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Treatment of Advanced and Recurrent Carcinoma: Chemotherapy

Fernanda Musa

Abstract

Chemotherapy for endometrial cancer has evolved over the past two decades, with drug combinations convincingly showing to have a role in the treatment of advanced and recurrent endometrial cancer. Agents with established antitumor activity include doxorubicin, cisplatin, and paclitaxel. A combination of paclitaxel with the cisplatin analog carboplatin is currently the most commonly used regimen for first-line treatment of metastatic disease. Questions remain about the contribution of these regimens in adjuvant settings, about the role of drug therapy beyond first-line treatments, and about integration of targeted agents.

Keywords

Endometrial • Chemotherapy • Doxorubicin • Cisplatin • Paclitaxel • Carboplatin

Introduction

Advanced endometrial cancer is associated with adverse outcomes compared to early-stage disease, with a 5-year survival of 59.6 % for stage III disease and 28.6 % for stage IV disease. The prognosis, however, is impacted by the degree of tumor differentiation and histology. Women with stage III disease and grade 1 adenocarcinomas have an 83 % 5-year survival compared to 48 % for women with grade 3 adenocarcinomas. Similarly, papillary serous and clear cell histologies are well-described poor prognostic indicators associated with decreased survival, comparable to that of ovarian cancer. SEER data suggests that the 5-year survival for patients with stage III papillary serous endometrial cancer is 33.3 % and 18.3 % for stage IV, compared to 66.9 % and 36.8 % for stage III and IV endometrioid tumors, respectively (all grades) [1].

Recurrent endometrial cancer presents with differing patterns ranging from localized to diffuse, and involvement of nodal and visceral areas. Therapeutic options vary depending on whether the metastatic focus is in a previously

F. Musa (✉)
Division of Gynecologic Oncology, New York University Langone Medical Center, New York, NY, USA
e-mail: fernanda.musa@nyumc.org

irradiated field or not. The choice of chemotherapy in recurrent endometrial cancer, particularly in papillary serous tumors, is largely extrapolated from the ovarian cancer literature. Similarly to ovarian cancer, recurrences can be categorized as platinum-sensitive versus platinum-resistant depending on their temporal relationship to the completion of a previous platinum-containing treatment. This status provides a guide to the selection of the chemotherapeutic agent of choice; however, response rates are generally lower than those observed in recurrent ovarian cancer. Chemotherapy in this setting is palliative and mindfulness of the patient's quality of life while undergoing treatment is imperative in any therapeutic intervention.

Development of Systemic Therapies

The systemic treatment of endometrial carcinoma was first developed around progestins and doxorubicin and then mostly evolved from phase III studies by the Gynecologic Oncology Group (GOG) that have been performed since the 1970s. GOG 122, the first randomized phase III study demonstrating the superiority of chemotherapy (doxorubicin plus cisplatin, AP) over radiation (whole-abdominal radiation, WAI) in endometrial cancer, served as a powerful stimulus for extending the use of adjuvant systemic therapy for this disease. In GOG 122, women with stage III and low-volume (<2 cm residual disease after debulking surgery) stage IV endometrial carcinoma were randomized to receive WAI with a pelvic boost or AP chemotherapy with no radiotherapy. Seventy-five percent of women had stage III disease. Twenty percent had serous tumors. The hazard ratio for progression was 0.71 favoring AP (95 % CI, 0.55–0.91; $p < 0.01$). Women with both stage III and stage IV disease appeared to benefit from treatment. No prognostic feature including age, substage, or histology predicted lack of benefit from chemotherapy [2].

The adoption of chemotherapy as a preferred modality over pelvic irradiation was initially controversial. An Italian randomized phase III trial of lower risk patients compared to GOG 122 demonstrated no difference in PFS or OS between adjuvant chemotherapy and pelvic radiation therapy at 95-month follow-up. The study did demonstrate fewer distant relapses in the chemotherapy group and local relapses in the radiotherapy group [3]. The Japanese GOG reported similar findings and no difference when comparing cisplatin, doxorubicin, and cyclophosphamide versus whole pelvic radiotherapy in patients with stage IC–IIIC endometrioid adenocarcinoma [4].

