Endometrial Cancer State of the Science Meeting

Henry C. Kitchener, Edward L. Trimble,†*
and for the Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup

Abstract: There is a pressing need to improve our understanding of endometrial cancer (EC) and uterine carcinosarcoma and to develop new treatment strategies to improve outcomes. In recognition of this, a State of the Science meeting on EC was held last November 28 and 29, 2006, in Manchester, United Kingdom. The meeting was cosponsored by the National Cancer Research Institute (UK), the National Cancer Institute (US), and the Gynecological Cancer Intergroup.

The objectives of the meeting were as follows:

1. To review current knowledge and understanding of EC and its treatments.
2. To identify key issues for translational research and clinical trials.
3. To identify the most important trials for women with endometrial carcinoma and uterine carcinosarcoma, both those already underway or to be done, for which the Gynecological Cancer Intergroup might facilitate international cooperation.

Key Words: Endometrial cancer, Clinical trials, Translational research

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Endometrial cancer (EC), the second most common gynecologic cancer worldwide, has now become the most common gynecologic cancer in developed countries. Its rising incidence is related to increasing life expectancy, tamoxifen use, and the epidemic of obesity. The last is also responsible for comorbidity, notably adult-onset diabetes and hypertension. Together, comorbidity and obesity present challenges in delivering optimal therapy for many women with EC. The rising incidence of EC has been associated with a rising death rate. Although the prognosis of early disease is good with a survival rate of 80%, those with very high-risk disease and advanced disease at presentation have a survival rate below 50% with very little gain in therapeutic efficacy during the past 30 years. This lack of progress in treatment is, in part, related to our limited understanding of the molecular pathology of EC. There is a pressing need to improve our understanding of EC and to develop new treatment strategies to improve outcomes. In addition, compared with ovarian and cervical cancer, EC and uterine carcinosarcoma (CS) have been studied much less extensively. Fewer trials have been opened for women with these cancers, and accrual to those trials has been slow.

In recognition of this, a State of the Science meeting on EC was held last November 28 and 29, 2006 in Manchester, United Kingdom. The meeting was cosponsored by the National Cancer Research Institute (NCRI, UK), the National Cancer Institute (US), and the Gynecological Cancer Intergroup (GCIG). A multidisciplinary group of 75, drawing on surgeons, gynecologic oncologists, radiation (clinical) oncologists, medical oncologists, pathologists, translational scientists, and patient advocates from 18 countries and representing 14 trial groups attended.

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1. To review current knowledge and understanding of EC and its treatments.
2. To identify key issues for translational research and clinical trials.
3. To identify the most important trials for women with endometrial carcinoma and uterine CS, both those already underway or to be done, for which the GCIG might facilitate international cooperation.

The first half of the proceedings was dedicated to a series of presentations, which outlined our current knowledge. The second half of the meeting began with parallel sessions of early disease and advanced/recurrent disease to define staging, treatment, and translational research issues to lead to candidate clinical trials questions. This was followed by plenary discussion of the questions to be addressed in these candidate trials and an attempt to develop an international consensus of the most favored concepts for future development and international collaboration.

This paper reports the content and conclusions arising from this meeting.

CURRENT KNOWLEDGE

Molecular Pathology of EC

Endometrial Hyperplasia

There is broad agreement that type 1 (estrogen-related) EC progresses via a precursor lesion, atypical hyperplasia or endometrial intraepithelial neoplasia.[1] This has been clearly demonstrated

*UK National Cancer Research Institute and University of Manchester, Manchester, United Kingdom; and †National Cancer Institute, Bethesda, MD. Address correspondence and reprint requests to Edward L. Trimble, CIB, CTEP, DCTD, National Cancer Institute, National Institutes of Health 610 Executive Blvd, Suite 7025, Bethesda, MD 20892. E-mail: tt6m@nih.gov.

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by data that demonstrated a hazard ratio for EC of 89, when compared with benign endometrial biopsy during a period of 10 years.[2] Mutation of *PTEN*, a tumor suppressor gene, is implicated because the mutation rates for normal endometrium, endometrioid intraepithelial neoplasia (EIN), and endometrial carcinoma are 0%, 55%, and 83%, respectively. *PTEN* knockout mice demonstrate very high rates of EIN, and 20% develop EC. Progestins can achieve regression of precancerous lesions, which currently offer the best prospect for secondary prevention in predisposed women.

