1982	Intravenous etoposide	100 mg/m ² days 1, 3, 5 q 28 d	29	3
Muss ⁴²	1991	Teniposide	100 mg/m ² /wk	22	9
Rose ³⁷	1996	Oral etoposide	50 mg/m ² × 21 d	22	0
<i>Other</i>					
Jackson ⁸²	1986	Vincristine	0.25–0.5 mg/m ² CIV × 5 d	5	0
Von Hoff ³⁸	1991	Fludarabine	18 mg/m ² /d × 5 q 28 d	19	0
Moore ⁴³	1999	Dactinomycin	2 mg/m ² q 4 wk	25	12
Miller ³⁵	2002	Topotecan	0.5–1.5 mg/m ² × 5 q 21 d	22	9

CIV = continuous intravenous infusion; RR = response rate.

considerable hematologic toxicity and only a 9% RR.³⁵ Oral etoposide, although easy to administer at a low dose of 50 mg, displayed only very modest activity (RR, 14%) in a Southwest Oncology Group (SWOG) study as first-line therapy³⁶ and there were no objective responses in a GOG study of etoposide as second-line therapy.³⁷ Other cytotoxics tested as single agents that have been relatively ineffective (RR <15%) include: fludarabine, dactinomycin, mitoxantrone, vinblastine (RR, 12%), methotrexate, and teniposide.³⁸⁻⁴³

5-Fluorouracil (5-FU) was tested in studies performed in the 1970s before the routine use of computed tomography imaging to assess response.⁴⁴ RRs of 21%

were reported, but it is probable that response rates would be lower using current assessment standards. The drug is not widely used in the treatment of endometrial cancer. Similarly, cyclophosphamide is no longer used because its minimal efficacy in recent studies does not confirm the promising activity demonstrated in earlier trials.⁴⁵ Gemcitabine and oxaliplatin are cytotoxic agents with established activity in other gynecologic tumors that have not been tested to date in endometrial cancer. Vinorelbine has been tested in combination with platinum, and though the combinations were quite active (RRs, 57% and 69% in two trials), the contribution of vinorelbine remains uncertain.^{46,47}

Table 3. Combination Chemotherapy Trials

Trial	Year	Regimen	N	RR, %	Median OS, mo
EORTC-55872 Aapro ⁵⁰	2003	Doxorubicin 60 mg/m ² q 4 wk	87	17	7
		Doxorubicin 60 mg/m ² + cisplatin 50 mg/m ² q 4 wk	90	43	9 (<i>P</i> =.06)
GOG-107 Thigpen ⁴⁹	2004	Doxorubicin 60 mg/m ² q 3 wk	150	25	9.2
		Doxorubicin 60 mg/m ² + cisplatin 50 mg/m ² q 3 wk	131	42	9.0
GOG-48 Thigpen ⁴⁸	1994	Doxorubicin 60 mg/m ² q 3 wk	132	22	6.7
		Doxorubicin 60 mg/m ² + cyclophosphamide 500 mg/m ² q 3 wk	144	30	7.3
GOG-139 Gallion ⁷⁹	2003	Doxorubicin 60 mg/m ² + cisplatin 60 mg/m ² q 3 wk	169	46	11.2
		Doxorubicin 60 mg/m ² (6 am) + cisplatin 60 mg/m ² (6 pm) q 3 wk	173	49	13.2
GOG-163 Fleming ⁵¹	2004	Doxorubicin 60 mg/m ² + cisplatin 50 mg/m ² q 3 wk	157	40	12.6
		Doxorubicin 50 mg/m ² + paclitaxel 150 mg/m ² /24 hr + G-CSF	160	43	13.6
GOG-177 Fleming ⁵²	2004	Doxorubicin 60 mg/m ² + cisplatin 50 mg/m ² q 3 wk	129	34	12.3
		Doxorubicin 45 mg/m ² + cisplatin 50 mg/m ² + paclitaxel 160 mg/m ² + G-CSF	134	57	15.3 (<i>P</i> =.037) 2-sided
GOG-209	Ongoing	Paclitaxel/carboplatin doxorubicin 45 mg/m ² + cisplatin 50 mg/m ² + paclitaxel 160 mg/m ² + G-CSF	-	-	-

EORTC = European Organization for Research and Treatment of Cancer; G-CSF = granulocyte colony-stimulating factor; GOG = Gynecologic Oncology Group; OS = overall survival; RR = response rate.

