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Gynecologic Tumors: Molecular Oncology

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ABSTRACT

Both oncologists and pathologists have acknowledged that the broad histologic classifications, particularly for ovarian and endometrial carcinomas, do not consistently separate groups with comparable clinical trajectories or therapeutic response patterns. When the findings from the Cancer Genome Atlas (TCGA) project were released during the previous decade, a paradigm shift was triggered. Instead of the two subtypes proposed by Bokhman in the 1970s, extensive genomic profiling data from TCGA has revealed that there are four molecular subgroups of endometrioid carcinomas.

Key words: Ovarian cancer; Diagnosis

INTRODUCTION

It is now clear that molecular factors are equally important for ovarian carcinomas (OC). Although OC is sometimes referred to as a single entity, it is actually a collection of diseases with distinct morphologies and biologic behaviours.

Advanced cervical cancer and recurring illness continue to be extremely challenging due to treatment resistance, similar to endometrial cancers. The most significant human papillomavirus (HPV) varieties can be prevented with effective preventive vaccinations, however uptake is still low. Oncoproteins E6 and E7 are desirable targets for cancer treatment. They are constitutively expressed in HPV-positive malignancies, particular to the tumour, crucial to the activity of the tumour cells, and identified as tumour antigens by the adaptive immune system. This paper provides an overview of recent developments in molecular pathology [1,2].

LITERATURE REVIEW

Under estrogenic hyperstimulation, this form of tumour typically occurs in peri and postmenopausal women. The majority of patients receive their diagnosis during the sixth and seventh decade of life, however in 5% of cases; the tumour affects women before the age of 40. The majority of women with endometrial cancer are discovered at an early stage and have a fair prognosis; however the high grade group is responsible for a disproportionately high percentage of endometrial cancer fatalities [3]. The subject of numerous investigations, there are currently no routinely accessible biomarkers in clinical practise that can predict the chance of progression from endometrial hyperplasia to invasive carcinoma. However, there are a number of molecular biomarkers under investigation that have the potential to be employed for therapeutic purposes in the future [4].

Endometrial cancer

In affluent nations, endometrial cancer is the most prevalent gynecologic malignancy [5]. Over 380,000 new cases were reported globally in 2018. Endometrial cancer cases that have just been discovered in the US have been rising over time. This sad fact is only anticipated to get worse due to the growing obesity pandemic and the significant relationship between weight gain and the risk of endometrial cancer.

Gene-based biomarker

Biomarkers are quantifiable indications used to forecast clinical prognosis and immunotherapy susceptibility. They are crucial for determining which individuals are most likely to

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react to treatment and preventing negative drug side effects in those who are unlikely to benefit. Mutations involving distinct sets of genes are linked to both endometrioid and non-endometrioid tumours. 9 genes' targeted exon sequencing on 393 endometrial carcinomas [6]. While TP53 and PPP2RIA were linked to serous type, PTEN, KRAS, and ARID1A were linked to endometrioid type.

PTEN: Phosphoinositol-3-kinase/AKT signalling is inhibited by the tumour suppressor phosphatase and tensin homolog (PTEN), which also inhibits cell growth. In 83% of cases of endometrial cancer, PTEN is mutated. Undifferentiated and mixed carcinomas can also lose PTEN expression.

KRAS: KRAS is a proto-oncogene that is largely involved in the cellular response to extracellular signals and is found at chromosome 12 (12p12.1). It has a strong correlation with the down-regulation of the phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene (PI3K/AKT) and mitogen-activated protein kinase (MAPK) pathways. Ten to thirty percent of endometrioid endometrial tumours had KRAS mutations. The majority of studies—but not all of them—show that MSI tumours have a greater frequency of KRAS mutations. Activated KRAS is typically linked to increased cell survival, proliferation, and transformation during cancer. On the other hand, KRAS mutations are equally common in tumours with and without hyperplasia, and epidemiologic findings appear to support the idea that KRAS activation is linked to the development of malignant endometrial tumours without the necessity for a switch to hyperplasia.

ARID1A: Cancers with endometrium-related characteristics, such as ovarian clear cell carcinoma, ovarian endometrioid carcinoma, and uterine endometrioid carcinoma, have been linked to mutations in the tumour suppressor gene AT Rich Interactive Domain 1A (ARID1A).

p53: According to research on the function of p53 in endometrial cancer and hyperplasia, the p53 gene mutation is absent in endometrial hyperplasia but present in a subgroup of aggressive endometrial adenocarcinomas. Furthermore, p53 mutations, which are the hallmark of this histotype and are present in 80–90% or more of these tumours, are substantially more common in serous carcinomas than in endometrioid carcinoma [7-9]. The single most crucial molecular determinant for predicting prognosis in endometrial carcinomas is p53 mutational status, with the presence of a p53 mutation being associated with a poor prognosis.

PPP2R1A: A missense mutation in PPP2R1A is present in about 41% of serous carcinomas, but only in 5% of endometrial endometrioid carcinomas. PPP2R1A mutations are also common in undifferentiated carcinomas and very aggressive uterine carcinosarcomas. The Aa subunit of type 2A protein phosphatases (PP2A), which is encoded by PPP2R1A, may have a significant but as-yet-unidentified role in the aetiology of several cancers.

