Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(11): 229
https://doi.org/10.31083/j.ceog5011229

Editorial

Pathogenesis and Treatments of Endometrial Carcinoma

Aris Raad Besharat[1,2], Andrea Giannini[2,*], Donatella Caserta[1]

[1]Gynecology Division, Department of Medical and Surgical Sciences and Translational Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, 00189 Rome, Italy
[2]Department of Medical and Surgical Sciences and Translational Medicine, PhD Course in "Translational Medicine and Oncology", Sapienza University, 00189 Rome, Italy
*Correspondence: andrea.giannini@uniroma1.it (Andrea Giannini)

Academic Editor: Michael H. Dahan
Submitted: 2 August 2023 Revised: 24 August 2023 Accepted: 28 August 2023 Published: 9 November 2023

Endometrial cancer (EC) is a common gynecological malignancy with an estimated incidence of more than 65,000 new cases in the United States in 2022 [1]. Considering the increase in incidence over the last decade and the continuing high mortality, it is crucial to better understand the causes and the treatment of this malignancy [2,3]. The essential prerequisite to understand EC pathogenesis is an effective classification of ECs, to better determine oncological outcomes [4,5]. The year 2013 marks a turning point, when the Cancer Genome Atlas (TCGA) Research Network surpassed the limits of dualistic EC classification by incorporating molecular analysis of EC using the most modern array and sequencing-based technologies [6]. Consequently, ECs were re-classified and divided into the following four classes with individual recurrence risk and progression-free survival (PFS): DNA polymerase epsilon (POLE), microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR), copy-number-low/TP53-wild-type (CNL), and copy-number-high/TP53-mutant (CNH/p53abn). Since TCGA classification had some practical limits for immediate clinical application, a new algorithm whose acronym is ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) was adopted as determined by the Institute of Medicine's guidelines. Numerous steps are included in this model that has been widely validated [7]. Moreover, the available data confirmed the applicability of this model to the final and diagnostic specimens (i.e., hysterectomy, curettages or endometrial biopsies) [5]. These innovative steps had been applied in the last European Society for Radiotherapy and Oncology (ESTRO)—European Society of Gynaecological Oncology (ESGO)—European Society of Pathology (ESP) 2020 Guidelines for the approach to women with EC with the objective to use specific profiling to determine the most suitable and personalized adjuvant approaches [3].

As known, surgery (independently from any adjuvant treatment) is the gold standard treatment for early-stage EC. Advanced and recurrent diseases can be treated with few therapeutic alternatives. Surgery with adjuvant chemotherapy or chemotherapy alone is the treatment of choice for the disease at Federation International of Gynecology and Obstetrics (FIGO) stage III-IV and metastatic and recurrent EC, respectively [8,9]. To date, no standardized second-line therapy exists and starting from this strong scientific evidence, the adoption of genomic and molecular profiling has turned out to be an excellent tool to prognosticate and treat EC. However, no strong evidence to support the use of molecular profiling for the choice of post-surgical management in patients with FIGO I-II stage disease exists. In contrast, higher-stage cancer might profit from tailored post-operative therapies based on molecular analysis, mainly as advanced MSI-H/dMMR.

The immune checkpoints are highly expressed in the tumor microenvironment and the use of immune checkpoint inhibitors (ICIs) makes tumor cells susceptible to immune system response. The most known are the ICIs targeted against Programmed Death Ligand1 (PD-L1) and Programmed Death-1 (PD-1) [8,10]. Pembrolizumab is a humanized anti-PD-1 monoclonal antibody used as second-line treatment for patients with advanced MSI-H/dMMR tumors and its efficacy has been demonstrated in a phase II study KEYNOTE-158. The use of Pembrolizumab was approved in 2017 by the Food and Drug Administration (FDA) for patients suffering solid metastatic tumors, including EC [10]. In 2019, the efficacy of Lenvatinib, which inhibits vascular endothelial growth factor receptor 1, combined with Pembrolizumab, was demonstrated by a phase II study for patients with recurrent or advanced EC, regardless of MMR status, after multiple (first or second lines) previous treatment with of platins chemotherapy. Due to strong evidence, the combined use of Pembrolizumab and Lenvatinib is the second-line currently in use for the treatment of advanced/metastatic EC after progression following platinum-based chemotherapy. Many studies on this topic are in progress [9,10]. There are currently several prospective studies in progress to detect the maximum effective approach for the treatment of endometrial cancers, especially for patients with involved lymph nodes and low disease load. Studies are setting first-line ICIs, with the aim of identifying a treatment for newly diagnosed recurrent or advanced disease without chemotherapic drugs.