Integration of Chemotherapy and Radiation for Early-Stage Disease

The results of the Nordic Society of Gynecologic Oncology (NSGO), European Organization for Research and Treatment Center (EORTC), and ILIADE-III (MaNGO group) trials randomizing women to receive pelvic radiation therapy with and without chemotherapy were published together. Several different chemotherapy regimens were allowed including doxorubicin, cisplatin, and carboplatin–paclitaxel. The pooled results including 534 evaluable patients with surgically resected high-risk FIGO stage I–III endometrial cancers showed that combined modality treatment was associated with a 36 % reduction in the risk of relapse or death (HR 0.64, CI 0.41–0.99, $p = 0.04$). The pooled results also demonstrate an improvement in the cancer-specific survival (HR 0.55, CI 0.35–0.88, $p = 0.01$) [5]. The study concluded that addition of chemotherapy to radiation improves PFS in endometrial cancer patients with no postoperative residual tumor and a high-risk profile.

Many women with endometrial cancer are elderly (median age at diagnosis is 60–65 years) and dose-intense regimens need to be approached cautiously. GOG 184 randomly assigned women with stage III and IV disease who underwent volume-directed or involved-field radiation therapy to chemotherapy containing either doxorubicin plus cisplatin or doxorubicin, cisplatin, and paclitaxel. Both arms required granulocyte colony-stimulating factor support given limited

hematologic reserve following RT. The study concluded that addition of paclitaxel to doxorubicin and cisplatin was not associated with an improvement in recurrence-free survival but was associated with increased toxicity [6]. A recently published review by the Cochrane Library pooling the results of four major randomized controlled trials [2–4, 6] concluded that there is moderate-quality evidence that chemotherapy increases survival time after primary surgery in endometrial cancer by approximately 25 % relative to radiotherapy in stage III and IV disease. There is insufficient evidence at this time relative to the risks and benefits of adjuvant chemo-radiation versus chemotherapy alone in this setting [7]. In an attempt to answer this important question, the GOG has an ongoing phase III study which randomizes women with optimally cytoreduced advanced-stage endometrial cancer to carboplatin and paclitaxel with or without tumor volume-directed irradiation preceding the chemotherapy (GOG 258).

Chemotherapy for Metastatic or Recurrent Disease

The amount of residual disease after surgery for advanced endometrial cancer has an impact on median survival and progression-free interval [8–13]. For women who present with extensive metastatic disease and/or are not candidates for surgical therapy, chemotherapy is a mainstay of treatment. Stage III–IV endometrial cancer is comprised of a diverse patient population with a small proportion of women with well-differentiated endometrioid cancers and a larger proportion of high-risk disease subtypes such as uterine papillary serous carcinoma, clear-cell carcinomas, or carcinosarcoma of the uterus.

The overall poor prognosis of this group is highlighted by the Cochrane Library meta-analysis comparing different treatment strategies in this population. The review discusses the findings of 14 randomized clinical trials and offers multiple comparisons: administration of multi-agent combinations ("more intensive") versus fewer agents ("less intensive"), comparison across different chemotherapy doublets, and a comparison across different single chemotherapeutic agents. The conclusions are sobering. Compared with the administration of "less intensive" regimens, the use of "more intensive" regimens (eight trials including 1519 patients) resulted in improved PFS from 6 to 7 months (HR 0.82, CI 0.74–0.90) and OS from 9 to 10.5 months (HR 0.86, CI 0.77–0.96). Trials that compared doxorubicin (plus or minus cisplatin) with or without additional drugs favored the arms incorporating additional chemotherapy at the cost of additional toxicity. No single agent or combination chemotherapy regimen or schedule stood out.

