International Journal of Clinical Oncology (2019) 24:910–916
https://doi.org/10.1007/s10147-019-01437-7

REVIEW ARTICLE

Immune check-point in endometrial cancer

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Received: 26 January 2019 / Accepted: 25 March 2019 / Published online: 2 May 2019

Abstract

Background Endometrial cancer (EC) is one of the most frequent tumors in women. Despite recent advances in treatment approaches, the prognosis in advanced, recurrent, or metastatic disease remains poor. The aim was to provide the clinician with an update, the current status, and the new developments in the management of EC. Based on the new EC molecular classification, we focused on the impact of immune check-point inhibitors.

Methods Pivotal trials, published literature, and conference proceedings were reviewed. PubMed and Scopus databases were searched to select English-language articles.

Results Immune check-point inhibitors are the subject of ongoing studies and their benefit seems to be related to microsatellite instability (MSI) status.

Conclusions Immune check-point inhibitors should be considered a promising treatment option to better personalize therapeutic strategies in EC.

Keywords Endometrial cancer · Immunotherapy · Immune check-point · Survival · Microsatellite instability · Mismatch repair

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, accounting for 5.9% of cancers in women [1]. Surgery is the gold standard. Adjuvant therapy determinations are based on risk factors and pathologic findings, including age, tumor grade, depth of myometrial invasion, involvement of the lower uterine segment, lymphovascular space invasion, tumor size and lymph node status [2]. As a general principle, in uterine confined disease, patients at high-intermediate risk for recurrence may benefit from adjuvant radiotherapy, whereas adding carboplatin/paclitaxel systemic regimen to adjuvant radiotherapy may reduce risk of distant metastasis in high risk cases [2]. In extra-uterine, recurrent or metastatic disease, multidisciplinary team is recommended to tailor the best treatment to provide long survival. Adjuvant systemic therapy combined or not combined with radiotherapy is considered the appropriate strategy, although the prognosis remains poor (5-year overall survival $<50\%$ and $<20\%$ in case of nodes and distant metastasis, respectively) [2, 3]. At present, limited treatment options remain for EC that have progressed following prior treatment. Latest researches showed exciting development of immunotherapy, especially check-point inhibitors, in gynecological malignancies [4, 5].

Our aim was to review the state-of-art of immune check-point inhibitors in EC. We analyzed the rationale of these emerging molecules and their main approaches under investigation in advanced, recurrent or metastatic disease. We also discussed tumor microenvironment and the new molecular classification of EC.

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Literature search

A search of PubMed and Scopus databases was conducted. We performed a Boolean search strategy using the following combinations of keywords: "endometrial cancer", "high risk", "recurrent", "metastatic", "immunotherapy", "immune check-point", "inhibitors", "PD-1", "anti-PD-1", "PD-L1", "pembrolizumab", "nivolumab", "microenvironment", "POLE-ultramutated", "mismatch repair", "microsatellite instability". We provided a comprehensive picture of immune check-point inhibitors perspectives in EC using hand searching (meeting proceedings of European Society for Medical Oncology and Society of Gynecologic Oncology) and clinicaltrials.gov. Literature search strategy was performed up to August 2018. Only English written publications were selected. Titles and abstracts of search results were screened to determine eligibility in the manuscript. Additional references were selected from relevant articles. Abstract from international meetings were included only if with appropriate and sufficiently powered statistical data.

Microenvironment in normal endometrial tissue

Under physiological conditions, it is well established that endometrial microenvironment is characterized by fluctuations in immune cell composition due to hormonal influences, to guarantee both immune protection and procreation [6, 7]. In the female reproductive tract, the innate and adaptive immune system is precisely modulated by sex hormones, including estradiol and progesterone. These hormones regulate the migration of macrophages, dendritic cells, T and B cells into the uterus, cervix and vagina. On the one hand, the endometrial epithelium represents the first-line protection against sexually transmitted pathogens. In addition, resident epithelial cells confer immune protection through the production of cytokines and chemokines, that recruit and activate other immune migratory cells, both innate and adaptive components [7]. Endometrial epithelial cells are also potent antigen-presenting cells [8]. Besides major histocompatibility complex (MHC) class I and class II expression, the presence of B7-H family molecules have been described [9].