KEYNOTE-C93/GOG-3064/ENGOT-en15 and DOMENICA trials are analyzing ICIs (Pembrolizumab and Dostarlimab) *vs.* chemotherapy in recurrent dMMR

or advanced EC. Further trials are evaluating the use of immunotherapy-added chemotherapy. The RUBY trial (a double-blind randomized trial) aims to demonstrate the effectiveness of Dostarlimab in advanced stage or recurrent EC. The aim is to assess the safety and efficacy of Dostarlimab added to carboplatin-paclitaxel in recurrent or advanced endometrial cancer compared to chemotherapy alone. Outcomes of patients will be assessed based on proficient DNA mismatch repair (pMMR) and dMMR. Finally, with the aim of combining tumor data, the RAINBO-umbrella program is considering new molecular profile-based adjuvant therapies, specific to each subclass, as an alternative to standard post-surgical therapy in EC. For p53-mutant, the p53abn-RED will compare adjuvant chemoradiation only versus adjuvant chemoradiation and Olaparib for two years. Moreover, adjuvant pelvic external beam irradiation and Durvalumab versus adjuvant pelvic radiotherapy in MMRd EC are compared in the MMRd-GREEN trial. For no specific molecular profile EC, in the NSMP-ORANGE study, the strategy of oral progestins for two years after adjuvant pelvic external beam radiotherapy will be investigated. The last POLEmut-BLUE will evaluate the security of adjuvant therapy de-escalation in POLE-mutant EC. In the era of precision medicine, these ongoing trials may overcome current limitations in EC subclass management by obtaining a tailored adjuvant treatment guarantying effectiveness, safety, quality of life, and cost-utility [11,12].

EC has a generally favorable prognosis. The surgical approach is the mainstay of early treatment. A tailored adjuvant therapy is necessary for selected patients, in particular for older and/or frail patients [13]. Another important role has been recently attributed to radiomic analysis in EC risk stratification, which provides additional information [14–16]. Radiomic analysis may assist in choosing the surgical treatment as demonstrated by several studies, however, additional research is needed. In addition, further studies will confirm these therapeutic products as initial standard treatment in metastatic and recurring EC.

The aim of this editorial is to briefly summarize the new scenarios in the treatment of endometrial cancer, adding a new point of view. The approach for endometrial cancer has become increasingly personalized, and the future is to define the genetic characteristics of the tumor at the outset, in order to the guide the therapeutic strategy, accurately and less invasively.

Author Contributions

ARB and DC designed the article. AG contributed to the analysis of the publications and supervision. ARB and AG wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Andrea Giannini and Donatella Caserta are serving as one of the Editorial Board members of this journal. Andrea Giannini and Aris Raad Besharat are serving as one of Guest editors of this journal. We declare that Andrea Giannini, Aris Raad Besharat and Donatella Caserta had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: A Cancer Journal for Clinicians. 2022; 72: 7–33.

[2] Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022; 399: 1412–1428.

[3] Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International Journal of Gynecological Cancer. 2021; 31: 12–39.

[4] Golia D'Augè T, Cuccu I, Santangelo G, Muzii L, Giannini A, Bogani G, *et al*. Novel Insights into Molecular Mechanisms of Endometrial Diseases. Biomolecules. 2023; 13: 499.

[5] Giannini A, D'Oria O, Corrado G, Bruno V, Sperduti I, Bogani G, *et al*. The role of L1CAM as predictor of poor prognosis in stage I endometrial cancer: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics. 2023. (online ahead of print)

[6] Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, *et al*. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497: 67–73.

[7] Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, *et al*. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017; 123: 802–813.

[8] Cuccu I, D'Oria O, Sgamba L, De Angelis E, Golia D'Augè T, Turetta C, *et al*. Role of Genomic and Molecular Biology in the Modulation of the Treatment of Endometrial Cancer: Narrative Review and Perspectives. Healthcare. 2023; 11: 571.

[9] Di Donato V, Giannini A, Bogani G. Recent Advances in Endometrial Cancer Management. Journal of Clinical Medicine. 2023; 12: 2241.

[10] Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, *et al*. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. The Lancet. Oncology. 2019; 20: 711–718.

[11] Slomovitz B, Cibula D, Gultekin M, Mansoor M, Maćkowiak-

Matejczyk B, Taylor A, *et al*. TP016/#1442 Keynote-C93/GOG-3064/ENGOT-EN15: phase 3, randomized, open-label study of first-line pembrolizumab versus platinum-doublet chemotherapy in mismatch repair deficient advanced or recurrent endometrial carcinoma. International Journal of Gynecological Cancer. 2022; 32: A230.

[12] NIH, U.S. National Library of Medicine. ClinicalTrial.gov. Available at: https://clinicaltrials.gov/ct2/results?cond=Endometrial+Cancer&term=&cntry=&state=&city=&dist=last (Accessed: 30 July 2023).

[13] Di Donato V, D'Oria O, Giannini A, Bogani G, Fischetti M, Santangelo G, *et al*. Age-Adjusted Charlson Comorbidity Index Predicts Survival in Endometrial Cancer Patients. Gynecologic and Obstetric Investigation. 2022; 87: 191–199.

[14] Bogani G, Chiappa V, Lopez S, Salvatore C, Interlenghi M, D'Oria O, *et al*. Radiomics and Molecular Classification in Endometrial Cancer (The ROME Study): A Step Forward to a Simplified Precision Medicine. Healthcare. 2022; 10: 2464.

[15] Di Donato V, Kontopantelis E, Cuccu I, Sgamba L, Golia D'Augè T, Pernazza A, *et al*. Magnetic resonance imaging-radiomics in endometrial cancer: a systematic review and meta-analysis. International Journal of Gynecological Cancer. 2023; 33: 1070–1076.

[16] Vizza E, Bruno V, Cutillo G, Mancini E, Sperduti I, Patrizi L, *et al*. Prognostic Role of the Removed Vaginal Cuff and Its Correlation with L1CAM in Low-Risk Endometrial Adenocarcinoma. Cancers. 2021; 14: 34.