Neoadjuvant chemotherapy is an interesting strategy that allows the identification of chemosensitive disease that is more likely to benefit from debulking surgery when compared to chemoresistant disease. It also provides a feasible up-front strategy for patients with unresectable disease or who are not otherwise candidates for cytoreductive surgery due to medical comorbidities. Given the considerable risk of postoperative complications associated with primary debulking reported at 36–39 % in the endometrial cancer population [10, 11], coupled with the older age and increased medical comorbidities associated with this disease, neoadjuvant chemotherapy may be a reasonable first approach in patients with advanced disease. In a prospective clinical trial including 30 patients who received 3–4 cycles of neoadjuvant chemotherapy prior to an attempt at cytoreduction, the Leuven Group concluded that the degree of tumor regression after NACT for advanced-stage endometrial cancer was a new prognostic marker. In their study, carboplatin and paclitaxel chemotherapy achieved a response rate of 74 %, with 2 complete responses and 20 partial responses. They did not operate on patients with progression of disease. Their optimal cytoreduction rate was 80 % ($\leq$1 cm) with a low postoperative morbidity rate [14].

The most active drugs in women with no prior chemotherapy are platinum agents, taxanes, and anthracyclines, all producing response rates of

20–30 % as single agents. Combination chemotherapy has produced higher response rates and improved survival in randomized trials. Several combination regimens have been tested in phase III trials and are summarized in Table 1. Based on phase II evidence reporting response rates between 40 and 74 % at acceptable toxicity for carboplatin and paclitaxel in both a chemo-naïve and a pretreated population, this combination was further studied in the phase III setting [14, 22–25]. Notably, in GOG 209, which utilized a non-inferiority design, carboplatin and paclitaxel (CT) as a doublet was not inferior to paclitaxel, doxorubicin, and cisplatin (TAP) with a more favorable toxicity profile, leading to its adoption as the standard doublet moving forward in clinical trials [21]. Interestingly, both treatment arms were associated with more than doubled median OS compared with previous studies. The marked improvement in median OS when compared to previous studies is likely to be multifactorial and reflect differential inclusion of a group of patients with improved prognosis, improvements in subsequent therapy, wider availability of imaging studies, and possible earlier detection of recurrences [26].

Single-Agent Chemotherapy

A large number of cytotoxic agents have been tested in endometrial carcinoma since the early 1960s. Results of single-agent trials for drugs that are commercially available are presented in Table 2.

Anthracyclines were among the first agents proven to be effective. Doxorubicin has been studied in phase II and III clinical trials at doses of 50–60 mg/m^2, yielding overall response rates between 25 and 37 % (see Table 2). Epirubicin produced a similar response rate of 26 % in one small phase II study [40]. Pegylated liposomal doxorubicin (Doxil®) proved disappointing in first-line treatment, producing a response rate of only 11.5 % [42]. However, additional data demonstrated RR of 36 % in the first line and 22 % in second line [43, 44]. Moreover, activity in combination with carboplatin is encouraging [26].

Platinum agents also have good activity. Cisplatin and its less neurotoxic analog, carboplatin, have produced response rates between 20 and 42 % in a number of single-agent trials (see Table 2). A trial of oxaliplatin by the GOG in patients with prior platinum therapy reported a response rate of 13.5 % [41]. The taxanes, paclitaxel and docetaxel, are the only agents ever shown to have meaningful activity in previously treated patients and have, therefore, now been incorporated into most frontline regimens (see Table 2). The data for agents beyond taxanes, anthracyclines, and platinum is summarized below [15, 32, 34, 35, 51, 52]. The combination of cisplatin and gemcitabine achieved 50 % RR in a population of chemo-naïve patients with recurrent disease [53]. The response rate observed for single-agent chemotherapy is rarely over 20 %. Ixabepilone appeared promising but a subsequent phase III trial did not see any benefit over the control arm (doxorubicin or paclitaxel) [54]. New treatment strategies including further developing the "chemotherapy backbone" are urgently needed for this disease [26] (Table 3).

