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The Pathology of the Endocervix

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The most important recent advances in endocervical pathology relate to the following:

1. Lobular endocervical hyperplasia and its relationship to minimal deviation adenocarcinoma and primary gastric type adenocarcinoma of the cervix.

There is increasing evidence, particularly emanating from Japan and including immunohistochemical findings, that lobular endocervical hyperplasia is a form of gastrointestinal metaplasia of the cervix; more precisely gastrointestinal metaplasia of gastric pyloric type. The recent literature also suggests that there is a relationship between lobular endocervical hyperplasia and minimal deviation adenocarcinoma (adenoma malignum).

Lobular endocervical glandular hyperplasia may exhibit a pyloric gland phenotype, being positive for HIK1083 (an antibody directed against a gastric mucin-type oligosaccharide) and M-GGMC-1 (an antibody that reacts with pyloric gland-type mucin. The gastric phenotype is also frequently expressed in minimal deviation adenocarcinoma and a possible link between minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia has recently been suggested. Stromal immunoreactivity for alpha-smooth muscle actin is seen in minimal deviation adenocarcinoma and well differentiated endocervical adenocarcinoma, whereas stromal cells in lobular endocervical glandular hyperplasia and adenocarcinoma-in-situ are alpha-smooth muscle actin negative. This finding may aid the recognition of destructive stromal invasion in difficult cases.

2. The role of p16 and other markers of cell proliferation/apoptosis in the immunolabelling of glandular intraepithelial neoplasia

p16 is a tumour suppressor gene that plays a central role in the regulation of cell cycle progression and differentiation by controlling the activity of tumour-suppressor protein pRb. In squamous cervical neoplasia, overexpression of p16 protein is induced by HPV. P16 is also proving to be a useful marker for the detection of adenocarcinoma of the cervix and its precursors. All cases of cervical glandular intraepithelial neoplasia exhibit strong positivity. Its overexpression is associated with the presence of high-risk HPV. It has been argued that p16 expression is a surrogate marker of human papillomavirus (HPV) infection. Whilst this may be true for cervical squamous epithelium, the position is more complicated for endocervical epithelium. However, tubo-endometrioid metaplasia and endometriosis may show focal p16 immunoreactivity. MIB-1 is also a useful marker of endocervical neoplasia, although in rare cases an overlap between benign and neoplastic cases may exist. Recent evidence suggests that rare HPV – negative cervical adenocarcinomas may express p16.

3. The application of immunohistochemistry in the distinction between primary endocervical adenocarcinoma and endometrial adenocarcinoma metastatic to the endocervix

Great emphasis has been placed in the literature on the immunohistochemical distinction between endocervical and endometrial adenocarcinoma in biopsy specimens. Those histopathologists who regularly attend multidisciplinary team meetings in gynaecological oncology are aware, however, that this is often an artificial diagnostic scenario created by the pathologist working in isolation. In reality, such a diagnostic conundrum is often satisfactorily and accurately resolved by modern gross imaging techniques, rendering time consuming immunohistochemistry unnecessary. Nevertheless, the (often redundant) immunocytochemical gymnastics that may be performed to resolve such a diagnostic dilemma include CEA, hormone receptors, vimentin, p16, CD10 and even HPV typing.

However, there continue to be difficult/controversial aspects of endocervical pathology including:

1. The recognition of benign lesions that may be erroneously diagnosed as intraepithelial or invasive glandular neoplasia

In reality, whilst much is made of the distinction between a variety of benign and neoplastic endocervical lesions, most cases of tunnel clusters, microglandular and mesonephric hyperplasia provide little diagnostic challenge and the detailed discussion of their potential misdiagnosis is sometimes perhaps, somewhat contrived. Hopefully, the time has long since gone when florid mesonephric hyperplasia, for example, was erroneously diagnosed as adenocarcinoma. Uncommon lesions such as “diffuse laminar endocervical hyperplasia”, endocervical-type adenomyoma and ectopic prostatic tissue, however, still have the potential for diagnostic confusion whilst Aria-Stella change in the endocervix may be diagnosed erroneously as cervical glandular intraepithelial neoplasia by the unwary.