Programmed death-1 ligand (PD-L1) (B7-H1) and programmed death-2 ligand (PD-L2) (B7-DC) are both ligands for the death receptor programmed death receptor 1 (PD-1). PD-L1 and PD-L2 are differently expressed. PD-L1 was found in more than 80% of normal endometrium; whereas PD-L2 expression was restricted to approximately half (47%) of normal endometrium [9]. Therefore, PD-1/PD-L interactions play an important role in the protection of normal tissues from T cells activation.

Microenvironment in endometrial cancer

Innate—natural killer (NK) cells, dendritic cells, macrophages and neutrophils—and adaptive—B cells and T cells, including cytotoxic (CD8 + T or CTL) cells, helper (CD4 + T) cells and NK T cells—immune cells are involved in EC development. Usually, when CD8 + T cells recognize tumor antigens, first processed by dendritic cells and then expressed on the cell surface bound to MHC class 1, they become CTL and attack tumor cells. In contrast to physiological conditions, both MHC class I and II molecules are down-regulated, facilitating immune escape [8]. In addition, as stated above, PD-L molecules are also described in EC tissue and its surrounding microenvironment. PD-L1 is present in 70–80% of malignant endometrial cells and in all uterine sarcoma cases. PD-L2 is expressed in a minority of EC patients (40–70%) and uterine sarcoma histology (0–32%) [9]. These data indicate that the PD-1/PD-L interactions could be a possible target for immune intervention in EC.

Immune check-point inhibitors

Malignant cells have numerous mechanisms to evade immune system, including the up-regulation of immune check-point proteins [10]. Immune check-point proteins refer to those different surface proteins that are expressed by activated lymphocyte. They are initiated by a ligand-receptor interactions and a dynamic balance between stimulatory and inhibitory signals regulate immune response [10]. This equilibrium phase is primarily guaranteed by PD-1/PD-L pathway—that inhibit T cell activation, proliferation and cytokine production—and cytotoxic T lymphocyte associated antigen 4 (CTLA-4) pathway—that induces cell-cycle arrest and apoptosis, in Tregs and activated T cells. But, once tumor cells express tumor antigens able to elude immune system, the equilibrium is altered and cancer progression becomes evident due to a dynamic and uncontrolled cells growth [4, 5]. Each immune check-point can be properly blocked by agonist or antagonist antibodies.

Microsatellite instability and mismatch repair deficiency

Traditionally, EC have been classified in type I tumors (mainly endometrioid carcinoma related to obesity, hormone-receptor positivity and favorable prognosis) and type II tumors (almost all serous carcinoma, hormone-receptor negative, with unfavorable prognosis, more common in older and non-obese women) [11]. Recent investigations have revealed that EC is a heterogeneous malignant disease. Molecular sub-classifications identify four distinct

subgroups: (1) polymerase DNA directed, ε, catalytic subunit (POLE)-ultramutated, (2) hypermutated/microsatellite-unstable, (3) copy number low/microsatellite-stable, (4) copy number high (serous-like) [12]. For the purposes of this review, we focused on POLE-ultramutated group and hypermutated/microsatellite-unstable group and we summarized the main features of remainders.

The PI3 K pathway is altered at high frequency (92%) in the copy number-low/microsatellite-stable subgroup. Whereas, as the name suggests, mutated genes involved in chromatin remodeling and ubiquitin-mediated protein degradation, which have a well established role in serous EC, are altered in the copy number high (serous-like) group [11, 13].

