Treatment for Advanced and Recurrent Endometrial Carcinoma: Combined Modalities

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the role of radiation therapy for advanced stage endometrial cancer in order to differentiate between patients who should receive only radiation therapy and patients requiring surgery and/or chemotherapy in addition to radiation.
2. Evaluate the role of surgery for stage IV and recurrent endometrial cancer in order to select patients most likely to benefit from cytoreductive surgery.
3. Evaluate the role of chemotherapy, particularly in conjunction with radiotherapy, in advanced stage endometrial carcinoma and select appropriate candidates for multimodality therapy.

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ABSTRACT

Women with recurrent or advanced endometrial cancer constitute a heterogeneous group of patients. Depending on previous treatment, women with recurrent endometrial cancer may be appropriate candidates for surgery, radiation therapy, hormonal therapy, or chemotherapy. Women with advanced stage disease at pre-

sentation may also be appropriate candidates for systemic and local therapies. We review the treatment options available to treat recurrent and locally advanced endometrial cancer.

Treatment choice depends largely on the localization of disease, the patient's performance status and previ-

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ous treatment history, as well the tumor's hormonal receptor status. Radiation therapy is appropriate for isolated vaginal recurrences in patients with no previous history of radiation therapy. Patients with recurrent low-grade tumors overexpressing estrogen and progesterone receptors may be treated with progestin

therapy. Systemic therapy is appropriate for patients with disseminate recurrences or advanced stage disease at presentation, or for those with receptor-negative tumors. We review all these different treatment strategies available to patients with advanced or recurrent endometrial cancer. *The Oncologist* 2010;15:852–861

TREATMENT OF ADVANCED AND RECURRENT CARCINOMA: COMBINED MODALITIES

Endometrial cancer is generally associated with a good prognosis, largely because of the fact that approximately 75% of patients present with stage I disease and 13% of patients present with stage II disease [1]. For early-stage disease, surgery alone or in combination with local therapy is generally curative. For patients with stage III or stage IV disease and for those with recurrent endometrial cancer, the prognosis remains poor and the optimal adjuvant therapy is yet to be established. A subset of these patients may benefit from hormonal manipulation, systemic chemotherapies, or combination treatment with volume-directed radiotherapy and systemic chemotherapy. The choice of therapy depends on the extent of residual disease after initial surgery, site and nature of the recurrence, prior therapy used, and intent of treatment, be it curative or palliative. This review focuses on combined treatment modalities for this group of women.

RADIATION THERAPY

The following section reviews the role of radiation therapy in the management of women with locally recurrent and advanced endometrial cancer.

Radiation Therapy for Locally Recurrent Endometrial Cancer

Important prognostic factors affecting survival in patients with recurrent endometrial cancer include site of recurrence, previous treatment with radiation therapy, relapse-free interval, and histology. A longer relapse-free interval, low-grade histology, isolated vaginal recurrence, and endometrioid adenocarcinomas are factors associated with longer survival in recurrent endometrial cancer patients [2, 3]. In general, patients with tumors of nonendometrioid histologies have a worse prognosis than those with tumors of endometrioid histologies. Women with recurrent endometrial cancer following primary surgical treatment alone may be appropriate candidates for radiation therapy.

For a select group of patients not previously radiated and with small vaginal recurrences, radiation therapy may be curative. The use of primary radiation therapy influences sites of recurrence and survival after relapse. As docu-

mented by the Post Operative Radiation Therapy in Endometrial Carcinoma trial, survival is longer for women with recurrent disease not previously treated in the adjuvant setting with radiation therapy [4, 5]. In that trial, women with stage I disease, not all of whom had complete surgical staging, were randomized to surgery alone or in combination with adjuvant pelvic radiation therapy [4, 5]. At 3 years, the actuarial survival rate for women, after any relapse, in the nonradiation therapy group was 51%, compared with 19% for women in the adjuvant radiation therapy group ($p = .004$) [4, 5]. After an isolated vaginal cuff recurrence, the 5-year survival rate for the nonradiated group was 65%, compared with 43% for women randomized to the adjuvant radiation therapy arm of the study [4, 5]. For women treated with radiation therapy in the recurrent setting, the long-term survival rate is reported to be in the range of 18%–71% [6–9]. The 5-year survival rate for these women is documented to be in the range of 25%–50% [9–11].

