Gynecologic Oncology 150 (2018) 569–580

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Endometrial cancer: Molecular markers and management of advanced stage disease

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HIGHLIGHTS

- Controversy exists regarding the role of radiation in the management of advanced stage endometrial cancer.
- Immunotherapy and novel treatments that target molecular defects show promise in the treatment of endometrial cancer.
- Understanding how and when to test the tumor for molecular markers and how to use the findings remain a challenge.
- Personalized treatments and the use of new biologics have shown promise in the pre-clinical and clinical settings.
- Additional trials are needed to understand how to combine targeted therapies with other therapies to maximize response.

ARTICLE INFO

Article history:
Received 5 March 2018
Received in revised form 7 May 2018
Accepted 8 May 2018
Available online 27 May 2018

Keywords:
Endometrial cancer
Advanced disease
Chemotherapy
Radiation therapy
Biomarkers

ABSTRACT

Endometrial cancer is the most prevalent gynecologic cancer in the United States. Over the last 10 years, death rates from endometrial cancer have been rising about 1.4% per year. Traditionally endometrial cancer treatment has been driven by stage and histology. Recent studies have, however, shown that cancers of the same stage and histology have very distinct molecular and genomic profiles. Translational research is progressing rapidly and endometrial cancer-specific precision medicine is evolving. The first tissue agnostic therapy based on the molecular profile of the tumor was approved by the FDA this year. The approval of immune checkpoint inhibitor, pembrolizumab (anti-PD-1), for all solid tumors with defective DNA mismatch repair, could benefit 20–30% of patients with advanced endometrial cancer. Other genomic changes and molecular markers in endometrial cancer, such as hormone receptor status, could lead to more tailored therapy in the future. Pre-clinical and clinical investigations of targeted therapies suggest efficacy for some agents. Single agent targeted therapies, however, have modest activity. Identifying biomarkers that effectively determine response to targeted therapy remains a challenge. The next generation of clinical trials will focus on novel combinations and how to best utilize the advances that have been made in sequencing technology and bioinformatics. Although there is currently an immense body of data and many options for obtaining genomic characteristics of endometrial cancer, how to interpret and utilize this data is still being explored. This review will summarize the important trials that have led to the treatment options we have for advanced and/or recurrent endometrial cancer and discuss the important studies that have led to a better understanding of the distinctive molecular and genomic profiles within endometrial cancer. We will review the current status of biomarker-driven targeted therapy in endometrial cancer and the rationale behind ongoing clinical trials that are utilizing novel targeted agents.

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https://doi.org/10.1016/j.ygyno.2018.05.015
0090-8258/

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1. Introduction

Endometrial cancer will affect 61,380 women in the United States in 2017 and will result in 10,920 deaths with similar incidence and mortality rates world-wide [1]. Frequently, outcomes for adenocarcinoma of the endometrium are favorable because of the early symptoms of irregular/postmenopausal vaginal bleeding that trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate [2,3]. This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an older age. For women who present with advanced stage or recurrent disease that is not amenable to localized therapies, outcomes are poor. Controversies exist about the role of radiation in advanced stage disease. After initial therapy, there are limited treatment options, with no standard options available at the time of subsequent recurrence or progression. To further improve outcomes for endometrial cancer patients overall, better approaches to identify high-risk patients to tailor treatment are needed to provide the best long-term survival.

Molecular characterization of endometrial cancer is advancing rapidly, and understanding how specific mutations or combinations of molecular features can lend themselves to targeted therapeutics is paramount in the treatment of advanced or recurrent endometrial cancer. Multiples studies, including the landmark Cancer Genome Atlas Project (TCGA) for endometrial cancer, have revealed common endometrial cancer mutations and features that are highly characteristic of uterine epithelial malignancies [4]. Findings from several of these studies will be highlighted in this review [4–15].

1.1. Staging and NCCN treatment guidelines

High-risk endometrial cancer usually refers to either stage III/IV endometrioid histology or high-risk histology (UPSC, clear cell, carcinosarcoma). In 2009, several changes in the staging of endometrial cancer were made to better reflect outcomes associated with stage. Specifically, in advanced stage disease, stage IIIC was subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes. For stage IIIA to IIIC disease, the National Comprehensive Cancer Network (NCCN)-recommended treatment options are systemic therapy and/or external beam radiotherapy (EBRT) with or without vaginal brachytherapy (Fig. 1A). For stage IVA/IVB disease that is debulked with no gross residual disease or microscopic abdominal disease, systemic therapy remains the mainstay of treatment and can be combined with EBRT and/or vaginal brachytherapy (Fig. 1A). For high-risk tumor histologies at stage 1B or higher, the NCCN treatment recommendation is for chemotherapy with or without either EBRT or vaginal brachytherapy (Fig. 1B). Table 1 summarizes the NCCN recommendations for systemic therapy for recurrent, metastatic, or high-risk disease. It is important to note that the NCCN strongly encourages all of these patients (recurrent, metastatic or high risk) to participate in clinical trials. The landmark trials that led to the NCCN recommendations are summarized below.

2. Summary of landmark clinical trials

2.1. Role of radiation

The role of radiation in advanced stage endometrial cancer remains an on-going debate. Key areas of uncertainty include: 1) Which patients should have radiation—all or select subsets?, 2) When should it be used? Before, during, or after chemotherapy?, and 3) What sort of radiation therapy—EBRT or brachytherapy?

Advanced stage patients receiving radiation alone are generally treated with extended field radiation after surgery. Survival rates for this group are modest (30–40%) with clear indication that surgical procedures and a range of other clinicopathologic features impact outcomes. Mariani et al. reported on 122 patients with node-positive disease. At 5 years, risk of pelvic recurrence in patients with inadequate lymph node (LN) dissection and/or no radiotherapy (RT) compared to patients with adequate LN dissection and RT was 57% and 10% respectively [16]. A study by Greven et al., reported 105 irradiated patients with stage IIIC had a pelvic failure rate of 21% [17]. Similarly, Mundt and colleagues described two series with 30 stage IIIC patients treated with irradiation after surgery that had an infield failure rate of 23%