Molecular Genetics of Endometrioid EC

Type 1 and type 2 tumors (non–estrogen-related) have different genetic profiles.[3] In addition to *PTEN*, type 1 features mutations in mismatch repair genes as well as K-*ras* and β-*catenin*. Type 2 features aneuploidy and p53 mutations. Microarray technology has been used to demonstrate upregulated and downregulated genes in EC compared with normal endometrium. A variety of differentially expressed genes can also be identified between early and late stage diseases. Some of the most significant overexpressed genes are involved in key pathways: cell proliferation (eg, *CCNE1*), angiogenesis (eg, *MMPG*), and chromosomal instability (*BIRC5*). These have been confirmed as predicted target genes by means of microRNAs, most differentially expressed in EC compared with normal endometrium. Greater understanding of key genes involved in endometrial carcinogenesis will help in developing biomarkers of prognosis and therapeutic targets. Fundamental studies of these candidate genes will be important in elucidating mechanisms of causation, progression, and metastasis.

Serous and Clear Cell Carcinoma

Type 2 EC, which comprises around 5% to 10% of ECs, includes both serous carcinoma and clear cell carcinoma.[4,5] The term serous carcinoma is preferred to the commonly used as papillary serous carcinoma because a glandular variant exists without papillary formation. Unlike type 1 tumors, type 2 neoplasms are associated neither with estrogen excess nor with endometrial hyperplasia, although a proportion may evolve from a type 1 tumor via progression and mutation. Serous carcinomas are thought to arise in atrophic endometria from a precursor lesion known as serous endometrial intraepithelial carcinoma (serous EIC). They are, by definition, high grade and have a much poorer prognosis than type 1 tumors. The precursor lesion serous EIC has a propensity to arise in endometrial polyps and may give rise to extrauterine disease, even in the absence of endometrial stromal or myometrial invasion. Immunohistochemical studies have shown that p53 is diffusely positive in approximately 90% of serous carcinomas. Other markers such as HER-2 *neu* and ER/PR are inconsistently expressed (many cases are hormone receptor–negative). Most serous carcinomas are associated with mutations in the *p53* tumor suppressor gene. These mutations occur early in the evolution of uterine serous carcinoma and are demonstrable in the precursor lesion serous EIC. In clear cell carcinomas, which are also aggressive neoplasms and which are rarer than serous carcinomas, molecular events have been less well studied. *p53* and ER/PR are both inconsistently expressed. Mixed type 1 and type 2 carcinomas are not uncommon and may evolve from a type 1 neoplasm secondary to *p53* mutation.

Lynch Syndrome

The term Lynch syndrome is now used to encompass HNPCC and Lynch syndrome I/II. Endometrial cancer as a result of the Lynch syndrome accounts for 2% to 3% of all cases.[6] In women with EC below the age of 50 years, 9% have Lynch mutations. Individuals who exhibit the Lynch syndrome have around a 50-fold lifetime risk of developing EC compared with unaffected women, with studies suggesting a range of 40% to 60% lifetime risk for those with a mutation. The syndrome can be defined clinically using the Amsterdam criteria or genetically by germ line mutation in *MLH1*, *MSH-2*, or *MSH-6* defective DNA repair.

These mutations can be tested for on a tumor specimen to demonstrate a mutation carrier using immunohistochemistry and, if both normal and tumor tissue are available, microsatellite instability can be tested for, which, in hereditary cancer, is associated with a germ line mutation in the mismatch repair gene. In sporadic tumors, it is associated with hypermethylation of the *MLH1* promoter.

Thirty percent of individuals with Lynch syndrome will develop a second cancer within 10 years of the first cancer (compared with around 3%–4% of unaffected), and for women diagnosed with EC, the median time for a second cancer is 11 years. The only proven means of prevention of EC is hysterectomy; however, endocrine chemoprophylaxis is currently being explored in trials both in the United States and in the United Kingdom.

ER/PR Expressions

Two isoforms of both ER (ERα and ERβ) and PR (PRA and PRB) have been described.[7] Progesterone treatment is capable of inhibiting invasion of endometrial cells by down-regulating a number of genes, for example, *integrins* and *K-cadherin*. PRA is nuclear, whereas PRB shuttles between the nucleus and cytoplasm. Whereas ER and PR tend to be abundant in well-differentiated EC, they are sparse in poorly differentiated disease.

G-protein coupled with receptor for estrogen (GRP30), whose function is unknown, is highly expressed in some high-grade ECs, and its underexpression is significantly correlated with improved survival.

In GOG-119, tamoxifen in combination with medroxyprogesterone acetate was used in women with metastatic cancer; tumors with abundant ER had improved survival up to 5 years.[8] This hormonal regimen should be considered to be combined with temsirolimus, an M-TOR inhibitor, in a randomized study in women with advanced/metastatic disease.