2. The recognition of the spectrum of cervical glandular intraepithelial neoplasia of a lesser degree than adenocarcinoma-in-situ

This remains one of the most controversial areas of endocervical pathology and, it is fair to say, that there is a greater acceptance in the United Kingdom than in the United States of a spectrum of endocervical glandular neoplastic change that falls short of adenocarcinoma-in-situ. The evidence base provided by special techniques for this spectrum has recently been rehearsed. A new scoring scheme for non-invasive endocervical glandular lesions has recently been proposed based on nuclear atypia, stratification and mitoses/apoptosis.

3. The clinical significance of involvement of margins cervical excision biopsy specimens by cervical glandular intraepithelial neoplasia

Residual disease was found at hysterectomy in 43%, 50% and 33% for low grade, high grade cervical glandular intraepithelial neoplasia and microinvasive adenocarcinoma respectively. This was correlated with positive margins, or disease within 3mm of margins of loop specimens. It has been suggested that some apparent post biopsy “failures” might be due to

de novo neoplasms that begin at the neosquamocolumnar junction rather than recrudescence of persistent adenocarcinoma-in-situ.

4. The recognition of “microinvasive adenocarcinoma”

We are indebted to the work of the late Andrew Östör who provided much of the evidence base to guide our recognition and management of this lesion. Microinvasive adenocarcinoma is a distinct pathological entity that can be confidently diagnosed in most cases. Because it seems to behave in the same manner as its squamous counterpart, it should be treated similarly. However, only one-third of patients with microinvasive adenocarcinoma (as with squamous lesions) are eligible for cold knife conization as conservative treatment because of compromised margins. To be treated successfully, the cone biopsy must be adequately sampled. There is no role for loop electro-excision procedures in the management of glandular neoplasms, either in situ or early invasive, as the state of the margins cannot be assessed adequately due to fragmentation and/or diathermy artefact.

5. The recognition of rare variants of endocervical adenocarcinoma

Whilst minimal deviation adenocarcinoma continues to cause diagnostic difficulty (one can be reassuring that most putative cases seen in consultation are, in fact, benign lesions), the single biggest problem in this area is the over-enthusiastic use of the term villoglandular adenocarcinoma, since the mere presence of a villoglandular architecture is insufficient for this particular diagnosis. Well differentiated villoglandular (papillary) adenocarcinoma is a term that should be reserved only for those cases showing minimal (Grade 1) cytological atypia.

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Predicción de la recidiva tras la conización en lesiones intraepiteliales del cérvix uterino

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La neoplasia cervical intraepitelial de grado 2 o 3 (CIN2-3 en su acrónimo inglés) es una lesión precancerosa causada por la infección persistente por el virus del papiloma humano (VPH). Dicha lesión presenta un elevado riesgo de transformación a carcinoma invasor. Por ello en los protocolos clínicos actuales se considera a estas lesiones como tributarias de tratamiento escisional, con el objeto de prevenir la progresión. En los últimos años la conización realizada con el asa de diatermia se ha convertido en el tratamiento de elección para estas lesiones, puesto que ha demostrado numerosas ventajas sobre los otros métodos.

A pesar de que la escisión resulta efectiva en la mayoría de los casos, entre un 5% y un 25% de las pacientes tratadas por CIN2-3 desarrollan recidivas tras la conización. Estas nuevas lesiones pueden ser resultado de la persistencia de la lesión previa (lesión residual por escisión incompleta o fallo de tratamiento) o bien estar causadas por una nueva infección tras la conización (lesión recurrente). Por todo ello, se considera obligatoria la vigilancia estrecha tras la conización para identificar las recidivas, las cuales son también tributarias de tratamiento. El seguimiento de las pacientes conizadas se ha realizado clásicamente mediante citología cérvico-vaginal. En los protocolos vigentes la citología debe ser realizada durante largos períodos de tiempo tras el tratamiento. Así, por ejemplo, los protocolos clínicos del Reino Unido o de los Estados Unidos de América recomiendan citología anual hasta 5-10 años después del tratamiento.