DISCUSSION

Endometrial cancer

A missense mutation in PPP2R1A is present in about 41% of serous carcinomas, but only in 5% of endometrial endometrioid carcinomas. PPP2R1A mutations are also common in undifferentiated carcinomas and very aggressive uterine carcinosarcomas [8]. The Aa subunit of type 2A protein phosphatases (PP2A), which is encoded by PPP2R1A, may have a significant but as-yet-unidentified role in the aetiology of several cancers. Patients with familial non-polyposis colon cancer syndrome are more likely to develop endometrioid endometrial carcinoma (EEC), with premenopausal women being the most frequently affected.

Classification of endometrial carcinomas

Based on epidemiological, clinical, and endocrine characteristics, Bokhman postulated that endometrial carcinomas can be divided into two pathogenetic kinds. Hyperestrogenism is hypothesised to be connected to type I cancers. Infertility in the premenopausal period, anovulatory bleeding, obesity, and related metabolic disorders are phenotypical characteristics of patients with these malignancies. These tumours frequently exhibit frequent progesterone sensitivity, high or moderate levels of differentiation, superficial myometrial invasion, and a good prognosis. In contrast to type I tumours, type II tumours appear unconnected to hyperestrogenism, and the endometrium in these women frequently appears atrophic. Poorly differentiated tumours, profound myometrial invasion, and pelvic lymph node metastases are more prevalent in type II cancers.

Since there was no distinct difference between the categories and too many patients defied type I or type II classification, the type I and type II classification did not enter diagnostic practise. In actuality, it is also difficult to distinguish between the related histotypes, such as endometrioid or serous, and some tumours have unclear shape. Numerous studies have examined the prognostic and predictive implications of one or more biomarkers or molecular features as a result of the demand for more physiologically meaningful molecular tools to categorise cancers and stratify according to risk of metastasis and recurrence. The Joint Cancer Genome Atlas was the most thorough of these analyses (TCGA).

Within The Cancer Genome Atlas (TCGA) cohort, the copy-number high subgroup had the worst prognosis, whereas the POLE subgroup had the best clinical outcome. There has been a lot of interest in creating a panel of tests that recreate TCGA classification in order to assess the usefulness of such classifiers in risk prediction because integrated genomic analysis is currently not viable in the clinical setting [10]. By using straightforward, inexpensive, molecular-based classification methodologies that closely resemble TCGA subtypes, a team from the University of British Columbia has made an effort to close the gap by demonstrating that molecular classification of endometrial cancer is feasible in routine clinical practise on formalin-fixed paraffin-embedded samples.

This molecular classification technique, known by the Vancouver group as "Proacted Molecular Risk Classifier for Endometrial Cancer" (ProMisE), makes use of three immunohistochemistry stains: p53, MMR proteins PMS2 and MSH6, and POLE exonuclease domain hotspot sequencing. The resulting molecular subtypes are referred to as the p53 wild type/nonspecific molecular profile (p53wt/NSMP, surrogate

of TCGA copy-number low), p53 abnormal (p53 abnormal for staining patterns consistent with missense or null mutations, surrogate of copy-number high), MMR defective (MMR-D, surrogate of MSI-H), and POLE exonuclease domain mutant.

Therapeutic targets

Surgery, including abdominal or laparoscopic hysterectomy and salpingo-oophorectomy, with or without lymph node assessment, is the main treatment for endometrial cancer in women. Currently, adjuvant therapy is advised based on a patient's unique risk (low, middle, and high risk), which is composed of clinical (age) and pathological (FIGO stage, tumour type, grade, and the existence of unambiguous lymphovascular space invasion) elements. Recurrent or metastatic gynaecological cancers continue to be fatal despite advancements in cancer treatment and the advent of new treatments with unique mechanisms of action. The Cancer Genome Atlas and subsequent, more streamlined classifiers have improved our understanding of this disease, and these molecular classifications are now starting to guide our therapy choices.

Endocrine therapy

Endometrial cancer (EC), especially endometrioid EC, frequently expresses oestrogen (ER) and progesterone (PR) receptors, with a reported frequency of 72-81%. ER and PR are linked to low-grade tumours, better tumour histology, and favourable prognoses [11]. They can also activate or inhibit the transcription of a number of genes.

Lower disease-free survival and higher grade malignancies are associated with ER or PR expression loss. Progestins alone and progestins alternated with tamoxifen are two often used regimens. The use of progestins alternated with tamoxifen in patients who had never received chemotherapy led to response rates between 27 and 33%.

Epithelial ovarian cancer

The majority of women present with symptoms of advanced disease, which frequently involves the peritoneal cavity in addition to the ovary, which contributes to the high mortality rate associated with EOC. Since the 1980s, survival rates have not altered considerably (European 5-year survival is still about 40%). High-grade serous carcinomas (70%) predominate, followed by endometrioid carcinomas (10%), clear cell carcinomas (10%), mucinous carcinomas (3%), and low-grade serous carcinomas (<5%).

CONCLUSION

Sustained infection by human papillomavirus (HPV) is profoundly related to the carcinogenesis of cervical cancer. Researchers have conducted mechanistic analyses of the relationship between HPV status and PD-L1 expression in HPV-related solid tumors, primarily in head and neck squamous cell carcinoma and uterine cervical cancer.

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