Selective Estrogen Receptor Modulators and the Endometrium

Tamoxifen was the first selective estrogen receptor modulator.[9] It has a stimulating effect on uterine stroma and on epithelial cells, which may range from cystic change to proliferative, hyperplasic, to invasive cancer. These tissue-specific differential changes are dependent on differential ER conformation upon ligand binding, differential expression, and binding of coregulatory proteins to the ER.

Tamoxifen may also exert a carcinogenic effect via a genotoxic pathway through tamoxifen DNA adducts. Compared with non–tamoxifen-related tumors, a higher proportion of tamoxifen-related tumors exhibit *p53* mutations. It is not known whether some women are more susceptible to carcinogenesis by tamoxifen than other women, and if so, what may be the biomarkers for this.

Current State of Imaging

The most common event before the diagnosis of EC is postmenopausal bleeding, for which ultrasound examination of the uterus has considerable utility.[10] The negative predictive value of an endometrial echo less than 5 mm is 99%, which provides a very reliable means of excluding cancer. An ultrasound image that shows an abnormally thickened endometrium is not specific for benign or malignant lesions, which require further investigations, including hysteroscopy and biopsy. When a diagnosis of EC has

been made, magnetic resonance imaging can provide useful information for treatment planning for those cases not amenable to surgery. Magnetic resonance imaging can provide information on tumor bulk, depth of myometrial invasion, and cervical involvement and extrauterine spread.[11] Staging protocols are based on T2-weighted sequences, but contrast-enhanced T1-weighted sequences may be complementary and optimize the accuracy of interpretation. Magnetic resonance imaging has its limitations, including microscopic invasion and intranodal lymph node metastases; it is possible that sensitivity for detection of the latter will be improved by the use of ultrasmall particles of iron oxide (USP10) contrast agents. Evaluation of positron emission tomography, particularly for lymph node staging and early detection of recurrence, warrants evaluation.[12]

Treatment of EC

Role of Surgery

The role of primary hysterectomy for the treatment of endometrial carcinoma is well accepted. More controversial is the role of lymphadenectomy. Assignment of FIGO stage is based on presence or absence of metastatic disease in the retroperitoneal lymph nodes. As noted below, some gynecologic surgeons perform staging lymphadenectomies on all patients, some on no patients, and some tailor staging to include lymphadenectomy for patients thought to be at sufficiently high risk of lymph node involvement. In addition, the extent of lymphadenectomy remains a subject of debate.

Furthermore, understanding patterns of failure is critical in understanding how best to manage EC in postsurgical care. Of 612 women managed with hysterectomy and adjuvant radiotherapy (RT) at the Mayo Clinic, 141 (23%) relapsed and sites of recurrence were known for 132 cases; 60 hematogenous, 44 lymphatic, and 37 intraperitoneal.[13] Among women with myometrial invasion of less than 50%, 5% developed hematogenous spread compared with 23% in those with more than 50% invasion. Lymphatic embolization was found only in high-risk cases. Pelvic sidewall recurrence occurred at a rate of less than 1% in women without lymphovascular invasion (LVI) or positive nodes at presentation, and para-aortic recurrence was also as rare in women who were node-negative and had no LVI. In the presence of these, however, sidewall and para-aortic recurrences were 26% and 33%, respectively. Intraperitoneal spread was largely associated with advanced disease at presentation. Vaginal failure was associated with grade 3 histologic subtype and LVI.

GOG-99 is a randomized trial evaluating pelvic radiation to no further therapy among women considered at intermediate risk for recurrence after hysterectomy and lymphadenectomy.[14] Among those women with no evidence of disease in the retroperitoneal lymph nodes, age, grade, depth of myometrial invasion, and lymphovascular space invasion were independent predictors of recurrence. These same factors also predicted recurrence in the PORTEC 1 study that involved women who underwent hysterectomy but not lymphadenectomy as primary therapy for EC.[15]

Therefore, both hysterectomy and lymphadenectomy, if performed, can help determine both the risk of recurrent disease and the dominant patterns of failure, whether peritoneal or nodal. We do not know yet how to integrate adjuvant radiation therapy and chemotherapy to minimize the risk of recurrence.

