



Short Report:

Systemic Therapy in Endometrial Cancer: Recent Advances.

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Abstract: Endometrial cancer is a chemosensitive disease. Studies have established a clear benefit of chemotherapy in advanced stages and trials are ongoing to define its role in early stages as well. As more molecular pathways are being elucidated there is increasing role for targeted agents and future looks quite promising. We did an extensive search both online and offline for all the relevant articles including chemotherapy and targeted therapy for endometrial cancer.

Key Words: Chemotherapy; Endometrial cancer; Hormonal therapy; Targeted therapy.

Introduction:

Endometrial cancers comprise the most common group of gynaecological malignancies in the western world. In India, the incidence is third after cervix and ovary. Comparison of cancer rates per lakh population suggests that in India cervical cancer is 20 times more common than endometrial cancer, while in United states endometrial cancer is twice more common than cervical cancer.¹ Systemic therapy for advanced endometrial cancer traditionally included hormonal and chemotherapy but the recent studies have redefined this with a possible role in early stages as well. A better understanding of molecular pathways with development of targeted drugs to block these pathways has revolutionized the treatment. As majority of these patients present in 6th-7th decade often having associated comorbidities, a personalized approach towards each patient is required.

Histological Subtypes:

Bokham identified two types of endometrial cancer.² Type 1 represents 80% of tumors, exhibits endometrioid histology and is estrogen dependant, possessing a high rate of PTEN mutations. Type 2 tumors are nonendometrioid (papillary

serous or clear cell type) type and are unaffected by estrogen. In type 2 tumors, P53 mutations and HER2/Neu over expression are common.³ Extensive knowledge of the molecular pathology of tumorigenesis provides rationale for research and drug development. The most recent developments in these novel chemotherapy, hormonal and targeted agents will be reviewed.

Hormonal Therapy

Hormonal treatment is appropriate for hormone dependent type 1 tumors. It can be used both in recurrent and upfront settings in medically inoperable advanced stage patients who are not candidates for radiotherapy, chemotherapy or surgery due to associated co-morbidities. Adjuvant hormonal therapy after primary surgery in early stages is not effective to reduce recurrences.⁴

Hormones evaluated include progestational agents, selective estrogen receptor modulators, aromatase inhibitors and GnRh analogs.⁵ No particular drug, dose or schedule is found to be superior with response rates (range between 9 & 55%), average PFS is 4 months and OS of 10 months. A systematic review of 5 studies evaluating the predictive value of hormone receptor expression concluded that the response rate for progesterone receptor positive tumors was significantly greater than that of receptor negative tumors. Studies reveal that multiple factors seem to predict response to hormone therapy. On the basis of current level of evidence it is important to consider hormonal therapy even in women with receptor negative tumors. Biomarkers including P53, HER-2, PTEN and protein kinase B have been evaluated but have not shown any co-relation with response.

Progestogens: based on the Gynecologic Oncology Group study by Thipgen et al, who compared a high and low

medroxy progesterone dosing schedule and demonstrated that low dose regimen is equally effective.⁶ Low dose (200mg/day) is a logical initial approach in hormone positive tumors.

Progestogen in combination: Response to progestogens is limited by down regulation of progesterone receptors following prolonged administration. When tamoxifen is used in combination with progestin, promising response of 33% for an alternating dosing schedule and 27% for combination is obtained.^{7,8}

Aromatase inhibitors: Aromatase inhibitors have shown to reduce circulating estrogen levels. A phase II study evaluating letrozole demonstrated a response rate of 9.4% which included one complete response. The GOG reported a comparable response rate of 9% for anastrozole.^{9,10} This class of drug may be an alternative for women in whom progestogens are contraindicated.

Newly elucidated hormonal pathways are guiding drug development. The steroid sulphatase (STS) pathway is responsible for hydrolysis of oestrone and dehydroepiandrosterone sulphates to their active forms. STS may be considered a new promising drug target for treating estrogen mediated carcinogenesis.¹¹

Chemotherapy:

Endometrial cancer is a chemosensitive disease. The role of chemotherapy (with radiotherapy) is increasingly being defined in early stage endometrial cancer and ongoing studies (PORTEC-3) and future trials will clarify the same. Current NCCN guidelines suggest vaginal brachytherapy with or without pelvic irradiation for resected early stage endometrial cancers. Chemotherapy is a Category 2b recommendation for completely surgically staged Ib (with adverse risk factors) and stage II grade 3 tumors. Adverse risk factors being advanced age, lymphovascular involvement, large tumor size and lower uterine segment involvement.