At the time of relapse, both the anatomic site of recurrence and tumor size predict the likelihood of achieving successful local control. Local control, defined as eradicating pelvic disease, is possible in 40%–75% of women treated with salvage radiation therapy [3, 7, 9, 11]. In a series of 91 patients with isolated vaginal recurrences, local control was seen in 75% of those treated with salvage radiation therapy [9]. Tumor size at the time of recurrence also influences local control. In a series of 58 women with recurrent endometrial cancer, the 5-year local control rate was 80% for those with tumors ≤ 2 cm, compared with 54% for those with larger tumors. ($p = .02$) [11]. Women with noncentral tumor recurrences have a worse prognosis than those with an isolated vaginal relapse. Although only limited experience exists, salvage radiation therapy may be appropriate in the setting of a noncentral recurrence [12]. For women with a pelvic recurrence, the 3-year survival rate is reported to be 8%, compared with 73% for those with an isolated vaginal recurrence [4, 5]. This survival rate is comparable with the 3-year survival rate for patients with distant metastases [4, 5].

Patients with vaginal recurrences are usually treated with a combination of pelvic radiation and brachytherapy. Women with a previous history of pelvic radiation therapy

Table 1. Surgical cytoreduction for stage IV endometrial cancer

Study	n of patients	Residual tumor diameter	Median survival (mos)
Goff et al. (1994) [20]	47	Resected	18
		Unresected	8
Chi et al. (1997) [19]	55	≤2 cm	31
		>2 cm	12
		Unresected	3
Bristow et al. (2000) [18]	65	Microscopic	40
		≤1 cm	15
		>1 cm	11

who then develop an isolated vaginal recurrence are treated with brachytherapy alone [13]. In the presence of bulky disease, interstitial brachytherapy with supplementary external-beam radiation therapy has been reported to result in excellent pelvic control rates [13, 14]. It is important to underscore that, in the setting of recurrent disease, higher doses of radiation therapy than those used in the adjuvant setting are required. As a result, 3%–12% of patients suffer from severe treatment-related side effects, especially in the gastrointestinal tract [3, 6, 9, 14]. Patients with a previous history of radiation therapy are especially susceptible to severe toxicity at the time of radiation therapy in the recurrent setting [6, 14].

Radiation Therapy for Advanced Stage Endometrial Cancer

Approximately 5%–10% of patients with endometrial cancer present with clinical stage III disease [15]. Stage III disease, unfortunately, includes women with quite varying risks. For example, the ultimate outcome for women with positive cytology as their only risk factor is obviously quite different from that of patients with multiple positive pelvic or para-aortic lymph nodes. Radiotherapy alone as primary treatment for these patients carries a 5-year survival rate of 15%–40% and is associated with a high rate of distant failures, and as such surgery is often the mainstay of therapy [15]. The high rate of distant failure supports the use of systemic therapy for some of these patients and not just the use of radiation therapy. The role of adjuvant therapy and, more importantly, the type of adjuvant treatment for women with stage III disease remain controversial.