Combination Chemotherapy

Combination chemotherapy typically produces higher response rates than single-agent therapy, but it tends to produce more toxicity, and the effect on survival of combination therapy versus sequential single-agent therapy remains uncertain in most metastatic solid tumors.

Over the past 25 years, the GOG has attempted to improve the outcome for recurrent and metastatic endometrial cancer patients by performing randomized phase III trials comparing a standard regimen to a newer one (often the standard regimen plus another agent with established activity). Eight first-line randomized clinical trials in women with advanced or recurrent endometrial carcinoma have been published, six of which have been conducted by the GOG. It should be recognized that prior pelvic RT and the older age of many participants limited the dose intensity in some of these trials. Many protocols mandated reduced starting doses for these

patients. Table 3 presents a summary of randomized first-line chemotherapy trials.

The first GOG protocol (GOG-48) compared single-agent doxorubicin 60 mg/m² to the combination of doxorubicin 60 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks.⁴⁸ A total of 356 patients were enrolled, all of whom had failed treatment with progestins and were naive to cytotoxic therapy. While there was a statistically nonsignificant trend toward improved RR, there was no improvement in survival. Median progression-free survival (PFS) was 3.2 months for single-agent doxorubicin and 3.9 months for combination therapy and OS was 6.7 months versus 7.3 months, respectively.

GOG-107 explored whether combination doxorubicin and cisplatin (AP) was superior to doxorubicin alone. The study accrued patients from 1988 to 1992. A total of 278 women were treated with doxorubicin 60 mg/m² or doxorubicin 60 mg/m² and cisplatin 50 mg/m² every 3 weeks.⁴⁹ Patients receiving the com-

bination treatment demonstrated a significant improvement in overall RR (42% vs 25%) and PFS (median, 5.7 vs 3.8 mo). Interestingly, median survival was similar, at 9.0 months and 9.2 months for the combination and single-agent arms, respectively. Information on how many women receiving single-agent doxorubicin crossed over to cisplatin at the time of progression is not available.

The European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group conducted a similar randomized trial (55872) in which the same doses of doxorubicin alone and AP were administered every 4 instead of 3 weeks.⁵⁰ Again, the authors found that AP significantly improved RR (43%) versus doxorubicin alone (17%) at the expense of hematologic toxicity and nausea and vomiting. In the final analysis, the Kaplan-Meier survival curves revealed no significant difference in OS between the two treatment arms (9 vs 7 mo in the AP and single-agent doxorubicin arms, respectively), although the trend was in favor of combination therapy.

GOG-163 subsequently randomized women to either doxorubicin 60 mg/m² and cisplatin 50 mg/m² (cisplatin dose was reduced because of toxicities noted in prior trials) or doxorubicin 60 mg/m² and paclitaxel 150 mg/m² over 24 hours plus G-CSF.⁵¹ RR (40% vs 43%), PFS (median, 7.2 vs 6 mo), and OS (12.6 vs 13.6 mo) did not differ significantly between AP and doxorubicin/paclitaxel, and toxicities were similar. The 24-hour paclitaxel infusion proved cumbersome, precluding its adoption as routine care.