En los últimos años la citología ha recibido críticas crecientes debido a su relativa baja sensibilidad, que se traduce en un número alto de falsos negativos. Diferentes estudios han demostrado que este riesgo de resultado falso negativo parece ser mayor en las citologías de control post-tratamiento. Es por ello que en la última década se ha iniciado la introducción de estrategias diferentes de seguimiento con el objeto de reducir esta elevada tasa de falsos negativos.

Como se ha expresado anteriormente, la presencia de VPH es un requisito necesario, no solo para el desarrollo de CIN2-3, sino también para el desarrollo de recidivas tras el tratamiento. De este modo, en los últimos 10 años numerosos estudios ha demostrado de forma muy consistente el gran valor de la detección del VPH mediante técnicas moleculares en el seguimiento de las pacientes tratadas mediante conización. En todos los estudios publicados hasta el momento la determinación del VPH se ha realizado a los 6 o a los 12 meses del tratamiento. Bajo estas condiciones, dichos test moleculares están en la actualidad ampliamente aceptados en la práctica clínica para el seguimiento de las pacientes tratadas de CIN2-3. Estas pruebas han demostrado en todos los estudios publicados una sensibilidad y unos valores predictivos negativos próximos al 100%, muy superiores a los de la citología.

Nuestro grupo ha planteado recientemente la hipótesis de que tanto la citología como los test moleculares de detección del VPH podrían ser realizados en muestras tomadas de

forma intraoperatoria, inmediatamente tras la conización. Esta hipótesis se basa en la evidencia de que las lesiones precancerosas se originan prácticamente siempre en la zona de transformación y en que tras la escisión, que siempre debe incluir la lesión colposcópica y la zona de transformación, la mayoría de las pacientes resuelven tanto la lesión premaligna como la infección por VPH. Todo ello sugiere que la infección por el VPH está localizada en la zona de transformación y en el área de lesión colposcópica y que por tanto, la comprobación de su erradicación podría realizarse no ya a los 6 meses o al año, sino de forma inmediata tras realizar la exéresis de la zona.

En el primer estudio piloto realizado, en el que se han incluido 139 pacientes se ha evidenciado que la realización de test de VPH (captura de híbridos, Qiagen) en muestras de citología líquida tomadas inmediatamente tras la conización, durante el mismo acto quirúrgico tienen un valor semejante al de la determinación realizada a los 6 o 12 meses tras el tratamiento.

En nuestro estudio se demostró fallo del tratamiento (recidiva del CIN2-3) en el 9,1% de las mujeres. La detección del VPH en la muestra tomada de forma intraoperatoria tuvo una sensibilidad, especificidad y valores predictivos positivo y negativo para la detección de la recidiva de CIN2-3 de 91,7%, 78,3%, 62,2%, y 96,0% respectivamente. Estos datos fueron semejantes a los de la detección a los 6 meses (91,7%, 76,0%, 64,0%, y 95,1%) y mejores que los de la citología realizada en la muestra intraoperatoria o a los 6 meses, el análisis de los márgenes quirúrgicos del cono o el legrado endocervical. La detección del VPH en la muestra intraoperatoria se asoció de forma muy clara con el fallo de tratamiento en el análisis multivariado (odds ratio: 15,40; intervalo de confianza del 1,58-150,42). Es interesante resaltar que un número significativo de pacientes la muestra intraoperatoria no fue valorable para citología, debido al artefacto morfológico o a la escasa celularidad, mientras que fue siempre evaluable para el test molecular.