Carcinosarcomas

Uterine carcinosarcomas (malignant mixed müllerian tumors) have been traditionally classified as a subtype of uterine sarcoma but accumulating molecular evidence has reclassified these tumors as more closely related to carcinomas and frequently it is the carcinoma component that will metastasize.

Response rates for single-agent chemotherapy in carcinosarcomas range from 0 to 10 % for doxorubicin [55, 56], 18 to 42 % for cisplatin [57, 58], 32 % for ifosfamide, and 18 % for paclitaxel [59, 60]. As with endometrial carcinomas, combination chemotherapy regimens have been shown to improve response rates at the expense of added toxicity. GOG 194 randomized women with advanced, recurrent, or persistent carcinosarcoma to treatment with ifosfamide alone or ifosfamide plus cisplatin

Table 1 Landmark trials of combination chemotherapy for endometrial cancer

Reference	Accrual	Phase	Intervention	*N*	Study population	ORR (%)	PFS (mo)	OS (mo)
Thigpen GOG-048 [15]	1979–1985	3	Doxorubicin 60 mg/m^2 Q21D Doxorubicin 60 mg/m^2 + cyclophosphamide 500 mg/m^2 Q21D	132 144	Chemo-naïve	22 30	3.2 3.9	6.7 7.3
Thigpen GOG-107 [16]	12/1988–12/1991	3	Doxorubicin 60 mg/m^2 Q21D Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q21D	150 131	Chemo-naïve	25 42	4 6	9 9
Aapro EORTC-55872 [17]	9/1988–6/1994	3	Doxorubicin 60 mg/m^2 Q28D Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q28D	87 90	Chemo-naïve	17 43	7 8	7 9 ($p = 0.06$)
Gallion GOG-139 [18]	3/1993–8/1996	3	Doxorubicin 60 mg/m^2 + cisplatin 60 mg/m^2 Q21D Doxorubicin 60 mg/m^2 (6 am) + cisplatin 60 mg/m^2 (6 pm) Q21D	169 173	Chemo-naïve	46 49	6.5 5.9	11.2 13.2
Fleming GOG-163 [19]	8/1996–11/1998	3	Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q21D Doxorubicin 50 mg/m^2 + paclitaxel 150 mg/m^2/24 h Q21D + G-CSF	157 160	Chemo-naïve	40 43	7.2 6.0	12.6 13.6
Fleming GOG-177 [20]	12/1998–8/2000	3	Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q21D Doxorubicin 45 mg/m^2 + cisplatin 50 mg/m^2 + paclitaxel 160 mg/m^2 Q21D + G-CSF	129 134	Chemo-naïve	34 57	5 8	12 15 ($p = 0.03$)
Miller GOG-209 [21]	8/2003–4/2009	3	Carboplatin AUC 6 + paclitaxel 175 mg/m^2 Doxorubicin 45 mg/m^2 + cisplatin 50 mg/m^2 + paclitaxel 160 mg/m^2 Q21D + G-CSF	663 642	Chemo-naïve	NR NR	14 14	32 38

Reference arms listed first. p value only listed for significant differences

Table 2 Single-agent chemotherapy for endometrial cancer: anthracyclines, taxanes, and platinum

