Chemotherapy and/or Targeted Therapies for Advanced Endometrial Cancer: Time to Rethink?

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Summary Points

- Historically, chemotherapy forms the backbone of standard treatment for endometrial cancer. Can the published data forming the basis of this recommendation be easily applied to the world of oncology today, or is there a need for updated information in the era of increased molecular profiling of tumors?
- Given the demographics of patients with endometrial cancer, can we aim for a more individualized approach to treatment which takes into account relevant prognostic molecular information, patient health, and quality of life preferences?
- Are the data available regarding novel targeted agents sufficient to propose a new standard for therapy?

Introduction

Ninety-five percent of cancers of the uterine corpus are carcinomas [1]. Most endometrial carcinomas present at an early stage and are cured by surgery with or without radiotherapy. As a result, advanced or recurrent endometrial carcinoma has been perceived as a rare tumor. However, the American Cancer Society estimates that about 8,100 women in the United States will die from cancers of the uterine body in 2011 and advanced or recurrent endometrial cancer remains an incurable disease with limited treatment options. Data from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) program suggest that the 5-year relative survival for women with metastatic uterine cancer between the years 2001 and 2007 was only 15.9 % and the median survival only 12 months.

Should Chemotherapy Be the Standard Treatment?

Considerable data exist regarding the utility of chemotherapy in the context of recurrent and metastatic endometrial cancer, the majority of which precede the era of targeted therapy options. As such, conventional chemotherapeutic agents represent the mainstay of treatment for endometrial cancer and constitute the standard of care to which all new treatments should be compared.

A number of chemotherapy agents are active in the treatment of endometrial cancer. Platinum drugs, anthracyclines, and taxanes have produced 20–30 % single-agent response rates in women with chemotherapy-naïve advanced endometrial cancer [2] (Table 6.1). Given the known activity of free doxorubicin, pegylated liposomal doxorubicin produced a disappointingly low response rate of 11.5 %. Interestingly, it produced almost the same level of activity in women with pretreated disease (9.5 %), raising the question of whether some unknown adverse selection factors were present in the women treated on the frontline trial (e.g., since up-front combination chemotherapy was already established at the time, perhaps less fit patients elected to participate in a trial of single-agent liposomal doxorubicin). 5-Fluorouracil has been reported to produce response rates in the range of 20 %, but the trials testing this agent are older and somewhat difficult to interpret with modern benchmarks. Alkylating agents

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and vinca alkaloids generally have shown lower levels of activity and significant toxicities at the doses and schedules tested [3].

Is Combination Drug Therapy Superior to Single-Agent Chemotherapy?

Combination chemotherapy produces higher response rates than single-agent therapy. It should be realized, however, that this does not always translate into improved survival and the risk factors common in the endometrial cancer population such as advanced age (median age at diagnosis around 65 years), poor performance status, medical comorbidities, and a history of prior pelvic radiation may increase the risk of chemotherapy associated toxicities [4]. Nonetheless, with dose reductions and/or growth factor support, treatment is usually tolerable, and combination cytotoxic therapy is currently the standard frontline approach for advanced endometrial cancer.

Table 6.1 First-line single-Agent chemotherapy in endometrial cancer

Drug	Dose	RR (%)
Cisplatin	50–100 mg/m^2	20–42
Carboplatin	360–400 mg/m^2	24–32
Cyclophosphamide	666–1,200 mg/m^2	0–14
Docetaxel	35–70 mg/m^2	21–31
Doxorubicin	50–60 mg/m^2	19–37
Epirubicin	80 mg/m^2	26
Etoposide, oral	50 mg	14
Liposomal doxorubicin	40 mg/m^2	12
Hexamethylmelamine	280 mg/m^2	9
Ifosfamide	1.2–5 g/m^2	12–25
Paclitaxel	210–250 mg/m^2	36–60
Methotrexate	40 mg/m^2	6
Topotecan	0.8–1.5 mg/m^2	20
Vinblastine	1.5 mg/m^2	12
Vincristine	1.4 mg/m^2	18

Data adapted from Obel et al. [3]

Reported response rates to various combinations range from 30 to 75 % with median remission durations of 6–12 months (Table 6.2) [13]. In the early 1990s, two randomized trials (see Table 6.2) showed improved response rates (over 40 % versus 25 % or less) and progression-free survival with the addition of cisplatin to doxorubicin therapy. Despite increased toxicity and tvhe lack of a clear survival benefit, doxorubicin/cisplatin-based therapy became the standard.