En conclusión, aunque son aún necesarios más estudios para confirmar estos prometedores datos iniciales, nuestros resultados indican que la detección del VPH en la muestra intraoperatoria puede mejorar los protocolos de seguimiento de las pacientes tratadas por CIN2-3. Esta nueva estrategia puede permitir un re-tratamiento inmediato de los fallos de tratamiento y una reducción de controles innecesarios en pacientes con resultado negativo en el test de VPH, las cuales tienen un riesgo de recidiva muy bajo.

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Avances en la patología molecular del cáncer de endometrio

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In the western world, endometrial carcinoma (EC) is the fourth most common cancer among women, with an estimated incidence at 10-20 per 100.000 women. There are two main clinic-pathological variants of EC; endometrioid endometrial carcinomas (EEC) (type I), and non-endometrioid endometrial carcinomas (NEEC) (type II). EEC are estrogen-related carcinomas that usually develop in perimenopausal women and coexist or are preceded by complex and atypical endometrial hyperplasia. Histologic grading is a good prognostic indicator in EEC. The vast majority of EEC are low grade tumors (grades I and II, EEC I-II), and are associated with good prognosis when they are restricted to the uterus. Prognosis is poorer when the tumor recurs or metastasizes. Grade III EEC (EEC III) is an aggressive tumor, with increased frequency of lymph node metastasis, and some authors think that should be regarded as a type II tumor. NEECs are very aggressive, unrelated to estrogen stimulation, arising occasionally in endometrial polyps or from precancerous lesions developing in atrophic endometrium that mainly occur in older women; NEEC include serous (SC) and clear cell carcinoma. NEEC are regarded as high grade tumors, by definition. SC has a high tendency to develop lymph node metastasis and peritoneal spread. Classification of EC in these two types is probably too rigid, as tumor showing combined or mixed features are not infrequent in daily practice. EEC III and NEEC are considered high-grade tumors. SC and EEC III have been compared using the surveillance, epidemiology and End Results (SEER) program data from 1988 to 2001. They represented 10% and 15% of EC respectively, but accounted for 39% and 27% of cancer death respectively.

The molecular alterations involved in the development of EEC are different from those of NEEC. EEC shows Microsatellite Instability (MI), as well as mutations in PTEN, k-RAS, and CTNNB1, whereas NEEC exhibit alterations of p53,widespread loss of heterozygosity, as reflected by chromosomal instability as well as other molecular alterations. In both types of EC the molecular alterations can occur not only during the initial steps of the neoplastic transformation but also during tumor progression, especially in myometrial invasion and metastasis. MI is seen in in 25-30% of sporadic EC, in association with MLH-1 promoter hypermethylation. MI occurs more frequently in EEC (30%) than in NEEC. The MI-associated mismatch repair deficiency leads to the accumulation of mutations in coding and non-coding DNA sequences. Some small short-tandem repeats, like mononucleotide repeats, located within the coding sequence of some important genes; (BAX, IGFIIR, MSH3, and others) are targets in the process of tumor progression of MI+ EC. Mutations in these tracts are interpreted as secondary events in cancers with MI. PTEN is frequently abnormal in EC.

LOH at chromosome 10q23 occurs in 40% of EC. Somatic PTEN mutations are also common in EC, and they are almost exclusively restricted to EEC, occurring in 37-61% of them and lead to activation of the PI3K/AKT pathway. There are many evidences showing that EECs with mutations in PTEN have genomic instability.

Mutations in PIK3CA may contribute to the alteration of the PI3K/AKT signaling pathway in EC. Mutations are predominantly located in the helical (exon 9) and kinase (exon 20) domains, but they can occur also in exons 1 to 7. PIK3CA mutations occur in 24-39% of the cases, and coexisted frequently with PTEN mutations. PIK3CA mutations, particularly in exon 20, have been associated with adverse prognostic factors such as high-grade and myometrial invasion. Although initially described in EEC, PI3KCA mutations also occur in NEEC, and also mixed EEC-NEEC. Furthermore, gene expression profile differences in the PI3K-AKT signaling pathway identify two subgroups of high-grade EC with different molecular alterations (PI3K/AKT pathway versus p53 alterations) which may play distinct roles in endometrial carcinogenesis. Moreover, mutations in PIK3RI (p85α), the inhibitory subunit of PI3K, have been detected in 43% of EEC, and 12% of NEEC.Among AKT targets, downstream effectors' mTOR is of particular interest. mTOR inhibitors have been recently developed as potential anticancer agents. The RAS-RAF-MEK-ERK signaling pathway plays an important role in EC.