Both POLE-ultramutated and hypermutated/microsatellite-unstable groups consist of ECs exemplified by frequent mutations and it provides the underlying principle for a potential activity of immune check-point inhibitors. POLE-ultramutated EC is characterized by unusually high mutation rate (232×10^{-6} mutations per megabase), secondary to somatic mutations in the exonuclease domain of POLE. POLE is a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair [11]. This alteration is described in approximately 20% of EC and it is related to a more favorable progression-free survival compared to other molecular EC subgroups [13]. Basic knowledge of mismatch repair (MMR) deficiency and its relationship with microsatellite instability (MSI) should be useful to better understand the hypermutated/microsatellite-unstable subgroup. MMR process not only repair mismatched base pairs or incorrect insertion or deletion loops, but it is also involved in double-strand break repair, apoptosis and recombination [14]. To date, four genes are identified, including mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS homologue 6 (MSH6) and postmeiotic segregation increased 2 (PMS2). MMR deficiency can result from (1) a germline mutation in one of four MMR genes followed by a second inactivating somatic change in the remaining wild-type allele; or (2) a somatic mutation in both alleles of MMR gene. Independently of its origin, MMR deficiency harbors hundreds to thousands of somatic mutations, especially in microsatellite DNA regions. Mutations accumulation in these regions of the genome is defined as MSI. MSI status can be determined through the evaluation of selected microsatellite sequences that are particularly prone to copying errors when MMR is compromised. Generally, MSI-high (MSI-H) status is defined as two or more markers changed compared with matched normal; non-MSI-high (non-MSI-H) status is defined as one or no markers changed compared with matched normal. In total, 21 significantly candidate pathogenic driver genes have been identified in the hypermutated/microsatellite-unstable subgroup [13]. This molecular group includes tumors characterized by high mutation rate (18×10^{-6} mutations per megabase) and variable length of DNA microsatellites [15].

Approximately 30% of EC display MMR deficiency, up to 95% attribute to somatic mutations. The remained 5% is caused by germ-line mutations, especially linked to the autosomal dominant Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC). Strong evidence has shown increased EC incidence in breast-cancer susceptibility gene 1 (BRCA1) and breast-cancer susceptibility gene 2 (BRCA2) mutation carries (note: detailed analysis of this germline genomic alterations that confer susceptibility to EC is beyond the aim of this review) [16]. EC for defects in DNA MMR should be considered in all patients, but especially in patients younger than 50 years of age.

The real impact of MMR deficiency on EC prognosis and its predictive value remains unclear [14]. There are several retrospective series supporting improved survival outcomes in MMR deficient EC patients compared to those with proficient MMR [17–19]. Whereas, other reports suggested unfavorable prognosis in MMR deficient EC [20, 21] or showed no difference between groups [22, 23]. A recent meta-analysis explored the association between MMR status and clinical outcome in 23 EC studies [24]. Pooled analysis did not show any significant association between the presence of MSI and worse disease-free survival (hazard ratio [HR] 1.31, 95% confidence interval [CI] 0.39–4.34) and overall survival (HR 2.02, 95% CI 0.85–4.83). But there was marked inter-study heterogeneity (81% and 82%, respectively) and this can actually represent a relevant analysis limitation, as well as studies' retrospective nature. Moreover, 16 studies (73%) did not report multivariate analysis in their results. Definitive conclusions in term of association between MSI and outcome in EC patients cannot be drawn and further investigations are mandatory.

For sure, a proper subtype classification could be crucial to select appropriate adjuvant therapy. The available literature demonstrates an over-expression of PD-1 in both tumor-infiltrating and peritumoral lymphocytes of POLE-ultramutated and hypermutated/microsatellite-unstable EC tumors, supporting a potential role of immunotherapy targeting the PD-1/PD-L1 pathway [25, 26].

Current status

Immunotherapy for EC is still in its infancy. Only a small number of studies, with varying success rates, have been published. Details are listed in Table 1 [28–30]. At present, the Food and Drug Administration (FDA) expanded pembrolizumab approval also in EC patients with disease progression after standard therapy and without satisfactory alternative treatment options [31]. Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1

Table 1 Clinical trials on immune check-point inhibitors in endometrial cancer

Author	Phase	Patient population[a]	*N* patients	Treatment	Results
Ott et al. [28]	Ib	PD-L1 positive locally advanced or metastatic EC	24	Pembro 10 mg/kg every 2 weeks up to 24 months	ORR 13%; median PFS 1.8 months
Makker et al. [29]	Ib/II	Metastatic EC	23	LEN 20 mg/day + pembro 200 mg every 3 weeks	ORR 48%
Fleming et al. [30]	Ia	Advanced/recurrent EC	15	Atezo 1200 mg or 15 mg/kg every 3 weeks	ORR 13%; median PFS 1.7 months; median OS 9.6 months