The role of postoperative radiation therapy in conferring a survival advantage in patients with stage III endometrial cancer may be related to the impact of gross residual lymph nodal disease prior to initiating radiation therapy. In the Gy-

necologic Oncology Group study 33 (GOG 33), the documented 5-year survival rate for patients with para-aortic radiation therapy was noted to be 36% [16]. In that series, 16 patients had pathologically confirmed para-aortic nodal and pelvic nodal disease prior to the initiation of radiation therapy [16]. The radiation dose administered was in the range of 4,500–5,075 cGy, delivered through 8-cm wide by 18-cm long portals, starting from the pelvic brim [16]. The documented 5-year survival rate for patients with both para-aortic and pelvic nodal disease was 43%, compared with 47% for those with para-aortic nodal disease only [16]. This difference was not statistically significant. In a series of 18 patients with para-aortic nodal disease treated with radiation therapy, the 5-year overall survival rate for patients with microscopic nodal disease was noted to be 67%, compared with 17% for patients with gross para-aortic nodal disease prior to commencing radiation therapy [17].

SURGERY FOR STAGE IV AND RECURRENT ENDOMETRIAL CANCER

Cytoreductive surgery may play a role in the management of women with stage IV endometrial cancer. Several retrospective studies suggest a survival advantage in those patients who have their tumor optimally cytoreduced (Table 1) [18–20]. In all three series, successful cytoreduction was a statistically significant prognostic variable on multivariate analysis. In the work by Bristow et al. [18], young age (<58 years old) and a good performance status was also predictive of survival. Chi and his colleagues saw no difference in survival for those women who presented with optimal stage IV disease (defined as having unresectable carcinomatosis at initial evaluation and not undergoing cytoreduction at all) and those who had a disease burden that was surgically cytoreduced to an optimal extent (defined as a largest residual tumor nodule diameter ≤2 cm), suggesting the importance of aggressive surgery in addition to the role that tumor biology may play in dictating survival [19].

Recurrent disease isolated to the central pelvis following radiation therapy is rarely seen. Selected patients with such a recurrence may be candidates for pelvic exenteration [21, 22]. Pelvic exenteration has been associated with significant operative morbidity and poor overall survival in the setting of recurrent endometrial cancer [21, 22]. In a series of 44 patients, nine long-term survivors were seen [22]. This highly morbid procedure may be the only potentially curative alternative for selected patients with a central recurrence following initial surgery and radiation therapy. However, radical pelvic resection and extended pelvic resection in conjunction with intraoperative radiation have also been described [23]. In that study, the reported overall 5-year survival rate was 47%, versus 71% for those with a

gross total resection but close margins. The authors report that, at the time of study publication, two patients in their series with recurrences limited to the para-aortic area were alive without evidence of disease at 54 months and 71 months [23].

Surgical resection may be appropriate for some women with recurrent endometrial cancer. Pelvic exenteration, for example, is often entertained in the setting of central recurrences. Two recent retrospective analyses explored the role of surgery in this setting. Scarabelli and his colleagues operated on 20 women at the time of their first pelvic or abdominal recurrence [24]. Patients were classified as having no residual tumor or having tumor at the end of surgery [24]. Postoperative therapy was at the discretion of the treating surgeon but included both radiation and chemotherapy. Sixty-five (65%) patients were left with no residual disease and had median progression-free survival (PFS) and overall survival times of 9.1 months and 11.8 months, respectively. This was statistically significantly better than the survival times for those who were left with disease. The PFS interval for that group of women was 1.5 months, and none were alive 9 months after surgery. There were two perioperative deaths, but otherwise morbidity was acceptable [25]. Another review, by Campagnutta et al. [25], is an updated analysis from the same group in Italy. In that series of 75 patients, 56 (75%) were left with no residual disease, but at a significant cost, with a 30% rate of major surgical complications and an 8% postoperative mortality rate [25]. Those patients who did achieve optimal tumor cytoreduction had a higher cumulative 5 year survival rate, 36% versus 0%, when compared with those with residual disease [25]. In another retrospective study, evaluating the role of surgery in the management of women with recurrent endometrial cancer, 35 patients underwent salvage cytoreductive surgery, with a reported median survival time of 28 months, compared with 13 months for patients treated nonsurgically ($p < .0001$). In that investigation, complete cytoreduction (no gross residual disease) was achieved in 23 of 35 surgical patients (65.7%). A median postrecurrence survival time of 39 months was reported for patients undergoing complete salvage cytoreduction, compared with 13.5 months for patients with gross residual disease ($p = .0005$). On multivariate analysis, salvage surgery and residual disease status were significant and independent predictors of postrecurrence survival [26]. Given the improvement in survival documented in these reviews, women with recurrent disease should be considered for surgical resection when appropriate. The reported morbidity and mortality of surgery highlight the importance of appropriate patient selection prior to embarking on this management strategy of recurrent disease.