Table 1: Response with single agent in first line and recurrent setting [12-22]			
	Drug	Dose	Response rate
First line	Paclitaxel ¹²	250mg/m ² /24hr/3wks	36%
	Docetaxel ¹³	70mg/m ² /3wks	31%
	Cisplatin ¹⁴	50mg/m ² /3wks	20%
	Carboplatin ¹⁵	400mg/m ² /28days	30%
	Doxorubicin ¹⁶	60mg/m ²	37%
	Vinblastine ¹⁷	1.5mg/m ² /24h x5d/3wk	12%
	Epirubicin ¹⁸	80mg/m ² /3wks	26%
	Oral etoposide ²²	50mg daily d1-21/28days	14%
Recurrence after prior chemotherapy	Paclitaxel ¹⁹	110-200mg/m ²	27%
	Ifosfamide+mesna ²⁰	1.2gm/m ²	15%
	Liposomal doxorubicin ²¹	50mg/m ²	9.5%

A definite role of chemotherapy is established in advanced stages or in metastatic setting and recurrent setting. Based on GOG-122 study, chemotherapy in adjuvant setting improves both progression free survival and overall survival. Investigators of GOG 122 study predicted that at the end of 5 years, 50% of patients receiving doxorubicin (60mg/m²) with cisplatin (50mg/m²) chemotherapy would be alive and disease free compared to 38% of those in whole abdominal radiation arm.²³

Poor survival is noted in women with advanced stage or recurrent disease. The most active drugs in women with no

prior chemotherapy are platinum agents, taxanes, and anthracyclines, all producing response rates of 20% and 30% (Table 1).

Combination chemotherapy has produced higher response rates than single agent therapy with improved survival reported in few randomized trials. Numerous combination regimens have been tested as shown in Table 2. The response rate and overall survival with doublet chemotherapy is 20-40% and 12 months, while it is 30-50% and 15 months for 3 drug combination. Carboplatin and paclitaxel has become community standard because of its tolerability and convenience. Fleming et al²⁵ reported that a triplet regimen consisting of cisplatin, doxorubicin and paclitaxel (TAP) with granulocyte colony stimulating factor (G-CSF) was superior to doublet therapy. The TAP regimen is currently being compared with combination of carboplatin and paclitaxel in large GOG trial of women with stage III or IV or recurrent endometrial carcinoma.

Table 2: Distribution of Patients According to Regimen			
Regimens	No. of patients	RR	OS (months)
Carboplatin AUC 5-7+paclitaxel 175mg/m ² over 3hrs ²⁴	46	61	NA
TAP (doxorubicin 45mg/m ² + cisplatin 50mg/m ² + Paclitaxel 160mg/m ² over 3 hrs+ growth factor) ²⁵	134	57	15.3
Doxorubicin+ cisplatin ²⁶	157	40	12.6

Ixabepilone, an epitholone derivative is currently undergoing phase III testing, after promising results shown in a phase II study. In previously treated women with advanced endometrial disease an objective response of 12%, PFS benefit of 2.9 months and stable disease for at least 8 weeks in 60% of patients were reported.²⁷

Results of second line chemotherapy are generally poor and only taxanes have been shown to have a response rates of greater than 20%.¹⁹

Targeted Therapy

Advances within the field of molecular biology are enabling the development of rationally designed therapies which target pathways crucial to tumor proliferation. Molecular alterations observed in endometrial cancers within the mammalian target of rapamycin (mTOR) and epidermal growth factor receptor (EGFR) pathways provide rationale for treatments inhibiting these pathways. Antiangiogenic treatments are another potential treatment strategy.