N number, *PD-L1* programmed death ligand 1, *EC* endometrial cancer, *pembro* pembrolizumab, *ORR* objective response rate, *PFS* progression-free survival, *LEN* lenvatinib, *atezo* atezolizumab, *OS* overall survival

[a]Progressed after approved therapy

[32]. It derives from a nonhuman species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans [5, 32]. Pembrolizumab binds the PD-1 receptor on T cells and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, preserving T cell proliferation and cytokine production [30]. Durable response was noted in 24 patients with PD-L1 positive EC—from the KEYNOTE-028 study—who received this immunomodulatory monoclonal antibody [28]. Pembrolizumab 10 mg/kg was administered every 2 weeks for a maximum of 24 months or until disease progression, intolerable toxicity, death, consent withdrawal or investigator decision. Overall response was 13%. Only four patients experienced severe toxicity. No grade 4 toxicity, as well as immune-mediated reaction was observed. The median progression-free survival was 1.8 months (95% CI 1.6–2.7 months), whereas the median overall survival was not reached at the data cutoff. The 6-month and 12-month progression-free survival rates were 19.0% and 14.3%, respectively. The 6-month and 12-month overall survival rates were 67.0% and 51.0%, respectively. In total, 19 patients had tumor samples evaluable for MSI status; of these, the vast majority (94.7%) had not-MSI-H [28]. Of note, the only patient who was classified as MSI-high showed the best response.

Other anecdotal studies have been presented suggesting increasing responses in high-MSI endometrial cancer. Le et al. found a response rate of 71% in a cohort of mismatch repair–deficient patients, including two patients with endometrial cancer, treated with pembrolizumab [26]. It should also be underlined that other PD-1 positive patients have no clinical benefit with anti PD-1 therapy; therefore, the factors that determine whether patients will be drug sensitive or resistant are not fully understood and need to be investigated. Mehnert et al. [27] publish the case of a single patient with a rapid and prolonged (more than 14 months) clinical improvement once pembrolizumab treatment was initiated. Genomic assessment on the tissue sample of the patient showed a mutation in DNA polymerase epsilon (POLE) that associated with an ultramutator phenotype, and is associated with high mutational burden. This suggest that the presence of a POLE mutation might be considered as a driver of pembrolizumab response, a concept that should be investigated further.

The safety and efficacy of pembrolizumab and the utility of MSI status in advanced solid tumors, including EC, are currently investigated in the phase II MK-3475-158/KEYNOTE-158 trial and in the phase II NCT01876511 study [33, 34].

Ongoing trials Based on advances in molecular biology knowledge several immune check-point inhibitors, such as pembrolizumab, avelumab (anti-PD-L1), durvalumab (anti-PD-L1), atezolizumab (anti-PD-L1), nivolumab (anti-PD-1), are being tested in clinical trials for both primary treatment [35–37] and advanced, recurrent or metastatic EC that have progressed on standard of care therapy [38–49]. Due to scarcity of published results, all clinical trials, including those in set up, those active but not recruiting and those currently open to recruitment, are depicted in Table 2. Interestingly, there is a phase III trial, the KEYNOTE-775 [46]. In this study, patients with confirmed diagnosis of advanced, recurrent or metastatic EC will be randomly assigned to receive either pembrolizumab and lenvatinib or treatment of physician's choice (doxorubicin or paclitaxel). The primary study hypothesis is that pembrolizumab in combination with lenvatinib prolongs progression free survival and overall survival when compared to the treatment of physician's choice.

To date, the NivoPlus trial (NCT02423954) recruitment is terminated but currently no results are posted [50]. It is a phase Ib/II Study of nivolumab plus chemotherapy in patients with advanced metastatic cancer, including EC cases.