Radical Hysterectomy

Unlike a simple hysterectomy, a radical hysterectomy will remove parametrial tissue, uppermost vagina, and pelvic ± para-aortic lymph nodes. As noted below, the optimal extent of lymphadenectomy is not well defined. This combined surgical procedure could have the effect of reducing central pelvic and vaginal failures, as well as define women at low risk of lymphatic site relapse. There is, however, no evidence to support radical hysterectomy for stage I disease. Radical hysterectomy should be confined to women with known bulky involvement of the cervix, that is, IIB.[16]

Role of Lymphadenectomy

The role of lymphadenectomy is to stage disease and in so doing to define prognosis and determine the need for adjuvant therapy. The extent of lymphadenectomy also remains controversial, including the optimal number of lymph nodes to remove, the sites for lymphadenectomy, and how high up the aorta the lymphadenectomy should extend. Some groups have advocated to above the aortic bifurcation, others to the level of the IMA, and others to the renal vessels. Whether lymphadenectomy is therapeutic in itself by removing involved nodes is a highly controversial issue. Nonrandomized, retrospective case series have been analyzed to determine whether removal of a greater or lesser number of nodes or indeed any nodes is associated with improved survival. A number of such studies from the United States have suggested a survival benefit in women undergoing surgical staging, but most of these studies have not controlled for standard of care, comorbidity, and stage migration, that is, node-positive women are moved out of stage I disease, leaving node-negative women being compared with women of unknown node status. A recently published study by Chan et al reported that among women who had been staged and found to have positive nodes, those in whom 11 to 20 nodes were removed and more than 20 nodes were removed had a relative hazard rate of 0.77 and 0.60, respectively, compared with those who had up to 10 nodes removed.[17] The benefit of lymphadenectomy among women whose hysterectomy specimens puts them at low risk for extrauterine disease seems to be small. As noted above, there is no consistent approach to lymphadenectomy even in North America.

Decisive proof of whether lymphadenectomy is therapeutic requires data from a randomized trial in which adjuvant therapy does not confound the findings. The recently reported, but as yet unpublished ASTEC trial, performed in the United Kingdom, was designed to address the effect of lymphadenectomy on survival and the effect of adjuvant RT on survival of at-risk women. The published results of ASTEC are eagerly awaited, although a preliminary analysis presented at the Annual Meeting of the Society of Gynecologic Oncologists (Palm Springs, Calif, March 2006) suggested no survival benefit associated with lymphadenectomy.

Sentinel Node Biopsy

The rationale of sentinel node surgery requires high negative predictive value as a means of avoiding the need for systematic lymphadenectomy in all and using a positive sentinel node to determine the need for full lymphadenectomy or adjuvant therapy. Sentinel nodes can be identified laparoscopically, which could precede definitive surgery. Sentinel nodes can be identified using either toluidine blue or radiolabeled technetium.[18]

Using both hysteroscopically presented marker and cervical or subserosal corpus injection has achieved negative predictive value approaching 100%.[19] Sentinel node detection rates are more than 90%, mostly pelvic with para-aortic nodes being the sentinel site on much rarer occasions. Although sentinel node surgery seems to be feasible in EC, its use has not become widespread. In addition, the utility of sentinel node surgery in EC management needs to be established in clinical trials.

Pelvic Radiotherapy and Chemoradiation

Both radiation therapy and chemotherapy have shown activity in preventing recurrence of EC, although their utility varies as to sites of failure. Trials evaluating different modalities of treatment in the adjuvant setting have been complicated by heterogeneity both of risk of recurrence and most likely sites for recurrence. We need to determine how best to integrate radiation and chemotherapy after primary surgery to take advantage of both modalities.

Pelvic RT, both external beam and brachytherapy alone or in combination, has been widely used for many years as adjuvant therapy in unstaged women, with either intermediate (stage IC/IIA, grades 1–2) or high risk (stage IC, grade 3), as well as in staged women with positive nodes and staged women with negative nodes but other high-risk factors. It has also been used for unresectable, advanced disease in the pelvis. Three randomized trials of RT for intermediate-risk disease have been completed: the Norwegian trial, PORTEC 1, and GOG-99.[14,15,20] These all demonstrated a reduction in pelvic recurrence but no effect on overall survival. Risk factors for recurrence were grade 3 disease, depth of invasion, lymphovascular space invasion, stage IC, and aged 60 years or older. The PORTEC 2 trial is currently evaluating whether pelvic external beam therapy can be safely replaced by brachytherapy with results expected late 2008. In light of these trials, there has been a reduction in the use of adjuvant RT for intermediate-risk disease. The principal challenge now is achieving higher survival rates in women with high-risk disease by virtue of age and primary tumor features whether unstaged or with negative nodes or those found to have nodal metastases.