GOG-177, which accrued patients between 1998 and 2000, randomized them to AP or doxorubicin 45 mg/m² and cisplatin 50 mg/m² on day 1 followed by paclitaxel 160 mg/m² on day 2 (TAP) with G-CSF support.⁵² TAP produced a statistically significant improvement in RR (57% vs 34%), PFS (median, 8.3 vs 5.3 mo), and OS (median, 15.3 vs 12.3 mo) compared with AP at the expense of increased peripheral neuropathy. However, the finding that any chemotherapy improves survival for women with advanced or recurrent endometrial cancer is a milestone, and the trial confirms the activity of taxanes in this disease. A comparable EORTC study (55991) of AP versus TAP in patients with locally advanced or metastatic/relapsed endometrial cancer is currently underway. The results of these two phase III trials should help guide clinicians when treating patients with recurrent or metastatic endometrial cancer.

Oncologists frequently treat a variety of solid tumors with carboplatin and paclitaxel because the regimen is easily administered in the outpatient setting and avoids the renal and cardiac toxicity associated with cisplatin and doxorubicin. Multiple phase II trials have established the

activity and tolerability of carboplatin/paclitaxel in recurrent or metastatic endometrial cancer (Table 4).⁵³⁻⁵⁷ The GOG has launched a large phase III trial (GOG-209) in women with stage III, IV, or recurrent endometrial cancer comparing carboplatin/paclitaxel to TAP.

Adjuvant Therapy

It is well known that women whose endometrial tumors have unfavorable histology such as papillary serous or clear-cell adenocarcinoma, high histologic grade, lymphovascular involvement, and/or cervical or deep myometrial invasion, are at increased risk for both local and distant recurrence.⁵⁸ Adjuvant RT is typically administered to patients with poor prognostic features to reduce the incidence of recurrent pelvic disease. For high-risk patients who do not receive adjuvant RT, RRs range from 15% to 20%.⁵⁹⁻⁶¹ Trials of pelvic RT with or without vaginal brachytherapy have not reported a statistically significant impact on OS, in part because the risk for distant disease is not addressed by such modalities.^{62,63} Distant metastases have been documented in approximately 25% of patients with stage I disease and grade 3 histology⁶⁴ and 20% of patients with cervical involvement.⁶⁵

Until recently, there has been no systemic therapy proven to reduce the risk of recurrence for any stage of endometrial cancer. Three early randomized trials failed to demonstrate any benefit to the adjuvant use of progestins.⁶⁶⁻⁶⁸ However at the 2003 American Society of Clinical Oncology (ASCO) meeting, the GOG reported positive results for the use of adjuvant chemotherapy for stage III and "optimally debulked" stage IV disease.

GOG 122 randomized women to adjuvant whole abdominal irradiation (WAI) versus the AP chemotherapy regimen.⁶⁹ Patients receiving chemotherapy did not receive RT to any fields. Approximately 73% of the study population had stage III disease. At 52 months of follow-up, the authors reported that AP significantly improved OS (70% vs 59%) and PFS (59% vs 46%) when compared with WAI; benefits were seen in both stage III and stage IV disease. This trial represents a major advance in the treatment of endometrial cancer, and it should significantly change clinical practice. The subsequent adjuvant GOG trial, GOG-184, randomized women with stage III disease to involved field RT (ie, pelvic +/- para-aortic nodal +/- vaginal brachytherapy) followed by either cisplatin/doxorubicin or cisplatin/doxorubicin/paclitaxel. The trial has completed accrual, and results should be released in the next several years.

Another recent phase III trial compared systemic chemotherapy to RT in the adjuvant treatment of somewhat earlier stage disease. The Japanese Gynecologic

Table 4. Clinical Trials of Combination Paclitaxel/Carboplatin

Lead Author	Year	Regimen	N	RR, %
Price ⁵³	1997	Carboplatin AUC5 + paclitaxel 135–175 mg/m ² q 4 wk	8	63
Nakamura ⁵⁷	2000	Carboplatin AUC5–6 + paclitaxel 180 mg/m ² q 21 d	11	73
Hoskins ⁵⁴	2001	Carboplatin AUC5–7 + paclitaxel 175 mg/m ² q 4 wk	46	61
Weber ⁵⁶	2003	Doxorubicin 60 mg/m ² + cisplatin 50 mg/m ² q 3 wk	29	28
		Carboplatin AUC5 + paclitaxel 175 mg/m ² q 3 wk	34	35
Scudder ⁵⁵	2005	Carboplatin AUC6 + paclitaxel 175 mg/m ² + amifostine 740 mg/m ² q 4 wk	47	40

AUC = area under the curve; RR = response rate.