SYSTEMIC THERAPY

i.p. Chromic Phosphate

The management of patients with positive peritoneal cytology as their only risk factor is now a historical challenge, given the new Fédération Internationale de Gynécologie et d'Obstetrique (FIGO) staging system. The new FIGO staging system for endometrial cancer no longer incorporates cytology results as part of the staging criteria but does require that cytology information be collected. The new staging system may not alter the management of patients with positive washings because these patients no longer have tumors upstaged to stage IIIA because of positive cytology. To date, however, patients with FIGO stage IIIA disease have been treated via numerous modalities, including hormonal treatment, whole abdominal radiation therapy, and i.p. chromic phosphate. In a series of 22 patients with stage IIIA endometrial cancer, either defined as positive peritoneal cytology and/or adnexal metastases, the reported 5-year disease-free survival rate was 90% with the use of whole abdominal radiation therapy [15].

Historically, i.p. chromic phosphate has been used in the treatment of stage III endometrial cancer. The reported 2-year disease-free survival rate in a study of 65 patients with clinical stage I–III disease following the administration of i.p. chromic phosphate, for patients with stage I disease and positive peritoneal cytology, was documented to be 94% [24]. The administration of i.p. chromic phosphate with whole pelvic radiation therapy in that study led to gastrointestinal tract toxicity, requiring surgical intervention in 29% of patients [27]. Although i.p. chromic phosphate resulted in adequate disease-free survival, its concomitant use with radiation therapy is not appropriate, given the toxicity profile noted above. In a study by Creasman et al. [28] of 23 patients with positive peritoneal cytology treated with i.p. chromic phosphate, the recurrence rate was documented to be 13%, with a mortality rate of 9%. The highly controversial issue of positive peritoneal cytology as an isolated risk factor is evident in this study. Forty-six percent of patients with positive peritoneal cytology as an isolated factor were noted to be at risk for carcinomatosis recurrence and death [28].

Chemotherapy

In an attempt to try to improve on the outcome of patients treated with radiation alone, many have tried to combine cytotoxic chemotherapy with radiation. The safety and efficacy of combined postoperative chemoradiation have been demonstrated in both ovarian and cervical carcinoma patients [29–32]. The use of multimodality therapy in endometrial cancer addresses the fact that most relapses after adjuvant radiation occur outside the radiated field. Clearly

there is a need for both local and systemic control in advanced staged endometrial cancer. Multiple different chemotherapy agents have been combined with both volume-directed and whole abdominal chemotherapy with acceptable toxicity and response rates (Table 2) [33–37]. All these studies, unfortunately, are limited by their small size.

The GOG recently published the results of a phase III randomized trial for women with stage III disease and with low-volume stage IV disease (<2 cm residual disease following surgical resection) [38]. In that trial, patients were randomized to either whole abdominal radiation therapy or combination chemotherapy (cisplatin plus doxorubicin) [38]. A significant PFS and overall survival benefit for patients treated with combination chemotherapy was noted, when compared with the PFS and overall survival outcomes in patients treated with whole abdominal radiation (hazard for death, 0.68; 95% confidence interval, 0.52–0.89; $p < .01$). That trial commenced accrual in 1992, and since then radiation techniques, chemotherapeutic regimens, and supportive care measures have improved so that these patients have more options than available in the early 1990s [39]. As noted by Fleming, the GOG 122 study raised the question of the appropriateness of combining radiation therapy and chemotherapy for these patients [39]. In the GOG 184 trial (Table 3), radiation therapy was administered to involved fields (either the pelvis or the pelvis and the para-aortic lymph nodes) with subsequent delivery of six cycles of chemotherapy. The randomization in the GOG 184 trial was to different chemotherapeutic regimens—doxorubicin plus cisplatin versus doxorubicin, cisplatin, and paclitaxel. Accrual to the GOG 184 study is complete. Results will be available for publication in the next several years.