The feasibility of triplet chemotherapy regimens was tested in GOG 177, which was published in 2004. This phase III trial investigated the tolerability and efficacy of paclitaxel when added to the cisplatin/doxorubicin doublet. Filgrastim support was universally administered to avoid unacceptable bone marrow suppression. The three-drug regimen produced a superior response rate (57 % versus 34 %), PFS (median, 8.3 versus 5.3 months), and OS (median, 15.3 versus 12.3 months; $P = .037$). This triplet therapy became the only treatment shown to establish a survival benefit beyond results achieved with traditional doublet chemotherapy. However, the paclitaxel regimen produced significant neurotoxicity (≥ grade 2 in 39 % of patients) and required patients to come in on three successive days due to the recommended splitting of paclitaxel and doxorubicin and cisplatin treatments in an attempt to minimize cardiotoxicity and neurotoxicity. These

Table 6.2 Combination chemotherapy in chemotherapy-naïve endometrial cancer

Trial	Regimen	# of pts	RR (%)	Median OS (month)
Thigpen et al. [5]	DOX 60 mg/m^2 q 3 weeks	132	22	6.7
	DOX 60 mg/m^2+ CTX 500 mg/m^2 q 3 weeks	144	30	7.3
Pawinski et al. [6]	CTX 1,200 mg/m^2	29	14	
	IF 5 mg/m^2 q 3 weeks	32	25	
Gallion et al. [7]	DOX 60 mg/m^2 + CDDP 60 mg/m^2 q 3 weeks (circadian)	169	46	11.2
	DOX 60 mg/m^2 + CDDP 60 mg/m^2 q 3 weeks	173	49	13.2
Aapro et al. [8]	DOX 60 mg/m^2 q 4 weeks	87	17	7
	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 4 weeks	90	43	9
Thigpen et al. [9]	DOX 60 mg/m^2 q 3 weeks	131	42	9.2
	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 3 weeks	132	22	9
Fleming et al. [10]	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 3 weeks	157	40	12.6
	DOX 50 mg/m^2 + PTC 150 mg/m^2/24 h + G-CSF	160	43	13.6
Fleming et al. [11]	DOX 60 mg/m^2 + CDDP 50 mg/m^2 q 3 weeks	129	34	12.3
	DOX 45 mg/m^2 + CDDP 50 mg/m^2 + PTX 160 mg/m^2 + G-CSF	134	57	15.3
Miller [12]	PTX 175 mg/m^2 + CPL AUC 6 q 3 weeks	663	51	36.5
	DOX 45 mg/m^2 + CDDP 50 mg/m^2 + PTX 160 mg/m^2 + G-CSF	532	51	40.3

IF ifosfamide, *DOX* doxorubicin, *CTX* cyclophosphamide, *CDDP* cisplatin, *PTX* paclitaxel, *CPL* carboplatin, *EORTC* Eastern Cooperative Oncology Group, *GOG* Gynecologic Oncology Group, *G-CSF* granulocytic colony-stimulating factor

factors limited widespread adoption of the regimen, and instead, carboplatin/paclitaxel, which produced good response rates in a number of phase II trials and was already widely used for ovarian cancer, became commonly used. A recent study with weekly paclitaxel and carboplatin in chemotherapy-naive and pretreated populations showed partial response rates of 50 and 39 %, respectively [14]. The GOG therefore conducted a large non-inferiority trial comparing carboplatin and paclitaxel (TC) to paclitaxel/cisplatin/doxorubicin (TAP) in approximately 1,300 women with advanced or recurrent endometrial cancer which has been reported in abstract form. Both regimens were repeated every 21 days for a maximum of seven cycles. Half of the patients in each arm had objective responses and 30 % had stable disease. Both arms had equivalent response rates for those patients with measurable disease (51 %), and neither progression-free survival nor median overall survival differed significantly. Overall survival was shown to be 40 months with TAP and 36 months with TC. With regard to toxicity, the TAP arm had significantly more thrombocytopenia, neutropenia, sensory neuropathy, nausea, diarrhea, and vomiting [12].