The frequency of K-RAS mutations in EC ranges between 10 to 30%. RASSF1A inactivation by promoter hypermethylation may contribute significantly to increased activity of this signaling pathway. EC also shows frequent inactivation of SPRY-2 (a protein involved in the negative regulation of FGFR) and somatic mutations in FGFR2 (10-12%). FGFR-2 is of special interest, since it is a possible target for therapeutic approaches.

Mutations in exon 3 of beta-catenin gene (CTNNB1) occur in 14% to 44% of EC, and result in stabilization of the protein, cytoplasmic and nuclear accumulation, and participation in signal transduction and transcriptional activation through the formation of complexes with DNA binding proteins.

In contrast to EEC, NEEC show p53 mutations (90%), inactivation of p16 (40%) and E-cadherin (80-90%), c-erbB2 amplification (30%), alterations in genes involved in the regulation of the mitotic spindle checkpoint (STK15) and loss of heterozygosity at multiple loci, reflecting chromosomal instability. While p53 mutations occur in 90% of NEEC, they are only present in 10-20% of EEC. Mutation of the ARID1A gene and loss of the corresponding protein BAF250a has recently been found in 29% of EEC I-II and 39% of EEC III, 18% of SEC and 26% of uterine clear cell carcinomas.

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Características clínicas e histológicas del endometrio en el Síndrome de Lynch

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El Síndrome de Lynch (SL) es un síndrome de susceptibilidad genéticamente determinada a desarrollar distintos tipos de tumores, fundamentalmente cáncer colorrectal (CCR) y endometrial (CE), incluyendo el cáncer de ovario, urotelio y páncreas entre otros. Su herencia es autosómica dominante, asociada a mutaciones en los genes reparadores de los errores de replicación del DNA: MLH1, MSH2, MSH6 y PMS2 fundamentalmente. Las mujeres con SL tienen un riesgo alto de padecer CE; este riesgo es igual o mayor del riesgo de CCR (1) Más de la mitad de las mujeres con SL presentan el CE como "cáncer centinela" de esta enfermedad. Dicho riesgo es de 40-60%, siendo significativamente superior a la población general. La frecuencia de mutaciones germinales de los genes reparadores del DNA entre pacientes no seleccionados con CE es del 1,8-2,2%, similar al CCR (2). En mujeres jóvenes esta frecuencia aumenta hasta el 9%. Las mutaciones más frecuentes son en los genes MSH2 y MSH6.

Todos estos datos ilustran la importancia del CE en los pacientes con SL, a la vez que dan idea del enorme potencial contributivo que tiene el estudio del CE para la detección del SL. El conocer que pacientes con CE tienen SL permite el control para la prevención de otros tumores asociados a este síndrome, especialmente el CCR, beneficiando al propio paciente y a su familia.

Los datos clinicopatológicos del CE asociado al SL son escasos y difíciles de evaluar, ocurre dos décadas antes que el CE esporádico, asientan en el segmento inferior uterino, pueden presentarse de forma síncrona a carcinoma de ovario. Histológicamente pueden verse todos los tipos histológicos de CE, siendo el Carcinoma endometrioide el más frecuente, teniendo en cuenta que la variedad no endometrioide (puro o mixto) es alta cuando se compara con el CE esporádico. Existen ciertos rasgos morfológicos característicos (3), que incluyen un infiltrado denso linfocitario peritumoral a bajo aumento. Infiltrado inflamatorio linfocitario intratumoral, heterogeneidad tumoral, consistente en la yuxtaposición, de dos tipos. El prototipo es el componente de carcinoma desdiferenciado; carcinoma endometrioide bien diferenciado intimamente asociado a carcinoma indiferenciado. Y el carcinoma indiferenciado, constituido por una población monótona de células con escaso citoplasma, y nucleolo prominente. Probablemente el CE relacionado con el SL muestra generalmente rasgos anatomopatológicos más agresivos que su contrapartida esporádica (grado histológico alto entre carcinomas puros de tipo endometrioide, y casos con componente no endometrioide), invasión linfovascular y estadio avanzado.

