Chapter 6

The Impact of Genetic Mutational Typing of Endometrial Carcinoma for Adjuvant Oncologic Treatment and Treatment Outcome

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Abstract

The adjuvant treatment of endometrial carcinomas took a different turn when ESGO/ESTRO/ESP announced its prognostic risk group guide in 2020. The Cancer Genome Atlas (TCGA) Research Network Classification and the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) algorithm were integrated into clinical practice. Therefore, by combining genomic traits with molecular subtypes, doctors have enhanced patient care and risk stratification for endometrial cancer. Surgery (hysterectomy and bilateral salphingooopherectomy with or without lymph node dissection) is the primary treatment for early-stage, low-grade, low-risk tumors. Vaginal brachytherapy in an adjuvant setting has secured the treatment success for local control. Intermediate-high-risk cancer patients are scheduled for adjuvant chemoradiation and/or vaginal brachytherapy.

Nevertheless, there is still a 30% of high-risk, high-grade heterogenous endometrial cancer patients whose accurate prognostication needs to be elucidated. Recent and ongoing trials support the superior benefit of chemoradiation combined with targeted therapies for relapse-free and overall survival. This review summarizes the most recent trends in adjuvant oncologic treatments for endometrial cancer according to the validated four subgroups and discusses the results of ongoing trials for adjuvant chemoradiation with targeted therapies.

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https://doi.org/10.58830/ozgur.pub305.c1251

1. INTRODUCTION

Endometrial cancer is the most common type of uterine cancer. It arises from the endometrial cells that line the uterus. According to GLOBOCAN 2020 reports, 417000 women were diagnosed, and 917000 women died due to it [1]. The longer the estrogen exposure, the higher the risk of developing endometrial cancer [2]. SEER data reports a 96% survival rate for localized, 72% for regional, and 20% for distant cancer at five years [3]. Surgery (a total abdominal hysterectomy and bilateral salphingooopherectomy) is the primary treatment modality for the early stages. Recently, sentinel lymph node biopsy with indocyanine green is increasingly used with high sensitivity and negative predictive rate for low morbidity (e.g., less lymphedema) [4]. However, higher stages with extensive disease need other adjuvant oncologic treatment modalities of vaginal brachytherapy, pelvic external radiation therapy, and chemotherapy [5]. The cancer stage is not solely enough for proper patient management. Histopathological findings and risk group classifications recommended by international societies determine the cascade of adjuvant oncologic treatments to avoid over or undertreatment [5,6].

Patient's age, cancer stage, tumor grade, histopathologic type, depth of myometrial invasion, and lymphovascular space invasion (LVSI) are essential characteristics for risk group classification [5]. Because histopathological findings might cause conflicts between pathologists in up to 30% of cases, a surrogate system has been developed by The Cancer Genome Atlas (TCGA) Research Network in which four prognostically different groups were identified. The distribution of these prognostically distinct subgroups is DNA polymerase epsilon (POLE) (ultramutated) (7%), Microsatellite instability (MSI) -hypermutated (MMR-D) (28%), Copynumber low (CNL) (39%) and Copy-number high (CNH) (26%) [7,8].

Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) was developed using immunohistochemical analysis rather than molecular analysis to increase the applicability of molecular classification [9,10]. Several studies have confirmed the validity of the proposed molecular classifications over various endometrial cancer patient groups by combining immunohistochemistry (IHC) and mutation analysis for its determination and predicament of disease prognosis [11–13].

The subsequent studies related to TCGA classification have documented that four subgroups contain almost all grades, histologic types, and stages of endometrial cancer. Adjuvant oncologic treatments with new therapeutic targets are being developed in new clinical trials. This review summarizes the

most recent trends in adjuvant oncologic treatments in endometrial cancer according to the validated four subgroups.