How Effective Is Second-Line Chemotherapy?

The efficacy of second-line cytotoxic chemotherapy remains very limited. Table 6.3 shows results of trials with standard available cytotoxic agents. Taxanes showed good activity in the days before taxane-containing therapy was the standard first-line approach [18]. Doxorubicin is one second-line treatment option based on efficacy results obtained from frontline trials. Other agents such as topotecan and gemcitabine have shown minimal efficacy in previously treated populations [19]. Novel chemotherapeutic agents continue to be investigated, and ixabepilone, a semisynthetic lactam derivative of epothilone B, produced a response rate of 12 % in paclitaxel-pretreated patients. This prompted a randomized phase III trial comparing ixabepilone to doxorubicin or paclitaxel monotherapy, the treatment choice being dependent on the patient's first-line treatment. This study unfortunately closed for futility (ref not yet available).

In an attempt to optimize the utility of chemotherapy, much effort is being made to elucidate factors which may be predictive of response to chemotherapy. GOG 209 is investigating the effect of hormone receptor status on response to chemotherapy, but results are not yet available. Investigations are also ongoing to determine whether endometrial carcinomas that overexpress or amplify topoisomerase II might show increased sensitivity to doxorubicin-based treatment. Selective overexpression of β-tubulin subtypes such as β-tubulin III (β-III) and β-V has been demonstrated to promote taxane resistance in cell lines derived from lung, ovarian, prostate, and breast cancers [20], but this has not been confirmed clinically. Microtubule inhibitors are hydrophobic in nature and are susceptible to efflux by the product of the multidrug-resistant gene (MDR-1) and multidrug resistance protein (MRP), but, again, no clinical trials have been able to predict resistance to taxanes based on expression of either of these proteins [21]. As such, selection of chemotherapy regimens remains empiric, and pooled data from several randomized phase III Gynecologic Oncology Group (GOG) trials involving standard chemotherapy regimens show no relationship between response and histology (serous, endometrioid, and clear cell) [22].

Table 6.3 Second-line single-agent chemotherapy trials in endometrial cancer

Drug	Dose	RR (%)
Cisplatin	50 mg/m^2	4
Etoposide, oral	50 mg/m^2	0
Ifosfamide	1.2 g/m^2	15
Oxaliplatin	130 mg/m^2	13.5
Gemcitabine [15]	800 mg/m^2	4
Paclitaxel	110–200 mg/m^2	27.3
Liposomal doxorubicin	50 mg/m^2	9.5
Topotecan	0.5–1.5 mg/m^2	9
Docetaxel	36 mg/m^2	7.7
Pemetrexed [16]	900 mg/m^2	3.8
Ixabepilone [17]	40 mg/^{2}	12

Data Adapted from Obel et al. [3]

Time for Something Better

There is no doubt that chemotherapies, with their well-established levels of efficacy and their predictable toxicities, do indeed form the backbone of the currently accepted management of metastatic endometrial cancers. However, it is equally important to acknowledge that benefit from chemotherapy is modest at best and that overall survival remains in the 1 year range in spite of treatment. It is important to ensure that women who undergo chemotherapy in order to control disease and to potentially prolong life do not do so at the expense of significant toxicities which adversely affect quality of life. Alternative treatments which are better tolerated and for which response is more easily predicted are vital for the development of individualized treatment algorithms.

The phenomenal advances made with regard to the understanding of cancer biology in recent years are responsible for the exponential rate at which the scientific world is able to accumulate tumor-related data of a molecular nature. These data are critical as it spurs the development of targeted agents developed to inhibit pathways considered critical in the proliferation of cancer. Such an understanding of the intracellular signaling pathways also enables the elucidation of biomarkers which can be assessed as predictors of response to treatments.