Oncology Group randomized intermediate-risk patients (stage IC–IIIC) to either pelvic RT or cyclophosphamide/doxorubicin/cisplatin chemotherapy. Preliminary results were presented at the 2005 ASCO meeting.⁷⁰ There were no overall statistically significant differences in PFS or OS between treatment modalities. However, in a subgroup analysis of high-intermediate risk patients (defined as stage II and IIIA due to positive cytology), the group receiving chemotherapy had a significantly improved PFS (84.5% vs 64.2%) and OS (97.5% vs 80.3%) at 5 years.

Concomitant chemoradiotherapy has improved survival in numerous other tumor types, including cervical cancer. One current area of research centers on concomitant chemoradiotherapy for high-risk early-stage endometrial cancer with the goal of defining an optimal regimen and schedule. The Radiation Therapy Oncology Group (RTOG) recently completed and published a phase II trial testing chemoradiotherapy in women with grade 2 or 3 tumors with more than 50% myometrial invasion, cervical stromal invasion, or pelvic-confined extrauterine disease.⁷¹ A total of 44 patients received pelvic RT with cisplatin 50 mg/m² on days 1 and 28 followed by vaginal brachytherapy and then four cycles of cisplatin 50 mg/m² and paclitaxel 175 mg/m². At 24 months, pelvic recurrence, distant recurrence, PFS, and OS were 2%, 17%, 83%, and 90%, respectively. Ninety-eight percent of patients completed the protocol, but grade 3 and 4 acute (during RT/chemotherapy) and chronic toxicities were observed in 29% and 18% of patients, respectively.

Unfortunately, the follow-up randomized phase III trial (RTOG-9905) assigning high-risk stage I/II women to pelvic RT alone or pelvic RT combined with cisplatin/paclitaxel (at a lower paclitaxel dose) failed to accrue patients. The EORTC is currently conducting a phase III

trial randomizing patients with high-risk stage I/II disease (patients with clear cell, serous papillary, or anaplastic carcinoma) to adjuvant RT or to adjuvant RT followed by chemotherapy (cisplatin and either doxorubicin or epirubicin). The limited number of patients meeting criteria for adjuvant therapy makes accrual to these clinical trials slow. Disagreement on a number of issues, particularly the need for lymph node dissection in staging, has also hampered intergroup trial cooperation. At this time, phase III evidence supporting the addition of chemotherapy to adjuvant RT continues to be lacking in high-risk stage I/II disease. Nonetheless, the practice of administering adjuvant chemotherapy to women with early stage serous carcinomas of the endometrium has become common in the United States.

New Directions

Cytotoxic cancer chemotherapy has traditionally employed agents that affect all dividing cells. Newer targeted agents are being developed with the aim of greater specificity toward tumor cells. In addition, newer technologies, such as the Oncotype DX (Genomic Health) expression array currently being marketed for breast cancer patients, are helping physicians identify patients who are more or less likely to benefit from existing treatments. Currently, there are no validated molecular markers used to make treatment decisions for endometrial cancer patients, although estrogen/progesterone receptor status and tumor histology are sometimes used. Tumors with serous histology were believed to respond poorly to chemotherapy, although a recent overview of pooled data from four GOG trials demonstrated that the response rate of serous tumors to chemotherapy regimens that include

doxorubicin, platinum, and/or paclitaxel is identical to that of endometrioid tumors.