2. MANAGEMENT OF ADJUVANT ONCOLOGIC TREATMENTS

2.1. Management Of Adjuvant Oncologic Treatments For Patients With DNA-Polymerase Epsilon (POLE) Ultramutated Tumors

Patients with polymerase epsilon exonuclease domain mutated (POLE EDM) or ultramutated tumors constitute 6 to 12% of all endometrial cancers [8,14–16]. These tumors are often in the endometrioid histological subtype, tend to be of higher grade (grade III), and are rich in lymphocytic infiltrate, but with good prognosis, manifested by early onset of symptoms presented at early stages (stage I-II) in young women that have low body mass index (BMI) [16–19]. In a meta-analysis for pooled patients with POLE EDM tumors, estimated HR for overall survival was 0.90 (95% CI, 0.59 to 1.38), for disease-free survival was 0.41 (95% CI, 0.30 to 0.55), for progression-free survival, was 0.23 (95% CI, 0.08 to 0.64) emphasizing superior survival and favorable prognosis [19].

Previously PORTEC 1 trial showed that external beam radiotherapy was superior to no adjuvant treatment in locoregional disease control at 5 years (4% vs.14%, $p<0.001$) but without overall survival (85% vs. 81%; $p=0.31$)[20]. Furthermore, PORTEC 2 trial showed that neither vaginal brachytherapy nor external pelvic radiotherapy was different from each other in older patients with higher-grade endometrial cancer in locoregional disease control (5% vs. 2%, $p=0.17$) and overall survival (85% vs. 80%; $p=0.57$) at 5 years [21]. Patients with POLE EDM tumors were found to have no recurrence in a further analysis by Stello et al., where they integrated molecular and clinicopathological features into risk assessment for patient cohorts of these trials. The authors stated that the high mutation rate and increased immunogenicity in POLE EDM tumor patients are responsible for this outcome [14]. On the other hand, Van Gool et al. opposed and declared that an increased mutation rate would not be enough to explain the favorable outcome because while none of the POLE EDM patients had a recurrence in the control group of PORTEC 1 trial (0/16), in the POLE wild-type patients 44/229 (19.2%) had a recurrence in the absence of adjuvant oncologic treatment [22]

To support the PORTEC-1 data, van Gool et al. investigated POLE EDM treatment sensitivity in a model system and reported that these mutations exhibited increased sensitivity to nucleoside analogs like cytarabine and

fludarabine. Therefore, the authors concluded that the prognostic benefit of POLE mutations is independent of adjuvant treatment but can be explained by increased immunogenicity [22]. These tumors are platinum-based chemotherapy resistant. However, in vitro comparison to primary POLE wild-type tumors, they are naive to paclitaxel. Bellone et al. have attributed it to higher T-cell infiltration of POLE-ultra mutated endometrium cancers [17]. Among the systemic treatment options, POLE EDM patients are most potentially expected to benefit from immune check-point inhibitors [23].

In their recent metanalysis, McAlpine et al. advocated "de-escalating patient care" for POLE EDM tumor patients as adjuvant oncologic treatment (radiation therapy and chemotherapy) showed no survival benefit in this cohort [24]. Close observation can be advised for them. PORTEC 4a and TAPER trials are ongoing prospective studies to elucidate whether omitting vaginal brachytherapy in cases of favorable molecular profiles is safe and cost-effective [24,25]. The early results of these trials are expected in 2023.

2.2. Management of Adjuvant Oncologic Treatments For Patients With Microsatellite Instability (MSI)- Hypermutated (MMRd) Tumors

In this group of patients, mismatch repair deficiency leads to microsatellite instability because the nuclear expression of several mismatch repair proteins (e.g., MLH-1, MSH2, MSH6, PMS2) is missing. It results in the accumulation of insertions, deletions, and mismatches, predisposing conditions for tumor development [8,9,14]. Repair deficiency in MSH2, MSH6, and PMS2 is associated with hereditary endometrial carcinoma (Lynch Syndrome), whereas MLH1 repair deficiency is a somatic sporadic mutation. MLH1 methylation assays are used to differentiate one another [26].