Targeting the Biology of Endometrial Cancer

It has been long recognized that endometrial carcinomas exhibit differing biologic characteristics and this observation led to the description by Bokhman of two distinct types of endometrial cancer representative of two models of tumorigenesis [23]. These have been described as type I and type II. Type I tumors comprise 80 % of endometrial carcinomas and are believed to be estrogen-driven. They are exemplified as having endometrioid histology with low grade and more often present in premenopausal women [24]. Type II tumors are archetypically of non-endometrioid histology such as serous or clear cell and are more often diagnosed in postmenopausal women. They tend to present at a more advanced stage and have a poorer prognosis at any stage relative to type I tumors of similar stage. Differences at the molecular level have been described more recently (Table 6.4). Mutations leading to aberrant functioning of the PTEN/PI3K/mTOR pathway have been noted in a large proportion of type I tumors but are rare in type II tumors. Conversely, mutations in the critical p53 gene are rare in type I tumors but present in almost all type II tumors. Knowledge of overactive or aberrant cell signaling pathways observed at high frequency in endometrial cancers forms the basis of targeted therapies.

Table 6.4 Molecular alterations in endometrial cancer

Gene alteration	Type I (endometrioid) (%)	Type II (non-endometrioid) (%)
PTEN loss	80	5
PTEN mutation	30–50	0–11
PIK3CA	30–40	20
P53 mutation	20	90
KRAS mutation	10–30	0–10
E-cadherin loss	5–50	60–90
HER-2 amplification	1	17
HER-2 overexpression	3–10	32
β-catenin mutation	15–50	0
Microsatellite instability	15–25	0–5

Data adapted from Westin and Broaddus [25]
PTEN phosphatase and tensin homolog deleted on chromosome 10, *PIK3CA* phosphatidylinositol 3-kinase catalytic, *HER* human epidermal growth factor receptor

Hormonal therapy may be considered as the "original targeted therapy." Evidence suggesting a central role for estrogen in the development of type I endometrial cancers made hormonal therapy an excellent candidate for proposed treatment of such disease. Because the uterine endometrium is sensitive to progesterone and estrogen, and because unopposed estrogen is a strong risk factor for the development of uterine cancer, hormone therapy traditionally played a significant role in the treatment of advanced endometrial carcinoma [26]. Advanced endometrial cancer patients with no prior chemotherapy have demonstrated response rates of 20–30 % to progestin-based therapies in a number of published studies (see Table 6.5). Some studies suggest that hormonal therapy is more likely to be beneficial in a selected population of patients with low-grade tumors that are estrogen and progesterone receptor-positive [39]. Grade 3 or poorly differentiated tumors infrequently respond to hormone therapy, and chemotherapy remains the generally preferred treatment for patients with metastatic, high-grade tumors [40]. However, it is inappropriate to categorically rule out hormonal therapy options in patients whose tumors do not express high levels of hormone receptor. ER and PR status remains a very imperfect predictor of response rates to hormonal therapy in this disease, and an 8–17 % objective response rate in women with hormone receptor-negative tumors has been reported [41]. Megestrol acetate 160 mg/day is the most commonly used progestin in the United States for the treatment of endometrial carcinoma. Dose

Table 6.5 Hormone therapy in advanced endometrial cancer

Authors	Drug	*N*	RR (%)	Median OS (mos)	Prior chemotherapy
Lentz et al. [27]	MGA 800 mg/day	54	24	7.6	No
Thigpen et al. [28]	MPA 200 mg/day	145	25	11.1	No
	MPA 1,000 mg/day	154	15	7.0	
Thigpen et al. [29]	TAM 40 mg/day	68	10	8.8	No
Whitney et al. [30]	MPA 200 mg/day every other wk and TAM 40 mg/day	61	33	13	No
Fiorica et al. [31]	MGA 160 mg/day × 3 weeks followed by TAM 40 mg/day × 3 weeks	61	27	14	No
Pandya et al. [32]	MGA 160 mg/day	20	20	12.6	No
	MGA 160 mg/day + TAM 20 mg/day	42	19	8.6	
McMeekin et al. [33]	Arzoxifene 20 mg/day	29	31	13.9	No
Covens et al. [34]	Leuprolide 7.5 mg q 28 days	25	0	6	Yes (two patients)
Lhomme et al. [35]	Triptorelin 3.75 mg q 28	28	8.7	7.2	Yes
Asbury et al. [36]	Goserelin 3.6 mg q day	40	11	7.3	Yes (one patient)
Rose et al. [37]	Anastrozole 1 mg/day	23	9	6	No
Ma et al. [38]	Letrozole 2.5 mg/day	28	9.4	6.7	Yes (adjuvant)