Mammalian Target of Rapamycin (mTOR) Inhibition

PTEN is the most common defined genetic alteration identified in endometrial cancer. It is a tumor suppressor gene that inhibits of the phosphatidylinositol 3'-kinase/protein kinase B/mTOR (PI3K/Akt) signaling pathway needed for cell cycle progression and cell survival.²⁸ PTEN mutations are observed in 50-80% of type I and 10% of type II endometrial carcinomas. The resultant activation of mTOR affords scientific rationale for mTOR inhibitors in PTEN –mutated tumors.

Three mTOR inhibitors have been investigated namely, temsirolimus, everolimus and ridaforomilus.

Temsirolimus: A phase II trial in chemotherapy-naïve women with endometrial carcinoma reported a 14% partial response and stabilization of disease in 69%. In pretreated women 4% had partial response and stabilization in 48% patients.²⁹ These promising results have prompted additional trials with chemotherapy, hormonal and targeted agents. Ongoing studies combine temsirolimus and bevacizumab, temsirolimus with paclitaxel and carboplatin, and temsirolimus with or without hormonal therapy. The NCIC CTG recently reported a phase I study combining temsirolimus with paclitaxel and carboplatin, based on these

reports a three arm phase II trials of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus and ixabepilone/carboplatin/bevacizumab are undergoing.

Ridaforolimus (deforolimus: AP23573): Given at the dose of 40mg oral daily for 5days a week in 4 week cycle, this drug produced partial response in 7.7% and disease stabilization in 58% for a median duration of 6.6 months.³⁰ In comparison to hormonal therapy, it suggested near doubling of progression free survival.³¹ These results indicate clear activity for mtor inhibition and are being evaluated to assess future development strategy.

Everolimus (Radool): Everolimus is an oral rapamycin analogue administered daily at a dose of 10 mg. A phase II study investigating everolimus in previously treated women with endometriod type endometrial cancer reported results for 28 evaluable women. 44% percent had stable disease after 8 weeks of treatment and 21% maintained this status at 20 weeks.³² Common toxicities are fatigue, lethargy and mucositis.

P13 Kinase inhibitors

P13K hyper activation is observed in 26-36% of type I tumors and 5-21% of type II tumors can result from PTEN inactivity or mutations within P13K itself. Data suggests that P13 activation may be a predictor of poor prognosis. Phase I studies have tested several P13K Inhibitors and results warrant further study.³³ On the basis of the postulated significance of the P13K pathway in endometrial cancer, Novartis (Basel, Switzerland) is currently conducting a phase II study with BKM120 as second line therapy. PTEN and P13K functional status will be determined in patients to allow correlation of functional status and response.

Dual P13K – mTOR Inhibitors

Dual inhibitors of P13K and its downstream mTOR might be more effective than mTOR inhibitors alone as they lead to complete pathway inactivation. Many such molecules are in development which includes NVP-BEZ235 and XL765. These molecules have shown great promise both in invitro cell lines³⁴ and phase I trials. Phase II trials are now underway.

Angiogenesis Pathway:

Bevacizumab: Poor outcome is associated in tumors with high levels of markers of angiogenesis like VEGF. Bevacizumab is a recombinant, humanized monoclonal antibody directed against VEGF. Based on in vitro testing which have showed combination of chemotherapy with bevacizumab to have greater tumor inhibition than either therapy alone, several combination therapies were designed. GOG 229-E a phase II trial which evaluated single agent bevacizumab in patients with prior chemotherapy showed a response rate of 13.5%, with median PFS and OS of 4.2 and 10.5 months respectively.³⁵ This study showed single agent activity of bevacizumab. As a result several other trials are underway, which includes its combination with temsirolimus, and with carboplatin/paclitaxel.

Sorafenib, which also acts on VEGF receptors has shown a partial response rate of 5% and disease stabilization in 50% with median overall survival of 11.4 months.³⁶

EGFR Pathway:

Gefitinib: In vitro studies have shown its anti tumor activity in endometrial cancer cell lines, especially in type I tumor.³⁷

Trastuzumab: Tumors that over express HER2 are resistant to chemotherapy, targeting these pathways have great potential in improving survival. They have been evaluated in small number of patients with advanced endometrial carcinoma. Partial response rates ranging from 11-57% have been obtained, however most responses are of limited duration.³⁸ Larger trials are now underway to evaluate their therapeutic potential

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