Chemotherapy	Dose	Population	*N*	RR (%)
Carboplatin [27]	300 mg/m^2 q 4 weeks	Prior chemo	17	0
Carboplatin [27]	400 mg/m^2 q 28 days	Chemo-naïve	33	24
Cisplatin [28]	50 mg/m^2 q 3 weeks	Chemo-naïve	11	36
Cisplatin [29]	50 mg/m^2 q 3 weeks	Prior chemo	25	4
Cisplatin [30]	50 mg/m^2 q 3 weeks	Chemo-naïve	49	20
Cisplatin [31]	50–100 mg/m^2 q 4 weeks	Chemo-naïve	26	42
Cisplatin [32]	60 mg/m^2 q 21 days	Chemo-naïve	14	21
Cisplatin [33]	3 mg/kg q 3 weeks	Prior chemo	13	31
Cyclophosphamide [34]	666 mg/m^2 q 3 weeks	Chemo-naïve	19	0
Cyclophosphamide [35]	1200 mg/m^2/24 h q 3 weeks	Chemo-naïve	14	14
Cyclophosphamide [35]	1200 mg/m^2/24 h q 3 weeks	Prior chemo	15	0
Dactinomycin [36]	2 mg/m^2 q 4 weeks	Prior chemo	25	12
Docetaxel [37]	35 mg/m^2 q week	Chemo-naïve	34	21
Docetaxel [38]	70 mg/m^2 q 3 weeks	Chemo-naïve	19	37
Docetaxel [38]	70 mg/m^2 q 3 weeks	Prior chemo	13	23
Doxorubicin [34]	50 mg/m^2 q 3 weeks	Chemo-naïve	21	19
Doxorubicin [34]	50 mg/m^2 q 3 weeks	Prior chemo	9	11
Doxorubicin [39]	60 mg/m^2 q 3 weeks	Chemo-naïve	43	37
Epirubicin [40]	80 mg/m^2 q 3 weeks	Chemo-naïve	27	26
Oxaliplatin [41]	130 mg/m^2 q 21 days	Prior chemo	52	13.5
Liposomal doxorubicin [42]	40 mg/m^2 q 4 weeks	Chemo-naïve	52	11.5
Liposomal doxorubicin [43]	40 mg/m^2 q 4 weeks	Chemo-naïve	22	36
Liposomal doxorubicin [44]	40 mg/m^2 q 4 weeks	Prior chemo	19	22
Liposomal doxorubicin [45]	50 mg/m^2 q 4 weeks	Prior chemo	42	9.5
Paclitaxel [46]	175 mg/m^2 q 3 weeks	Prior chemo	19	37
Paclitaxel [47]	170 mg/m^2 q 3 weeks	Prior chemo	7	43
Paclitaxel [48]	200 mg/m^2 q 3 weeks	Prior chemo	44	27
Paclitaxel [49]	210 mg/m^2 q 3 weeks	Chemo-naïve	10	60
Paclitaxel [49]	210 mg/m^2 q 3 weeks	Prior chemo	13	7.7
Paclitaxel [50]	250 mg/m^2/24 h + G-CSF q 21 days	Chemo-naïve	28	36

RR response rate
G-CSF granulocyte colony-stimulating factor

[61]. The combination regimen produced better response rates (54 % versus 36 %), but there was no significant difference in OS (7.6 months versus 9.4 months, $p = 0.071$). A subsequent study randomized chemotherapy-naïve women with stage III or IV disease to ifosfamide alone or ifosfamide plus paclitaxel [62]. The combination arm produced a significant improvement in response rate, PFS, and OS (HR 0.69; 95 % CI 0.49–0.97; $p = 0.03$). In the phase II setting, carboplatin and paclitaxel have demonstrated an RR of 54 % with acceptable toxicity in 55 patients [63]. An ongoing phase III clinical trial is comparing the combination of carboplatin and paclitaxel to the standard ifosfamide and paclitaxel in this disease (GOG 261).

New Directions

A greater understanding of cancer biology and major advances in biotechnology in the last decade have led to the development of agents targeted against specific abnormalities in cancers, especially to aberrant growth signal transduction and microenvironment factors. A number of these novel therapeutic agents are currently being investigated in advanced endometrial cancer. Agents of interest include erlotinib (an EGFR tyrosine kinase inhibitor), trastuzumab (an epidermal growth factor receptor inhibitor), antiangiogenics (bevacizumab, cediranib among others), and mTOR inhibitors