In a recently published Italian trial, 345 women with stages IC/II (grade 3) and stage III were randomized to CAP or pelvic RT.[21] No difference in overall survival was found, but RT delayed pelvic relapse and chemotherapy delayed distal relapse. A recent phase 2 trial from the United States tested concurrent chemoradiation (cisplatin, 50 mg/m^2) with adjuvant cisplatin/paclitaxel (4 cycles of cisplatin 50 mg/m^2 and paclitaxel 175 mg/m^2).[22] This was feasible, and at 4 years, disease-free survival was 81%, indicating candidature for a phase 3 trial. On this basis, the PORTEC 3 trial opened as a collaborating PORTEC/NCRI intergroup study. It is planned to randomize 800 women with high-risk disease to either external beam RT or RT + concurrent cisplatin (weeks 1 and 3) followed by 4 cycles of carboplatin and paclitaxel (175 mg/m^2). The primary end point will be overall survival.

Whole Abdominal Radiotherapy

The rationale for whole abdominal RT (WART) is that the abdominal cavity is the commonest site of treatment failure in a number of studies involving with advanced disease, which included women with serous and clear cell tumors. Up to 30 gray is well tolerated, with shielding of the kidneys. In one of the largest reported studies, 132 women were treated with WART including 68% with stage III and 45% with serous or clear cell tumors.[23] Disease-free survival at 5 and 10 years was 55% and 45%, respectively; site of relapse was the abdominal cavity in 59%. Toxicity included 14% with gastrointestinal grades 3 to 4 and 2% renal.

In GOG-122, WART was compared with adriamycin/cisplatin in a phase 3 trial involving 396 women with stage III and IV endometrial carcinoma and less than 2-cm residual disease.[24] The results showed superiority for chemotherapy (hazard ratio, 0.71; 95% confidence interval, 0.54–0.94), although there was an excess of neurologic G_{1-2} and cardiac toxicity, with 8 treatment-related deaths compared with 4 in the WART arm. Eighty-four percent completed WART compared with 62% for chemotherapy. Almost twice as many women who had RT recurred outside the abdomen (18.3%) compared with AP (9.8%). We should note, however, that the survival curves for the 2 arms have grown together with time. Although WART is generally well tolerated, its role in the management of EC is not clear.

Vaginal Brachytherapy

The rationale of vaginal brachytherapy is that vaginal cuff recurrence is an important site of pelvic recurrence, and this type of treatment is very well tolerated. In studies reporting vaginal brachytherapy for adjuvant treatment of stage I disease, vaginal control approaches 100%. In PORTEC 1, 73% of recurrences among nonirradiated patients involved the vaginal cuff. Vaginal brachytherapy could substitute for external beam radiation if pelvic control rates were not compromised and, for higher-risk disease, could be combined with chemotherapy. An American survey of ASTRO and American Brachytherapy Society members produced 551 completed responses.[25] Most reported increased referral for vaginal brachytherapy with almost all treating the upper vagina only. Almost 70% of patients were treated with high–dose rate brachytherapy. The PORTEC 2 trial will determine whether brachytherapy can safely replace external beam RT for intermediate-risk disease. Future trials could combine vaginal brachytherapy with chemotherapy and better definition of the technical aspects of therapy.

Chemotherapy

Treatment of advanced/recurrent EC needs to take account of the proportion of women who may be obese, previously irradiated, and elderly. Among women who have not yet received chemotherapy, response rates in excess of 20% have been seen with the following drugs: doxorubicin/epirubin, paclitaxel/docetaxel, and cisplatin/carboplatin.[26] Two randomized trials have compared doxorubicin with doxorubicin/cisplatin. Response rates were higher for the combination (27% vs 45%; 17% vs 43%) with a median overall survival of 9 months for the combination arms in both trials.

GOG-177 compared the combination of doxorubicin and cisplatin with doxorubicin/cisplatin and paclitaxel with F-CSF support. There was an overall survival benefit. The response rate was 57% for the triplet compared with 34% for the doublet. The median overall survival rates were 15.3 and 12.3 months, respectively, but there was excess neurotoxicity with the 3-drug combination. The less-toxic combination of carboplatin and paclitaxel has been evaluated in several phase 2 trials with response rates in excess of 60%. This combination, which is now widely used in the community, is now being compared with doxorubicin/cisplatin/paclitaxel for women with stage III and IV diseases (GOG-209).

Role of Endocrine Therapy

The sex steroid hormones progesterone and estrogen bind to specific receptors with the resulting complex entering the nucleus and leading to specific patterns of gene expression, which lead to specific phenotypic effects, for example, progesterone leads to endometrial cell differentiation.