Approximately 25 to 30% of endometrial cancer patients have MMRd and show diverse heterogeneity in their histology, including cribriform and nonpapillary patterns and mucinous differentiation [27]. Tumor-infiltrating lymphocytes are present in the peritumoral areas. Microsatellite instability assessment is divided into three: high (MSI-H), which means evaluating mutations ≥2 genes; stable (MSS) mutations in zero genes; and low (MSS-L) mutations in 1 gene [28]. Histologically, patients with half of MSI-H tumors are heterogenous and undifferentiated carcinomas; meanwhile, 30% of endometrioid, 16% of serous, and 15% of clear cell carcinomas are MSI-H [29,30].

The microsatellite instability hypermutated/mismatch repair deficiency status is associated with intermediate prognosis due to their high

immunogenicity, and the prognostic value is essential only in early, low-grade, LVSI and/or endometrioid histology [10,14,18,31]. Patients with these tumors have higher BMI and can be of any age but younger than non-MMRd counterparts [18].

Patients with MMR/d MSI hypermutated tumors tended to have lower recurrence with adjuvant oncologic treatment (brachytherapy and pelvic radiotherapy) compared to non-MMR/d patients in the Kim et al. study. However, on multivariate analysis, MMR status was not associated with progression-free and overall survival [31].

MMRd cancers have a high mutational burden, which is essential in systemic treatment with immune check-point inhibitors. Belone et al. reported that the benefit of immune check-point inhibitor treatment is more effective on Lynch Syndrome and Lynch Syndrome-like tumors [32]. Pembrolizumab, a PD-1 inhibitor agent, has recently proven beneficial in MMRd/MSI-H patients by KEYNOTE-158 trial [33]. It is now included in the NCCN treatment guidelines as FDA approved drug for unresectable, advanced, metastatic, or recurrent MMRd patients [34,35]. Dostarlimab and darvalumab are other immune check-point inhibitors that are under study. Interim analysis of the GARNET trial presented a 45% objective response rate (complete response 11%, partial response 34%) with dostarlimab. Mirza et al. recently reported an advantageous progression-free survival with dostarlimab plus carboplatin-paclitaxel in patients with primary advanced or recurrent dMMR-MSI-H endometrial cancer [36]. Durvalumab is also promising, with similar response rates as dostarlimab in a phase II trial by Antill et al. [37]. In advanced or recurrent dMMR-MSI-H endometrial cancer, Avelumab either alone or in combination with either talazoparib (PARP inhibitor) or axitinib (tyrosine kinase) is found 27% objective response rate in a clinical trial which has just completed [38,39].

2.3. Management of Adjuvant Oncologic Treatments For Patients With Copy Number Low (CNL) Tumors

Copy number low patients have no specific mutation profile (NSMP), and they comprise 40-50% of all endometrium cancers. They are also called p53 wild type, MMR proficient, and POLE mut (-) [10]. Prognosis in this group of patients is generally intermediate; however, stage-dependent at a greater extent [8]. Typically, they are of endometrioid histology with squamous differentiation and hormone-positive status. They have a high response rate to hormonal therapy [40,41] Women with copy number low endometrial cancers have the highest BMI [18]. Some mutations like CTNNB1 (beta-catenin 1)

and L1 cell adhesion molecule (L1CAM) for patients are related to poor prognosis and distant recurrence [14,42].

NSMP tumors associated with the PI3K/Akt/mTOR pathway and hormone-positive status are subject to new studies targeting these pathways. A phase II trial on recurrent endometrial cancers evaluated everolimus and letrozol treatment superiority to medroxyprogesterone acetate, and tamoxifen showed 32% ORR [43]. Mirza et al. studied palbociclib (cyclin-dependent kinase inhibitor) and letrozole compared to letrozole alone. Combined treatment was superior to single treatment with a 64% control rate and 5 months of progression-free survival [44].