Both the appropriate timing of initiating chemotherapy treatment and the most appropriate agents to use remain controversial. It is unclear whether systemic treatment should be delivered prior to radiation, after radiation, or as a “sandwich” technique, with some chemotherapy delivered before and some delivered after radiation. The GOG continues to investigate multimodality therapy, and until the results of these studies mature, the answers to many of these questions will not be answered (Table 3).

Hormonal Therapy

The knowledge that the development of endometrial cancer is associated with excess estrogen production has resulted in the use of a variety of progestational agents in the treatment of endometrial cancer [40, 41]. Several agents have been used in the setting of recurrent and metastatic endometrial cancer. These agents include medroxyprogesterone acetate (MPA), hydroxyprogesterone caproate, and megestrol acetate. Reported response rates include 14%–53% for

MPA, 9%–34% for hydroxyprogesterone caproate, and 11%–56% for megestrol acetate [41–48]. Overall, response rates of 30%–35% have been reported [41–48]. Recent data suggest that the response rate to progestational therapy may be only 15%–20% [47, 49]. Responses to progestational agents are usually of short duration, with an observed median time of 4 months [50].

In the past, for patients with malignant cytology, the use of hormonal therapy was embraced as a potential treatment strategy. In a series of 45 patients with malignant cytology as their only risk factor for adjuvant treatment, all treated with progesterone therapy, 80% were noted to have estrogen receptor (ER)⁺ tumors and 90% were documented to have progesterone receptor (PgR)⁺ tumors [51]. Thirty-six of them underwent a second-look laparoscopic procedure, with 94.5% having no evidence of disease [51]. The remaining two patients were treated with progesterone therapy for an additional 2 years and had a negative third-look laparoscopy [51]. Importantly, there were no documented recurrences or disease-related death [51].

Combination Hormonal Therapy

The effectiveness of progestational agents has been theorized to be increased with the use of estrogenic compounds, such as tamoxifen [51, 52]. Estrogenic substances have been documented to increase PgRs in human endometrial cancers [51, 52]. Progestins may downregulate the PgR concentration so that the reduced effectiveness of progestational agents and their short duration may be the result of PgR depletion in tumors treated with these agents [51]. It has also been postulated that agents augmenting the PgR concentration, such as tamoxifen, may potentiate the effectiveness of progestin-based therapy [51]. Tamoxifen has been associated with a 10%–22% response rate in the treatment of endometrial cancer [53, 54].

Most studies have correlated response rates to hormonal agents with tumor grade [47, 55, 56]. The documented response rate for grade 1 tumors has been reported as 37%, significantly better than for grade 3 tumors, with a reported response rate of only 9% [47]. In this GOG study, the median survival durations were also significantly longer for patients with grade 1 tumors than for those with grade 3 tumors (18.8 months and 6.9 months, respectively). However, because patients with well-differentiated tumors have a significantly longer survival time than patients with less well-differentiated tumors regardless of therapy, interpretation of the impact that hormone therapy has on survival may be confounded.