Endocrine therapy has been shown to have some activity in advanced/recurrent EC for more than 40 years. In clinical trials of single-agent progestogens (GOG-48 and GOG-81), response rates of approximately 20% were achieved with higher response rates in PR-positive and lower-grade tumors.[27] Combinations of progestogens and tamoxifen (which increases progesterone receptor expression and may therefore counteract resistance to progestogens) have been assessed. Phase 2 trials of such combination strategies (GOG-119 and GOG-153) have demonstrated overall response rates of 33% and 27%, progression-free survival of 3

and 2.7 months, and overall survival of 13 and 14 months, respectively.[8,28] The aromatase inhibitors, anastrozole and letrozole, have been assessed but demonstrated limited clinical activity.[29,30] Progestogen has been shown to be relatively ineffective as an adjuvant in primary therapy.[31]

Further trials are required to identify the optimal role of hormone therapy, before or after chemotherapy, and what biomarkers may be informative in predicting response.

Biotherapies

The hallmarks of endometrioid (type 1) uterine cancer are beginning to be understood, with *PTEN* inactivation, activating mutations within the PI3K pathway, K-*ras*–activating mutations, *MLH1/6* epigenetic inactivation, and β-*catenin* activation being well described. In contrast, type 2 (nonendometrioid) uterine carcinomas are characterized by aneuploidy, *p53* mutation, and defects in *p53* pathway genes (such as *p21/waf1* and *MDM2*). Targets for type 1 tumors include components of the PI3K pathway, the β-*catenin* pathway, the epidermal growth factor receptor family, endocrine therapy (PgR and ER), and antiangiogenic targets. Recently described mouse models that are heterozygously deleted for *PTEN* develop endometrial hyperplasia and endometrioid endometrial carcinoma at a high rate. The incidence of these endometrial carcinomas is drastically reduced by crossing with an AKT1-deficient mouse.[32] This suggests a case for exploring endocrine or biotherapy manipulation of endometrioid uterine cancer.

Phospho M-TOR and phospho S6 kinase are expressed in type 1 endometrial carcinoma. Rapamycin analogs were shown to inhibit endometrial carcinoma cell lines growth in vitro and inhibit the development of endometrial carcinoma in *PTEN* heterozygote knockout mice.[33] Trials of temsirolimus (CCI-779) and RAD001 have been undertaken, which have shown activity in uterine cancer, although surrogate molecular markers of response have remained elusive. For example, temsirolimus has shown a 26% response rate with a substantial additional stable disease fraction. Responses were not correlated with expression of receptors. Currently, there is a drive to integrate M-TOR inhibitors into chemotherapy schedules for EC.

Epidermal growth factor receptor and Her-2 are overexpressed in 50% and 60% of ECs, respectively. TKIs prevent multiple intracellular signaling pathways from being activated. Including mitogen-activated protein kinase pathway, protein kinase B (Akt), trastuzumab, cetuximab, and lapatinib have begun to be evaluated in phase 2 studies.

DEVELOPING A PORTFOLIO OF KEY TRIALS

This body of current knowledge provides a platform for determining the key questions, which need to be answered in an attempt to improve the standard of care and improve survival. This requires a set of clinical trials combined with translational research to demonstrate the optimal role of surgery, RT, and chemotherapy and to begin to evaluate biological targeted drugs and discover biomarkers for likely response/nonresponse to therapy.

The Consensus Group discussed the key questions where there was a dearth of information from trials and where new and additional data were needed. Through consensus, the group focused on questions of broad interest, which could advance knowledge and were most likely to attract intergroup and international collaborations. These are outlined below:

Prevention of Endometrioid Endometrial Carcinoma

As discussed above, EIN seems to be a precursor lesion to endometrioid endometrial carcinoma. A relative excess of estrogen, whether endogenous or exogenous, to progesterone can result in the development of EIN. Several trials to evaluate the therapeutic benefit of progestins in the treatment of EIN were discussed. The first, GOG-0224, randomizes women with EIN to continuous (megestrol, 40 mg twice a day for 12 weeks) or cyclic (megestrol, 80 mg twice a day for 12 weeks, 2 weeks on/2 weeks off) progestins for 3 months before hysterectomy. The primary end point of interest is the presence or absence of EIN in the hysterectomy specimen. A follow-up study would compare a commercially available progesterone-releasing intrauterine device, Mirena, to the best-performing arm of GOG-0224.

For women with Lynch syndrome, who face a high lifetime risk of EC, The UK NCRI is undertaking the POET trial, which randomizes eligible women either to the Mirena or to observation. The primary outcome is development of atypical hyperplasia or EC, whichever is detected first. Women in both arms will be observed for 12 months with transvaginal scanning ± uterine biopsy, up to 36 months.