2.4. Management of Adjuvant Oncologic Treatments For Patients With Copy-Number High (CNH) Tumors

Patients in this group have a high number of somatic copy number alterations and, with their low somatic mutation rate, have high-grade tumors (serous 88%, undifferentiated-clear cell-high grade cancers ranging 30-40%), aggressive resulting in early metastasis and poor prognosis [8,9,14,45]. Almost all these tumors are TP53 mutated, comprising 13-18% of endometrioid tumors[10, 15]. The p53 status is associated with old age and a low BMI [10,46].

Adjuvant oncologic treatment (platinum-based chemotherapy and pelvic radiation) evaluation of p53 abnormal patients in the PORTEC 3 study significantly benefitted at a rate of 22.4% for relapse-free survival and 23.1% for overall survival at five years [45]. However, the diminishing benefit of relapse-free survival at 5 years when chemoradiotherapy and radiotherapy-alone comparison (59% vs. 39%; p=0.019) moves the benefit the patients get from irradiation into question [46].

Recent studies point out a new therapeutic target for p53 mutated endometrial cancers: overexpression of HER 2 protein. HER2++ or HER+++ was present in 31.4% of p53 mutated endometrial cancers. Amplification was prominent in serous, clear cell carcinomas and carcinosarcomas, emphasizing the potential benefits of HER2-targeted therapies for these aggressive forms [47–49]. First update results of an ongoing phase II trial have shown that adding trastuzumab to carboplatin/paclitaxel chemotherapy significantly improved progression-free and overall survival in advanced stages of p53 mutated endometrial carcinoma [50].

Another new therapeutic target regarding p53 mutated high-grade endometrial cancers is reported as homologous recombination deficiency (HRD). In their study, de Jonge et al. reported that HRD is strongly related

to non-endometrioid histology, and patients with p53 mutated HRD tumors may benefit from poly (ADP-ribose) polymerase (PARP) inhibitors added to the carboplatin and paclitaxel chemotherapy, targeting this deficiency [51]. Trials designed to evaluate the combined treatment of PARP inhibitors with chemotherapy are still in progress with promising preliminary results [52].

3. CONCLUSION

Identifying the endometrial tumors on a genomic level would potentially provide crucial clinical benefit because this data would help oncologists increase awareness and clinical point of view to design superior management and obtain therapeutic outcomes in their medical practice and future clinical trials**.** As a result, by focusing on these patients with accurate genomic characterization regarding their typing/grouping, the oncologists may have the comfort to direct the results towards a more appropriate clinical endpoint for the patient, avoiding undertreatment/overtreatment problems of endometrial cancer in which multiple risk factors alter its clinical manifestation and clinical aggressiveness pattern.

By the end of 2022, the RAINBO Research Consortium has announced its new program for refining the adjuvant treatment in endometrial cancer based on molecular features [53]. An overarching research program consisted of four international studies: RED Trial, a phase III trial of p53 abnormal endometrial cancer cases that compares adjuvant chemoradiation followed by two years of olaparib immunotherapy versus radiotherapy alone. The GREEN Trial, a phase III trial of stage II (LVSI positive patients) or stage III MMRd patients, compares adjuvant radiotherapy alone with radiotherapy plus concurrent darvolumab followed by one year of adjuvant darvolumab. The ORANGE Trial, a phase III trial of stage II (estrogen receptor and LVSI positive) or stage III NSMP patients comparing adjuvant chemoradiation to radiation followed by two years of progestin. The BLUE Trial, a phase II trial of stage I-III POLE-mut patients, compared no adjuvant therapy for the low-risk group and no adjuvant therapy or radiotherapy for the high-risk group.

The main results of the RAINBO clinical program are expected to be announced by 2028. The shareholders aim to fill the void of whether molecular-directed adjuvant treatment is the more effective, less toxic, better quality of life provider than the current patient management principles for patients with endometrial cancer[53].

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