TAM tamoxifen, *MGA* megestrol acetate, *MPA* medroxyprogesterone acetate, *Mos* months

escalation to 1,000 mg/day did not improve median overall survival or response rates [27, 28]. Tamoxifen, a selective estrogen-receptor modulator (SERM), binds to estrogen receptors and produces both estrogenic and antiestrogenic effects, depending on the target tissue. Tamoxifen has been widely used in the treatment of breast cancer (it appears to primarily act as an antiestrogen in breast tissue), and in breast cancer trials, it causes a fourfold increase in the number of uterine cancers in postmenopausal women with an intact uterus (presumably because it acts as an estrogen agonist in endometrial tissue) [42]. Interestingly, single-agent tamoxifen has shown modest single-agent antitumor activity in the setting of metastatic endometrial cancer with a reported response rate of 10 %. A third-generation SERM, arzoxifene, produced a response rate of 31 % (1 CR and 8 PR) in tumors selected for low grade (1 or 2) or hormone receptor positivity [33]. Combinations of tamoxifen and progestins were tried based on the hypothesis that resistance to progestin therapy developed because of downregulation of progesterone receptors with progestin therapy and the fact that progesterone receptors could be upregulated by tamoxifen. Whitney et al. explored the relationship between the expression of centrally determined hormone receptor expression and response to a regimen of daily tamoxifen 20 mg twice daily and intermittent medroxyprogesterone acetate 100 mg twice daily on even weeks in 45 patients. The response rate overall was 33 % [30]. In this trial, the ER H score derived by immunohistochemical evaluation using monoclonal antibody to estrogen-receptor protein was significantly related to both response and overall survival, while there was no statistically significant correlation of PR with clinical response. In a subsequent phase II trial, the GOG tested the use of megestrol acetate 80 mg twice daily for 3 weeks alternating with tamoxifen 20 mg twice daily for 3 weeks in 56 women with advanced endometrial carcinoma who had not received prior chemotherapy or hormonal therapy. The overall response rate was 27 %, median progression-free survival was 2.7 months, and median overall survival was 14 months [31]. Aromatase inhibitors including letrozole and anastrozole have been investigated but showed response rates of less than 10 % [37, 38, 43]. One small trial testing the use of letrozole found no relationship between expression of centrally assayed ER or PR and response to therapy [38]. GnRH receptors have been identified on endometrial cancers, but most studies evaluating GnRH agonists have shown limited efficacy [35, 36, 44]. Benefit from hormonal therapy appears to be sequence dependent with patients receiving hormonal therapy after chemotherapy demonstrating poor response rates. A recent trial randomized women with 1–2 prior chemotherapy regimens to the mTOR inhibitor, ridaforolimus, or progestin therapy (with medroxyprogesterone 200 mg/day or megestrol 60 mg/day), and the response rate in the progestin therapy arm was only 4.3 % [45].