Treatment of Endometrial Carcinoma

Adjuvant therapy after primary hysterectomy.

As discussed above, there seem to be 3 broad approaches to primary surgery and staging worldwide, namely, hysterectomy alone for most patients, hysterectomy and staging lymphadenectomy for most patients, and hysterectomy with staging lymphadenectomy for patients thought at sufficiently high risk for nodal metastasis. The group endeavored to design trials that might enroll patients with and without surgical staging for various risk groups.

For women with disease apparently confined to the uterus at time of hysterectomy (FIGO stage I–II), several trials were discussed. Overall, the goals of these studies was to delineate the appropriate roles for adjuvant pelvic RT, vaginal brachytherapy, systemic chemotherapy, and lymph node dissection in this patient population. Currently open to accrual is the PORTEC 3 trial, which randomizes women to pelvic RT versus chemoradiation and consolidation chemotherapy. Eligibility includes FIGO IB and IC/grade 3, II (occult) grade 3, IIIA or IIC, endometrioid, and stages IB to IIIC clear cell or serous histologic subtype. Chemoradiation includes concurrent cisplatin 50 mg/m^2 on days 1 and 22; after completion of chemoradiation, women will receive 4 additional cycles of carboplatin (AUC5) and paclitaxel 175 mg/m^2 thrice weekly. The planned accrual of 800 will detect a 10% difference in 5-year overall survival with 80% power.

One proposed trial would randomize women with node-negative EC defined as at high risk of recurrence to pelvic RT or chemotherapy plus vaginal brachytherapy. They would be stratified on the basis of lymph node evaluation, whether imaging or surgical dissection. A second proposal would randomize women who had undergone hysterectomy but not lymph node dissection to surgical staging and chemotherapy for positive nodes or pelvic RT and chemotherapy without surgical staging.

Consolidation Therapy After Hysterectomy for FIGO Stage III Disease

The recent studies documenting a role for systemic chemotherapy in women with advanced EC throw into question the benefits of local radiation treatment. The proposed trial would randomize women to systemic chemotherapy with or without radiation therapy targeted to the known or suspect sites of disease in the pelvis and/or para-aortic region.

Treatment of Isolated Pelvic Recurrence

About half of women with recurrent EC have their recurrences limited to the pelvis. Treatment approaches have included

surgical excision, pelvic radiation, and, more recently, chemotherapy. The proposed trial (GOG-0238) would randomize women experiencing pelvic recurrence of their ECs to radiation alone versus platinum-based chemoradiation. Surgical excision/debulking, but not exenteration, potentially curative surgery would be permitted before entry into the trial.

Treatment of Stage IV or Recurrent EC

The proposed trials seek to optimize chemotherapy regimens or decrease the toxicity of standard chemotherapy. In the United States, on the basis of GOG-177, paclitaxel seems to have been accepted as part of the standard treatment regimen for advanced EC. Outside the United States, paclitaxel is not widely used. In many countries, paclitaxel has not been approved for routine use among women with EC. In the United States, therefore, the GOG plans to complete accrual to GOG-0209, which compares a 3-drug combination of paclitaxel, doxorubicin, and platinum to a 2-drug regimen of carboplatin and paclitaxel. One proposed European trial would compare doxorubicin plus cisplatin with carboplatin plus liposomal doxorubicin. A novel agent, temsirolimus, an M-TOR inhibitor as described above, seems to have activity in EC. Two proposed studies would evaluate the addition of temsirolimus to chemotherapy or hormonal therapy in the treatment of women with stage IV or recurrent EC.

Treatment of Uterine CS

Uterine CS is a relatively rare histologic subtype compared with endometrial adenocarcinoma. Only intergroup and international collaborations will make possible timely completion of definitive trials for women with this disease.

Women with uterine CS are at high risk for both local and distant recurrences after primary hysterectomy. The proposed studies seek to define the benefit of pelvic RT, as well as the optimal chemotherapy regimen.

Adjuvant Treatment of FIGO Stage I to II Uterine CS

One proposed study would randomize women with CS after primary hysterectomy to pelvic RT or observation. A second proposed trial would use a bifactorial design to address both chemotherapy and radiation therapy questions. Women with CS after primary hysterectomy would be randomized to pelvic RT or not RT, as well as to paclitaxel plus cisplatin or paclitaxel plus cisplatin plus doxorubicin or epirubicin.

Consolidation Treatment for FIGO Stage II to IV Uterine CS

The proposed study would also use a bifactorial design to compare chemotherapy with or without a targeted agent and to compare pelvic radiation to no radiation.