El diagnóstico de SL se hace por la demostración en los pacientes de mutaciones en los genes reparadores de los errores de replicación del DNA: MLH1, MSH2, MSH6 y PMS2. La complejidad de su estudio genético hace que clásicamente se preseleccione a la población en base a criterios clínicos sobre sus rasgos clínicos más llamativos (edad de comienzo precoz y agregación familiar de cáncer), con sensibilidad y especificidad que se han revelado limitadas en CE. Modalidades de selección son el estudio de los tumores de pacientes mediante inestabilidad de microsatélites (IMS) y expresión de la tinción inmunohistoquímica

(IHQ) de las proteínas reparadoras del DNA, incluyendo en el caso de expresión patológica de MLH1, el estudio de metilación del promotor para descartar un CE esporádico.

Otras alternativas (3) lo constituyen la edad inferior a 50 años y rasgos morfológicos anteriormente descritos (heterogeneidad tumoral, carcinoma desdiferenciado/carcinoma indiferenciado, topografía y carcinoma síncrono de ovario), teniendo en cuenta que estos criterios morfológicos no han sido definitivamente establecidos y necesitarían una validación definitiva. Una de las propuestas actuales de selección, es el estudio mediante técnicas de IHQ de las proteínas reparadoras del DNA a todos los CE incidentes.

De forma análoga a lo observado en el CE asociado al SL, se puede observar la pérdida de la expresión de tinción IHQ de proteínas reparadoras de los errores de la replicación del DNA, concordante con el defecto genético germinal, en lesiones precursoras del CE, como la hiperplasia compleja, y no precursoras como el endometrio de características normales. Pudiendo ser indicativos de progresión a CE en mujeres portadoras de SL (4)

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Perfiles de expresión génica y nuevas dianas terapéuticas en cáncer de endometrio

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Endometrial cancer is the most common pelvic gynecologic malignancy in industrialized countries, and the incidence is increasing. The majority of endometrial cancers (72%) are detected in the early stage (stage I-II), whereas 20% have regional metastasis (stage III) and 8% distant metastasis (stage IV).

The needs for effective systemic therapies and for reliable prognostic markers in endometrial carcinoma have been addressed only partly. The most common basis for determining risk of recurrent disease has been the categorization of endometrial cancer in 2 subtypes. The majority are type I. This group comprises the endometrioid adenocarcinomas that are often preceded by atypical endometrial hyperplasia and express the estrogen (ER) and progesterone (PR) receptors. Type I endometrial cancers are usually low grade and rarely metastasize. The prognosis of type I cancer is favorable if diagnosed at an early stage, with a 5-year survival of >97% in stage I and >80% in stage II. Type II endometrial carcinoma are those of non-endometrioid histology, in particular serous or clear-cell morphology. These tumors are considered to be of high histological grade, poor prognosis, arise in the background of atrophic endometrium and do not seem to be related to the ER pathway. The molecular basis of the distinction between type I and II cancer is only partly understood. Type I endometrial cancers are usually microsatellite unstable and harbor *PTEN*, *KRAS*, *β-catenin* and *PIK3CA* mutations. In contrast, type II cancer is more often aneuploid and harbors alterations in *TP53, CDKN2A,* and *HER2*. Still, the value of this classification to predict prognosis and for treatment stratification is limited as 20% of type I endometrial cancers recur and 50% of type II cancer do not.