In vitro and nude mouse data have suggested that inhibiting the PI3K/AKT pathway reverses progestin resistance in endometrial cancer [46]. Recent results in breast cancer have shown that acquired resistance to hormonal therapy, both tamoxifen and exemestane, can be overcome by mTOR inhibition (exemestane/everolimus [47] and tamoxifen/everolimus [48] and tamoxifen/sirolimus [49] studies). In a phase III trial, 724 patients previously treated with nonsteroidal aromatase inhibitors with postmenopausal hormone-receptor-positive advanced breast cancer were randomized to combined everolimus and exemestane versus exemestane and placebo. At the interim analysis, the combination group demonstrated a median progression-free survival of 6.9 months compared to 2.8 months with exemestane plus placebo [47]. Unfortunately results in endometrial cancer to date have been less definitive. A phase II open-label single-arm study of the combination of everolimus and letrozole enrolled 28 patients who had received 1–2 prior chemotherapy regimens and showed a promising objective response rate of 21 % [50]. The GOG conducted a randomized phase II trial, GOG-0248, testing temsirolimus 25 mg IV weekly versus the combination of temsirolimus 25 mg IV weekly plus megestrol acetate 80 mg twice daily for 3 weeks alternating with tamoxifen 20 mg twice daily for 3 weeks. Unfortunately, the combination of temsirolimus with megestrol acetate/tamoxifen resulted in an unacceptable rate of venous thrombosis (7 events out of 22 patients), and the combination arm was closed to accrual after the first stage. The preliminary results indicated a 14 % partial response rate (3 out of 21 eligible patients) and no evidence of venous thrombosis in the single-agent temsirolimus arm [50, 51]. Publication of molecular marker data from these studies that may show subsets of patients most likely to benefit is awaited, but the addition of an mTOR inhibitor to hormonal therapy does add toxicity, such as hyperglycemia, asthenia, and mucositis.

While a few patients undoubtedly have major responses to hormonal therapy, the number is not large and median progression-free survival on trials of hormonal therapy is short. Newer targeted agents have thus far not been definitively demonstrated to increase sensitivity to hormonal therapy. The inability to select which patients benefit from therapy and the short overall progression-free survival reported in trials of hormonal therapy has dampened enthusiasm for first-line use of hormonal therapy. Indeed, a Cochrane database review found insufficient evidence that adjuvant hormonal therapy as a single-agent or as a combination treatment prolonged overall or 5-year disease-free survival in women with advanced or recurrent endometrial cancer [52].

Additional targeted agents have been investigated within the context of metastatic endometrial cancers. As with hormonal therapies, they are selective for a molecular receptor

present on a large proportion of endometrial cells and postulated to be central to regulation and proliferation mechanisms which are implicated in the survival of cancer cells.

The significant proportion of PTEN and PI3K mutations observed in type I endometrial cancers has implicated the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway in the development of endometrial cancer. This pathway is involved in cellular growth regulation, proliferation, motility, survival, protein synthesis, and transcription. It is considered to be a crucial checkpoint which when malfunctioning is implicated in tumorigenesis [53]. A series of intracellular proteins form the intracellular cascade of this pathway and include PTEN, PI3K, AKT, and mammalian target of rapamycin (mTOR). Mutations within any one of these proteins ultimately lead to the constitutional activation of mTOR, and drugs inhibiting the function of one or several of the proteins implicated in this pathway have been developed in the hope that inhibition of this cellular pathway will have cytotoxic capability.

Temsirolimus, an ester of the macrocytic immunosuppressive agent sirolimus (rapamycin), is a cytostatic cell cycle inhibitor with antitumor properties. It inhibits mTOR, a serine–threonine kinase involved in the initiation of mRNA translation and has demonstrated activity in several tumor types including renal cell carcinoma where it demonstrated improved progression-free survival and overall survival when compared to interferon alfa [54]. The scientific rationale for treating endometrial cancer with mTOR inhibitors led the NCIC CTG clinical trials group to assess the activity of temsirolimus in women with recurrent or metastatic endometrial cancer. Two single-arm phase II studies were conducted differentiating between chemo-naïve and chemotherapy-exposed patients receiving temsirolimus. The combined results of these trials were published by Oza et al. [55]. Of 29 evaluable chemo-naïve patients, four (14 %) demonstrated a confirmed partial response of 5.1 months median duration (range 3.7–18.4 months) and 20 (69 %) had stable disease with a median duration of 9.7 months (range 2.1–14.6 months). Only five patients (18 %) progressed while on treatment. Of the 25 patients previously exposed to chemotherapy, only one (4 %) had a partial response to treatment while 12 (48 %) showed stabilization of disease for a median duration of 3.7 months. The observation that activity rates vary significantly based on previous treatment status should be incorporated into the design of future studies in the knowledge that better efficacy is likely to be noted in chemo-naïve individuals. The proportion of women progressing while receiving temsirolimus was lower than has been seen in trials with chemotherapy, and hormonal therapy and ongoing investigations will assess further the patient-centered relevance of disease stability due to temsirolimus. These encouraging results have led to additional trials combining temsirolimus with other chemotherapy, hormonal, or targeted agents. The interim report of a study combining temsirolimus with bevacizumab at first recurrence was presented at ASCO this year. While 20 % of patients had an objective response to treatment and a further 20 % had stable disease, prespecified efficacy assumptions were not met. These results were in contrast to those obtained with the same combination in the context of second-line therapy [56].