Several studies have investigated combined therapy with progestational agents and tamoxifen in recurrent and advanced endometrial cancer patients. In an Eastern Coop-

Table 2. Phase I and II trials evaluating combination chemotherapy and radiation therapy in the management of stage III/IV and high-risk endometrial carcinoma patients

Study	Stages	Patients	Regimen	Comments
Duska et al. (2005) [33]	III/IV, HR	20	TAC f/b 45 Gy WPRT	SBO X2; 13 NED at median follow-up of 16 mos
Soper et al. (2004) [34]	III/IV	10	30 Gy WART + CDDP f/b Dox + CDDP	7 of 10 patients received CT; grade 4 neutropenia, 10 of 10 patients; 5 episodes FN; median survival, 14 mos
Bruzzzone et al. (2004) [35]	III/IV	45	CDDP + Epidox + cyclophosphamide f/b 50 Gy WPRT	Grade 4 neutropenia, 8% 9-yr PFS, 30%; OS, 53%
Frigerio et al. (2001) [36]	HR	13	Paclitaxel + 50 Gy WPRT	Minimal toxicity; no survival data
Greven et al. (2004) [37]	HR	46	45 Gy WPRT + CDDP f/b CDDP + paclitaxel	Grade 4 hematologic toxicity: RT, 2%; CT, 62%. 2-yr DFS, 83%; OS, 90%

CT regimens: Duska et al. [33]: TAC = paclitaxel (160 mg/m²), Dox (45 mg/m²), carboplatin (AUC 5); Soper et al. [34]: CDDP (15 mg/m²) with RT, Dox (50 mg/m²), CDDP (50 mg/m²); Bruzzzone et al. [35]: CDDP (50 mg/m²), Epidox (60 mg/m²), cyclophosphamide (600 mg/m²); Frigerio et al. [36]: paclitaxel (60 mg/m²); Greven et al. [37]: CDDP (50 mg/m²) on days 1 and 28 of WPRT, CDDP (50 mg/m²), paclitaxel (175 mg/m²).

Abbreviations: AUC, area under the concentration–time curve; CDDP, cisplatin; CT, chemotherapy; DFS, disease-free survival; Dox, doxorubicin; Epidox, epidoxorubicin; f/b, followed by; FN, febrile neutropenia; HR, high-risk endometrial cancer (papillary serous, clear cell, advanced stage); NED, no evidence of disease; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SBO X2, two small bowel obstruction events; WART, whole abdominal radiotherapy; WPRT, whole pelvic radiotherapy.

Table 3. Current Gynecologic Oncology Group trials for patients with stage III/IV endometrial cancer

Study no.	Eligibility	Regimen
184	Stage III, <2 cm	WPRT with or without PA or VB f/b CDDP and doxorubicin with or without paclitaxel
209	Stage III/IV, measurable disease	CDDP (50 mg/m ²) + doxorubicin (45 mg/m ²) + paclitaxel (160 mg/m ²) versus carboplatin (AUC 6) + paclitaxel (175 mg/m ²)
9907	Stage III/IV, <2 cm	WART with weekly CDDP (25 mg/m ²) + paclitaxel (20 mg/m ²)
9908	Stage III/IV, <2 cm	Doxorubicin + CDDP f/b WART
258	Stage III/IVA, <2 cm	CDDP-based chemoradiation therapy (tumor volume–directed radiation) f/b carboplatin and paclitaxel versus carboplatin and paclitaxel alone

Abbreviations: AUC, area under the concentration–time curve; CDDP, cisplatin; f/b, followed by; PA, para-aortic; VB, vault brachytherapy; WART, whole abdominal radiotherapy; WPRT, whole pelvic radiotherapy.

erative Oncology Group study, there was no difference in the response rate between patients treated with megestrol acetate as a single agent and those treated with the combination of tamoxifen and megestrol acetate [57]. In a GOG study of alternating tamoxifen and megestrol in the treatment of advanced or recurrent endometrial cancer patients, an overall response rate of 26% was noted [58]. In that trial, megestrol (80 mg twice daily) was given for 3 weeks, followed by tamoxifen (20 mg twice daily) for 3 weeks [58]. In another recent GOG study, patients with advanced endometrial cancer were treated with tamoxifen (20 mg twice daily) plus alternating weekly cycles of medroxyprogesterone (100 mg twice daily) [59]. The response rate was 33%, with