Currently, conventional chemotherapy regimens and anti-hormonal treatment are basis for adjuvant and systemic treatment of recurrent or metastatic endometrial cancer as targeted therapies are not yet available in the clinic. Several studies have aimed to detect and develop more applicable and improved markers for risk stratification for tailored treatment strategies in endometrial cancer. Several markers that could classify patients with endometrial cancer into low-risk, intermediate-risk, and high-risk groups have been suggested. New targeted therapy is not yet available in standard clinical practice. Recently, high-throughput mutation profiling analysis of primary and endometrial carcinomas has identified *KRAS*, *FGFR2* and *PIK3CA* to be frequently mutated in these tumors. Additionally, global genomic analysis of amplifications, deletions, and loss of heterozygosity in endometrial carcinomas suggested that PI3 kinase activation is associated with an aggressive behavior of the tumor. Thus, comprehensive molecular characterizations of primary tumors have identified several targets of which some have a potential for development and testing as targeted therapies in a metastatic setting, such as the PI3K/PTEN/AKT/mTOR pathway and FGFR 2 in particular.

The relevance and the antitumor effect of mTOR inhibitors for treatment of endometrial cancer is supported by the high prevalence of *PTEN* loss of function, *PI3K*

mutations, PI3K signalling activation, and amplifications in metastatic disease, all being linked to mTOR activation. The mTOR inhibitor rapamycin and its analogues are believed to inhibit mTOR signalling by forming a complex with FK506-binding protein 12 and mTOR.

Drugs targeting mTOR have been tested in clinical phase 1 and 2 trials as single agents. Unfortunately these have shown only modest effects, however they might have a yet unexplored potential because of a lack of biomarker restriction and because they were tested in mainly heavily pretreated patients. Also, the modest results could reflect a compensatory positive feedback loop from mTOR complex (mTORC) 2 on the AKT pathway thus escaping the inhibition of the mTORC1. Thus, second generation mTOR inhibitors targeting both mTORC1 and mTORC2 are in development and are being assessed in clinical trials. Still, accurate surrogate markers of clinical benefit from rapalogues have not been established. PTEN expression was not predictive of response to treatment, but this might be due to suboptimal PTEN antibodies for immunohistochemical analyses in formalin-fixed paraffin-embedded tissue. Evidence also suggests that *PIK3CA* mutations could predict response to mTOR inhibition. This suggestion is further supported by the recent study by Janku and colleagues, which showed that patients with *PIK3CA* mutations treated with PIK3/AKT/mTOR inhibitors had significantly higher response rates than did patients without mutations. Still, clinical trials ought to include more detailed biomarker analyses to identify potential predictive markers of sensitivity. One approach might be to test additional members of the PI3K/PTEN/AKT/mTOR pathway.

The fibroblast growth factor (FGF) and FGF receptor signalling axis plays a part in normal organ and vascular development. FGFR signalling through genetic modification or overexpression of the receptors or their ligands plays a key role in tumor angiogenesis. Activating and oncogenic *FGFR2* mutations located in the extracellular and kinase domains of the receptor have been described in 12% of endometrial carcinomas. Importantly, the *FGFR2* mutations identified in endometrial cancer were associated with sensitivity to FGFR inhibition. Preclinical in-vitro and in-vivo models show that inhibition of FGFR signalling leads to antiproliferative and proapoptotic effects, further supporting the FGF/FGFR axis as a promising therapeutic target in cancer. Still, the intimate involvement of FGF/FGFR signalling in normal biological processes remains a challenge, although recent advances in development of more selective inhibitors of the FGF/FGFR signalling pathway could allow further clinical testing. Accurate surrogate markers for clinical benefit from targeting the FGF/FGFR signalling need to be established.

Also EGFR, HER2, and VEGFR inhibitors have been tested in clinical phase 1 and 2 trials, with modest response rates. Still, these inhibitors could have a yet unexplored potential because they have only been administered as monotherapy to heavily pretreated patients. As shown for HER2-positive breast cancers, the biomarker-restriction approach and combination with chemotherapy has been important to facilitate implementation of new drugs into clinical practice.

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