Table 2 Immune check-point inhibitors ongoing trials in endometrial cancer

	Trial identifier	Phase	Patient population	*N* planned	Treatment	Primary outcome	Status	Estimated study completion date
Primary treatment	NCT02728830	I	Gynecologic neoplasms	15	Pembro 200 mg 14–21 days prior to surgery	Tumoral immunoprofile	Recruiting	April 2020
	NCT02630823	I	High grade surgically resectable EC	15	Pembro 200 mg every 3 weeks prior to standard treatment	Safety	Recruiting	September 2020
	NCT02549209	II	Stage III–IV/recurrent EC who have had definitive surgery	46	Pembro 200 mg every 3 weeks, paclitaxel 175 mg/mq, carboplatin AUC 6	ORR	Recruiting	December 2019
After standard of care	NCT02912572	II	Recurrent/persistent MSS, MSI-H and POLE EC	70	Avelumab every 28 days	ORR; PFS at 6 months	Recruiting	April 2024
	NCT02899793	II	Recurrent POLE and MSI EC	25	Pembro 200 mg every 3 weeks	ORR	Recruiting	June 2018
	NCT02501096	Ib/II	Metastatic selected solid tumors	191	LEN 20 mg/day + pembro 200 mg every 3 weeks	MTD (phase I); safety, efficacy (phase II)	Recruiting	February 2020
	NCT02646748	Ib	Advanced or metastatic solid tumors	237	Pembro 200 mg every 3 weeks + itacitinib once daily	Safety and tolerability	Recruiting	August 2019
	NCT03015129	II	Recurrent or persistent EC	80	Durvalumab 1500 mg ± tremelimumab 75 mg every 4 weeks	ORR	Recruiting	January 2019
	NCT02982486	II	Non resectable/metastatic EC	60	Nivolumab 240 mg every 2 weeks + ipilimumab 1 mg/mq every 6 weeks	ORR	Not yet recruiting	December 2020
	NCT03310567	II	Recurrent/metastatic EC	49	Pembro 200 mg every 3 weeks + epacadostat twice a day	ORR; PFS and OS at 6 months	Not yet recruiting	January 2021
	NCT03276013	II	Advanced, recurrent or metastatic EC	51	Doxorubicin 60 mg/kg + pembro 200 mg every 3 weeks	PFS at 6 months	Not yet recruiting	May 2020
	NCT03517449	III	Advanced, recurrent or metastatic EC	780	LEN 20 mg/day + pembro 200 mg every 3 weeks (ARM 1); paclitaxel 80 mg/mq or doxorubicin 60 mg/mq every 3 weeks (ARM 2)	PFS; OS	Recruiting	January 2023
	NCT03192059	II	Advanced/refractory cervical cancer and EC	43	Immunomodulatory cocktail followed by pembro 200 mg every 3 weeks and RT	ORR	Recruiting	June 2022
	NCT02178722	I/II	Advanced or metastatic selected cancers	444	Pembro + epacadostat 25 mg twice a day	DLTs; ORR	Active, not recruiting	February 2020
	NCT02914470	Ib	Advanced gynecologic neoplasms	12	Carboplatin AUC 5, cyclophosphamide 600 mg/mq, atezolizumab 840 mg	Toxicity	Active, not recruiting	June 2018

N number, *MSI-H* high microsatellite instability, *POLE* polymerase DNA directed, *ε* catalytic subunit, *EC* endometrial cancer, *ORR* objective response rate, *PFS* progression-free survival, *pembro* pembrolizumab, *MTD* maximum tolerated dose, *LEN* lenvatinib, *OS* overall survival, *RT* radiotherapy, *DLTs* dose limiting toxicities

Conclusion

Even though high-risk, recurrent or metastatic disease represent a smaller EC cohort, the need to improve its clinical outcomes is urgent. Immunotherapy researches are still in an early phase, but with promising results. Preliminary data suggests that response to treatment seems to be highly dependent on MSI status. Identification of mutational data and predictive biomarkers could be paramount to better personalize and open new opportunities for therapeutic strategies in EC patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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