Kollmannsberger et al. recently reported activity of temsirolimus in combination with carboplatin and paclitaxel in a phase I study [57]. A dose-expansion cohort suggested promising activity in women with recurrent endometrial and ovarian cancer. This combination was incorporated into a randomized phase II investigation of the GOG, GOG 86P, which randomized women with chemotherapy-naïve advanced or recurrent disease to carboplatin/paclitaxel/temsirolimus followed by temsirolimus maintenance, carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance, or carboplatin/ixabepilone/bevacizumab followed by bevacizumab maintenance. This trial has completed accrual, and results are awaited.

Two additional rapamycin analogs have shown activity in endometrial cancer patients. Ridaforolimus was administered to previously treated women with metastatic endometrial cancer. Primary endpoint was defined as clinical benefit response defined as a complete or partial response or prolonged stable disease of at least 16 weeks duration. Initial results showed a clinical benefit response of 35 % [58], and clinical development of ridaforolimus continues. In addition, the results of a trial comparing ridaforolimus with hormonal or chemotherapy treatments were presented at the International Gynecologic Cancer Society meeting in 2010 and demonstrated significant advantage for ridaforolimus with a hazard ratio of 0.55. An oral formulation mTOR inhibitor everolimus has similarly shown activity warranting additional development demonstrating a 21 % confirmed clinical benefit at 20 weeks of therapy [59].

Importantly, the mTOR inhibitors have proven to be reasonably well-tolerated agents. Most of the toxicity observed has been of grade I or II severity and consists largely of fatigue, rash, mucositis, and pulmonary interstitial pneumonitis. Hyperglycemia is an issue especially in poorly controlled diabetics. The majority of the pneumonitis is asymptomatic with only a small proportion requiring pharmacologic steroid administration. NCIC data found toxicity rates to be somewhat higher in previously treated patients, and this information may ultimately be factored into decisions relating to optimal treatment sequencing. The tolerability of these convenient agents is highly relevant when considering treatment options for the average endometrial cancer patient given their relatively older age and frequent comorbidities and obesity and fuels the argument that non-chemotherapy treatment options are of huge significance in this population.

The high observed rate of PTEN loss in endometrial tumor tissue led to the belief that mTOR inhibition would be effective in this cohort. Extensive correlative studies assessing the archival tissue from the time of diagnosis of women participating in the NCIC studies have been performed. These assessed via immunohistochemistry techniques and mutational analyses the presence of PTEN, mTOR, AKT, and pS6 mutational loss [60]. PTEN loss was observed in over 60 % of women with previously untreated disease and in 40 % of previously treated women. Despite the high frequency of noted mutations in both PTEN and other implicated proteins in the pathway, disappointingly, no correlation has been demonstrated between mutations and response to mTOR inhibition. Likewise, no correlation has been observed between histologic subtype and response to mTOR inhibition. This is despite predictions that endometrioid-type disease, which harbors the highest number of alterations in the PI3K/mTOR pathway, would benefit most from mTOR inhibitors. Elucidation of an accurate predictor of response remains a crucial aim in the path towards achieving individualized cancer treatments, and all future trials must continue to focus on the incorporation of tissue sampling and well-designed correlative studies as a fundamental part of study design.

The current lack of understanding regarding predictors of response to mTOR inhibitors highlights the intricacy and the complexity of intracellular signaling pathways and the potential feedback mechanisms and protein interplay which may be responsible for the apparent lack of correlation between loss of PTEN function and response to therapy. This fact, as well as the presence of mutations in other critical proteins in the PI3K/AKT/mTOR pathway, has led to the development of different types of inhibitors. These include PI3K inhibitors as well as dual catalytic site inhibitors which may be superior to mTOR inhibitors or alternatively when administered in combination with mTOR inhibitors may provide tolerable therapies which have more substantial tumoricidal potential [61]. Trials are ongoing with several such novel agents, and once again, information from correlative studies will be essential to allow increased and in-depth understanding of mechanism of action.