a median PFS interval of 3 months and median overall survival time of 13 months [59]. The results of that trial demonstrate the promising activity of combination daily tamoxifen and intermittent weekly medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial cancer patients [59]. The PFS and median survival times in that trial were similar to those reported for progestin therapy alone [43, 45, 49]. The reported adverse effects were also comparable with those reported in series of patients treated with hormonal therapy. However, the reported 33% response rate is one of the highest seen among the GOG trials investigating the use of hormonal therapy in patients with advanced or recurrent endometrial cancer. Com-

bination hormonal therapy for advanced or recurrent endometrial cancer is an attractive treatment alternative for selected patients, especially those with hormone receptor-positive tumors. The potential response rate and the low toxicity profile associated with these agents make them a suitable therapeutic first choice for many such patients.

Combination Chemohormonal Therapy

Combination regimens using chemotherapy with hormonal therapy have also been investigated in the treatment of advanced and recurrent endometrial cancer. The use of chemotherapy alone for recurrent or advanced endometrial cancer is discussed in detail in a different section. Only a few studies have evaluated the use of chemotherapy concurrently with hormonal therapy. These investigations have several, serious methodological limitations, are underpowered, and have not included the most active chemotherapeutic agents in endometrial cancer. Only a few of the phase II clinical trials have accrued in excess of 20 patients. These trials document response rates in the range of 40%–50%, similar to the response rates seen with combination chemotherapeutic regimens without hormonal therapy [60, 61]. A limited number of randomized trials compared two different chemotherapeutic regimens containing progestins [60, 62]. In a study by Ayoub et al. [63], the use of cyclophosphamide, doxorubicin, and 5-fluorouracil was compared with the same treatment plus sequential medroxyprogesterone acetate alternating with tamoxifen. In that study of 43 patients, the response rate in the hormone-containing regimen was 43%, compared with 15% in the chemotherapy-only arm [63]. The documented median survival time for patients in the combination chemotherapy–hormone therapy arm was noted to be 14 months, compared with 11 months for the chemotherapy-only arm [49]. This difference in median survival times was not statistically significant [63].

In a study by Cornelison et al. [64], two groups of 50 women were treated during two different time periods. Both groups were treated consecutively and prospectively. Specifically, 50 consecutive patients were treated with melphalan, 5-fluorouracil, and medroxyprogesterone acetate as first-line therapy [64]. Fifty additional patients were treated prospectively and at a later time with cisplatin, doxorubicin, etoposide, and megestrol acetate [64]. The response rates for the two regimens were similar [64]. Significant advantages in terms of the 2-year survival rate (45% versus 14%), 5-year survival rate (30% versus 5%), and median survival duration (22 months versus 9 months) were seen with the second regimen (cisplatin, doxorubicin, etoposide, and megestrol acetate), when compared with the first regimen (melphalan, 5-fluorouracil, and medroxyprogesterone acetate) [64].

In a more recent study, 23 patients were treated with carboplatin, methotrexate, and 5-fluorouracil in combination with medroxyprogesterone acetate [65]. Seventy-four percent of patients had an objective response, with a long-lasting response seen in two patients (9%) [65]. The documented median response duration was >10 months (3 months to >45 months), with a median survival time >16 months (2 months to >45 months) [65]. The earlier trials failed to show that simultaneous chemotherapy and hormonal therapy is superior to the more traditional treatment strategy of using hormonal therapy followed by chemotherapy at the time of disease progression. The most recent trials are promising. However, the question of whether these regimens are better than paclitaxel-containing combination chemotherapy is not known and will require further investigation through a randomized trial.