Many of the ongoing single-agent trials in endometrial cancer incorporate advances in the understanding of endometrial cancer's molecular biology. For example, like breast cancers, endometrial cancers can overexpress the HER2/neu protein. HER2/neu amplification has been detected by fluorescence in situ hybridization (FISH) in 15% of endometrial cancer specimens collected from patients enrolled in a recent GOG randomized first-line chemotherapy trial.⁷² The rate of amplification is somewhat higher in patients with serous tumors.⁷³ Patients with breast cancers that display HER2/neu amplification benefit from therapy with trastuzumab (Herceptin, Genentech), a monoclonal antibody directed at the HER2/neu protein. The GOG is currently conducting a phase II trial (GOG-181b) of single-agent trastuzumab in patients with recurrent or metastatic endometrial cancer. A preliminary analysis of 23 patients (all subjects had 2+ or 3+ staining by immunohistochemistry) presented in abstract form at the 2003 ASCO meeting proved disappointing; single-agent trastuzumab had limited activity.⁷⁴ However, there has been a case report of response to trastuzumab in a woman with metastatic serous endometrial carcinoma,⁷⁵ and GOG-181b has been reopened, with eligibility limited to women whose tumors amplify HER2/neu by FISH analysis.

The tumor suppressor gene *PTEN* induces cell cycle arrest and apoptosis by regulating the phosphatidylinositol 3' kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway essential to cell cycling. Mutations in *PTEN* can engender increased cell survival by constitutive activation of AKT and upregulation of mTOR. A loss of *PTEN* is seen in up to 40–60% of endometrial cancers and *PTEN* mutations have been identified in endometrial hyperplasia suggesting that *PTEN* inactivation may be an inciting event in the pathogenesis of endometrial cancer.⁷⁶ Three phase II trials have been opened to explore the activity of mTOR inhibitors (AP23573, CCI-779, and RAD001) in recurrent or metastatic endometrial cancers based on this preclinical data. Preliminary results for CCI-779 were reported at the 2005 American Association for Cancer Research–National Cancer Institute–EORTC conference on Molecular Targets and Cancer Therapeutics, and showed an overall response rate of 31% in chemotherapy-naïve women.⁷⁷

The epidermal growth factor receptor (EGFR) is overexpressed in up to 80% of endometrial cancers, and its expression may correlate with a poor clinical outcome. Erlotinib (Tarceva, Genentech/OSI), a small-molecule inhibitor of the EGFR tyrosine kinase, has been tested in a phase II trial for chemotherapy-naïve recurrent and advanced endometrial cancer patients. Of 27 evaluable

patients, there were 2 partial responses (7%), and 14 patients with stable disease (57%) lasting a median of 3.7 months.⁷⁸

Results of trials testing other EGFR and vascular EGFR tyrosine kinase inhibitors, such as gefitinib (Iressa, AstraZeneca) and sorafenib (Nexavar, Bayer/Onyx), will also soon be available. Endometrial cancers may, like colon cancers, exhibit microsatellite instability and mismatch repair deficiency, and it is possible that this will predict sensitivity or resistance to specific agents. Selecting which patients will benefit from therapy and the development of newer, more effective treatments remain research priorities.

Conclusion

Over the past decade, cooperative groups have made significant inroads into treating recurrent and advanced endometrial cancer through performing rigorous randomized trials. Pivotal studies, such as GOG-177 and GOG-122, have finally demonstrated some improved survival for women with advanced endometrial cancer. However, an enormous amount of progress remains to be made. Participation in clinical trials is critical to answering many questions that still exist. In the setting of metastatic disease, the testing of newer agents must be expedited, and the integration of these newer agents with traditional therapies addressed. In the adjuvant setting, future randomized trials need to be directed at selection of appropriate patients with high-risk, early-stage disease, and optimizing a regimen integrating chemotherapy and radiotherapy.

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