How Important Is Targeting of Angiogenesis in Endometrial Cancers?

Angiogenesis has long been known to be critical to tumor development, and correlations between vascular endothelial growth factor (VEGF) expression and clinical and prognostic factors have been observed. Several publications have shown correlation between clinical stage, grade, and prognosis in VEGF receptor overexpressing tumors [62]. Bevacizumab is a well-recognized recombinant, humanized monoclonal antibody directed against VEGF. Two partial responses and five stabilizations of disease were observed in a small retrospective analysis of heavily pretreated endometrial cancer patients [63]. This led to the GOG-229-E phase II study which treated 56 previously treated patients with 15 mg/kg of bevacizumab (every 21 days) with results showing one complete and seven partial responses totaling an overall response rate of 15 % [64]. Several resulting combination trials including GOG 86P as discussed above are currently accruing in order to assess the potential benefit of the addition of bevacizumab to chemotherapy or targeted therapies. Sunitinib, a multiple tyrosine kinase inhibitor, is a second targeted agent with antiangiogenic activity to have shown promise in the treatment of endometrial cancer patients. As published in 2010 by Correa et al., sunitinib elicited 3 partial responses (15 %) and five durable stabilizations of disease demonstrating an encouraging median overall survival of 19 months [65].

Conclusions

Chemotherapy has traditionally formed the backbone of treatment for advanced endometrial cancer. The quantity and quality of evidence-based data relating to the use of chemotherapy in endometrial cancer confirms its utility while highlighting its limitations. Response rates averaging 40 % for combination regimens and a median overall survival of only 1 year for women with advanced disease leave the oncology community in no doubt that additional treatment options are urgently required. In addition, when considering the demographic characteristics of women in this cohort, the median age of presentation of 65 years, and the high rate of obesity and active diabetes, it becomes evident that alternatives to chemotherapy, if demonstrably better tolerated, would be advantageous for patients from a quality of life standpoint even if data confirming superior efficacy was lacking.

Hormonal therapy, with its preferential toxicity profile, remains a valid treatment option for women diagnosed with endometrial cancer. It is particularly attractive for those women who are unable or unwilling to tolerate chemotherapy and for whom a higher likelihood of response is predicted. With our increased ability to perform correlative studies, older and outdated studies should be revised in an attempt to better characterize those tumor types which will predictably gain benefit from hormonal therapy. Prediction of response remains the key factor in the optimization of treatment choice.

Targeted therapies, in particular mTOR inhibitors, have shown promising activity with tolerable toxicity profiles. Phase III studies are crucial to confirm this initial data and ultimately ascertain the level of activity of these agents when compared to standard chemotherapy. Given the difficulties associated with chemotherapy administration

in this population, proof of non-inferiority would be of considerable importance in establishing an active alternative to chemotherapy.

Future clinical trials whether for conventional chemotherapy agents, hormonal therapies, or highly selective targeted therapies need to incorporate well-designed correlative studies and novel clinical endpoints in order to accommodate for the gradual conceptual shift from a "one-fit-all" treatment approach to the more sophisticated goal of "individualized care." With this new paradigm of care, we must be cautious not to disregard obviously active treatment options due to logistic limitations and an inability to adapt our evidence-based methods to fit the ever-increasing number of novel agents underdevelopment. Novel agents give the opportunity for sequential rather than alternative therapy, and their availability will likely allow for improved patient-centered decision making as well as probable improvements in progression-free and overall survival.

Concluding Comments

- Targeted agents offer a potential alternative to current standards based on preliminary data demonstrating efficacy and manageable toxicity.
- Targeted agents demonstrating clinical promise must be directly compared with both conventional chemotherapy and hormonal therapy approaches in order to allow for their appropriate and optimal incorporation into clinical practice.
- Incorporation of well-designed correlative studies into future studies is paramount if treatment algorithms are to be more accurately tailored to specific patient subpopulations.

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