CONCLUSIONS

The Endometrial Cancer Consensus process allowed a successful presentation of the current state of knowledge and resulted in an effective consensus to emerge regarding the progress that needs to be achieved to impact patient care.

As noted above, compared with ovarian and cervical cancer, EC and uterine CS have been studied much less extensively. Relatively few trials have been opened for women with these cancers, and accrual to those trials has been slow. Through intergroup and international collaborations, we hope to ensure that the best science informs trials for women with EC and uterine CS and that these trials are completed as rapidly as possible. We plan to work through the GCIG to promote accrual to those trials already open as well as the timely development of those trials proposed above. We will also need to educate our sponsors and partners in research, including national governments, charities, and the pharmaceutical industry about the importance of identifying more effective treatment of women with EC and uterine CS.

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Endometrial Cancer Working Group participants: Chris Altgassen, University of Schleswig-Holstein (AGO); Carol Aghajanian, Memorial Sloan-Kettering Cancer Center (GOG), USA; Frederick Amant, Catholic University of Leuven (EORTC); Michael Birrer, US National Cancer Institute (GOG); Peter Blake, Royal Marsden Hospital (NCRI); Jeff Boyd, Curtis and Elizabeth Anderson Cancer Institute (GOG); Mark Brady, Roswell Park Cancer Institute (GOG); David Cantu, Mexican National Cancer Institute; Michael Cibull, University of Kentucky (GOG); Larry Copeland, Ohio State University (GOG); William Creasman, Medical University of South Carolina (GOG); Carien Creutzberg, Daniel den Hoed Cancer Center, Erasmus Medical Center (EORTC, PORTEC); Kathleen Darcy, Roswell Park Cancer Institute (GOG); Susan Davidson (NCRI); Philip DiSaia, University of California-Irvine (GOG); Ginny Filiaci, Roswell Park Cancer Institute (GOG); Gini Fleming, University of Chicago (GOG); Hani Gabra, Imperial College London (SGCTG); David Gaffney, University of Utah (RTOG); Patrica Goldman (patient advocate); Paul Goodfellow, Washington University (GOG); John Green, Liverpool University (EORTC, NCRI); Geoff Hall, University of Leeds (NCRI); Jane Hawnaur, University of Manchester; Thomas Hogberg, University of Linkoping (NSGO); Cath Holland, University of Manchester (NCRI); William Hoskins, Curtis and Elizabeth Anderson Cancer Institute (GOG); James Linsey; Anjua Jhingran, The University of Texas MD Anderson Cancer Center (RTOG); Sokbom Kang, Seoul National University (KGOG); Sean Kehoe, Birmingham Women's Hospital (NCRI); Jae Weon Kim, Seoul National University (KGOG); Henry Kitchener, University of Manchester (NCRI); Ikuo Konishi, Shinshu University (JGOG); Gunnar Kristensen, Norwegian Radium Hospital (NSGO); Jonathan Ledermann, Kings College Hospital (NCRI); Kim Leslie, University of New Mexico (GOG); Tracey Lively, NCI; Jac Livsey; Karen Lu, The University of Texas MD Anderson Cancer Center (GOG); Christian Marth, Innsbruck Medical University (AGO-Austria); Luiz Mathias, Brazilian National Cancer Institute; Glenn McCluggage, Royal Group of Hospitals Trust, Belfast (NCRI); Dynes McConnell, Wellington Hospital, NZ (ANZGOG); Scott McMeekin, University of Oklahoma (GOG); Larry Maxwell, Walter Reed Army Medical Center (GOG); David Miller, University of Texas-Dallas (GOG); Arno Mundt, University of Chicago (RTOG); George Mutter, Brigham and Women's Hospital (GOG); Jane Orton, Leeds Teaching Hospital NHS Trust (NCRI); Amit Oza, Princess Margaret Hospital (NCIC CTG); Tim Perren, St James's University Hospital, Leeds (NCRI); Ray Petryshun, NCI; Sandro Pignata, National Cancer Institute, Naples, Italy (MITO); Karl Podratz, Mayo Clinic (GOG); Melanie Powell (NCRI); Marcus Randall, University of Kentucky (GOG); Nick Reed, University of Glasgow (EORTC); Satoru Sagae, Sapporo Medical University, Japan (JGOG); Helga Salvesen, Haukeland University Hospital, Bergen, Sweden (NSGO); Jalid Sehouli, Charite Campus, Virchow Klinikum, Berlin, Germany (AGO); Eamonn Sheridan, St James's University Hospital, Leeds (NCRI); Brian Slomovitz, The University of Texas MD Anderson

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