THE FUTURE

For certain histologic subtypes of endometrial cancer, targeted therapies may be appropriate and more commonly embraced in the future. Approximately 17%–50% of uterine serous carcinomas overexpress the transmembrane receptor human epidermal growth factor receptor (HER)-2 [66–69]. It is thought that at least part of the aggressive biology associated with this histologic type of endometrial cancer may be related to the high levels of resistance to chemotherapy in vivo and to the natural killer cell- and complement-mediated cytotoxicity seen in vitro in cell lines that overexpress HER-2. Potential therapeutic options for serous carcinomas of the uterus may involve the anti-HER-2 monoclonal antibody trastuzumab or the orally active dual tyrosine kinase inhibitor affecting the epidermal growth factor receptor, lapatinib. The GOG recently published results of a phase II study evaluating the efficacy of single-agent trastuzumab in the treatment of advanced or recurrent HER-2⁺ endometrial carcinoma [70]. Trastuzumab was not active in treating endometrial carcinomas with HER-2 overexpression or *HER-2* amplification. Full planned accrual of women with *HER-2* amplified tumors was not reached secondary to slow study recruitment. In that study, serous and clear cell endometrial carcinomas were more likely to have *HER-2* amplification. The role that other targeted strategies may play in the treatment of advanced or recurrent endometrial cancer does, however, warrant further investigation through clinical trials.

Type I, estrogen-related endometrial cancer is associated with phosphatase and tensin homologue deleted on chromosome ten (*PTEN*) mutations [71–73]. *PTEN* activity suppression appears to be an early event in endometrial cancer development and has been noted in 55% of atypical hyperplastic and 83% of endometrial cancer lesions [71]. The

PTEN gene defect is associated with Akt hyperactivity. PTEN functions as a regulatory protein of the phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (mTOR) pathway primarily via the inhibition of Akt activation [74].

The mTOR pathway presents another opportunity for targeted therapy in the management of women with endometrial cancer. Activity of mTOR can be inhibited by rapamycin. Temsirolimus is a water-soluble rapamycin ester. In a phase II trial using this agent to treat 31 women with recurrent or metastatic endometrial cancer, a 26% partial response rate was documented, as well as a 63% stable disease rate [75]. Deforolimus, a selective nonprodrug mTOR inhibitor, was also evaluated via a phase II trial, conducted among 45 patients with advanced or recurrent endometrial cancer. In that study, 28% of the patients had a clinical response (complete response, partial response, or stable disease) for ≥ 16 weeks [76]. A third phase II trial with an mTOR inhibitor evaluated everolimus among 21 patients with advanced or recurrent endometrial cancer and documented stable disease in eight patients (53%) for a median time of 4.5 months [77]. mTOR inhibitors will require further investigation through the execution of larger scale trials and may prove to be an effective targeted strategy in the management of women with either advanced stage or recurrent endometrial cancer.

CONCLUSIONS

Locally advanced or recurrent endometrial cancer can be treated via surgery, radiation therapy, hormonal therapy, or chemotherapy. The treatment modality choice largely de-

pends on the localization of disease, the patient's performance status and previous treatment history, and the tumor's hormonal receptor status. Isolated vaginal recurrences in patients with no previous history of radiation therapy are amenable to primary treatment with radiation therapy. Patients with recurrent low-grade tumors that express ER and PgR may be treated with progestin therapy for prolonged periods of time, with adequate response rates and low toxicity. In the setting of hormone receptor–negative tumors or lesions that have progressed after hormonal therapy, chemotherapy offers another treatment alternative with modest response rates. Higher response rates and, potentially, a longer survival time may be reached through the use of combination chemotherapy, especially regimens containing paclitaxel, or with combinations of chemotherapy and hormonal therapy [78]. The best regimen is still unknown and the treatment choice should be based, again, on extent of disease recurrence, prior treatment history, and patient preference and performance status. The discovery of genetic alterations of several intracellular pathways in endometrial cancer offers the opportunity of adding targeted therapies to the treatment armamentarium in this disease. The optimal choice of agent, used alone or in combination therapy, awaits the results of larger scale clinical trials to verify these agents' efficacy and safety.

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