Table 3 Chemotherapy for endometrial cancer: beyond TAP

Chemotherapy	Dose	Population	*N*	RR (%)
Etoposide IV [66]	100 mg/m^2 days 1, 3, 5 q 28 days	Prior chemo	29	3
Etoposide PO [67]	50 mg/day × 21 days q 28 days	Chemo-naïve	44	14
Etoposide PO [68]	50 mg/m^2 × 21 q 28 days	Prior chemo	22	0
Ifosfamide [69]	1.2 g/m^2/day × 5 days q 4 weeks	Chemo-naïve	33	24
Gemcitabine [70]	800 mg/m^2 IV q 21 days	Prior chemo	24	4
Cisplatin + Gemcitabine [53]	P: 30 mg/m^2 IV, G: 900 mg/m^2 IV q 21 days	Prior chemo	21	50
Ifosfamide [71]	1.2 g/m^2/day × 5 q 4 weeks	Prior chemo	40	15
Ifosfamide [35]	5 g/m^2/24 h q 3 weeks	Chemo-naïve	16	25
Ifosfamide [35]	5 g/m^2/24 h q 3 weeks	Prior chemo	16	0
Ixabepilone [72]	40 mg/m^2 IV q 21 days	Prior chemo	52	12
Methotrexate [73]	40 mg/m^2/week	Chemo-naïve	33	6
Topotecan [51]	0.5–1.5 mg/m^2 × 5 q 21 days	Prior chemo	22	9
Topotecan [52]	0.8–1.5 mg/m^2 × 5 days q 21 days	Chemo-naïve	40	20
Vinblastine [57]	1.5 mg/m^2/24 h × 5 days q 3 weeks	Chemo-naïve	34	12
Vincristine [74]	1.4 mg/m^2 q week × 4 then q 2 weeks	Chemo-naïve	33	18
Vincristine [75]	0.25–0.5 mg/m^2 CIV × 5 days	Prior chemo	5	0

RR response rate
G-CSF granulocyte colony-stimulating factor

Table 4 Targeted therapies for recurrent endometrial cancer

Biologic agent	Dose	Population	*N*	RR (%)
Bevacizumab	15 mg/kg IV q 21 days	Prior chemo	56	13.5
Bevacizumab + temsirolimus [76]	B: 10 mg/kg q 14 days, T: 25 mg IV weekly	Prior chemo	53	24.5
Erlotinib [77]	150 mg daily	Chemo-naïve	34	12.5
Everolimus + Letrozole [65]	E: 10 mg PO daily, L: 2.5 mg PO daily	Prior chemo	38	32
Pilaralisib [64]	600 mg PO daily or 400 mg PO daily	Prior chemo	67	6
Trastuzumab [78]	4 mg/kg week 1 then 2 mg/kg weekly	Prior chemo	34	0

(everolimus, temsirolimus, and the novel dual-mTOR inhibitors). PI3K, AKT, and dual-mTOR inhibitors are also under investigation for this disease, some with disappointing results as single agents [64]. Metformin, a widely available oral biguanide, is also being studied in GOG protocol 286 in combination with chemotherapy for advanced endometrial cancer. In addition to its role in inhibiting gluconeogenesis, metformin is postulated to act as a dual-mTOR inhibitor in endometrial cancer cells. A recently published phase II study of the combination of everolimus and letrozole reports an objective response rate of 32 % in 38 patients who were previously considered incurable, with up to two prior cytotoxic chemotherapies. Nine complete responses were achieved with 15 cycles as the median number of cycles among responders. None of the patients in this promising trial discontinued therapy based on toxicity [65]. There is increasing opportunity to incorporate biologic agents in the treatment of women with advanced endometrial cancer; future directions include implementing small-molecule inhibitors to extend the role of systemic therapies and further improve patient outcomes (Table 4).

Conclusions

- Patients with advanced or recurrent endometrial carcinoma have a median survival of about a year.

- Platinum/taxane-based chemotherapy produces response rates between 40 and 60 % in the setting of metastatic endometrial carcinoma.
- A survival benefit has recently been demonstrated for the use of adjuvant chemotherapy in stage III endometrial carcinoma.
- Uterine carcinosarcomas are aggressive cancers with a 35 % overall 5-year survival. Preliminary data suggest a benefit to adjuvant chemotherapy.

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