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Review Article

Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis

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HIGHLIGHTS

- Mean objective response rate (ORR) to first-line hormonal therapy is 21.6%.
- Low histologic grade was associated with greater magnitude of response.
- ORR was greater in ER+ (26.5%) and PgR+ (35.5%) disease.
- Second-line ORR was 18.5%.

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ABSTRACT

Background. Hormonal therapy (HT) is used commonly in the treatment of advanced endometrial cancer (EC). However, a 2010 Cochrane Review did not show a survival benefit for HT. Here, we quantify its effects and explore the influence of clinico-pathologic factors and hormone receptor (HR) status on overall response rates (ORR).

Methods. A systematic search of electronic databases identified publications of HT in advanced EC. Data from individual studies reporting ORR, median progression-free (PFS) or overall survival (OS) were weighted by individual study sample size and pooled in a meta-analysis. Outcomes of estrogen (ER) and progesterone receptor (PgR) subgroups were collected. Studies of first- and second-line HT were analyzed independently. Mixed studies were included if subgroup data based on previous HT exposure were provided. Meta-regression was performed to evaluate the influence of clinico-pathologic factors on outcomes.

Results. Thirty-nine studies were included, with seven providing subgroup data based on HR status. First-line HT was associated with a mean ORR of 21.6% and clinical benefit rate (CBR) of 36.7%. Median PFS and OS were 2.8 and 10.2 months respectively. ORR was 20.4% in clinical trials and 25.3% in observational studies. Magnitude of ORR was lower in older age, adenosquamous histology and high grade. ORR was higher in ER+ (26.5%) and PgR+ (35.5%) disease, and lower in ER− (9.2%) or PgR− (12.1%) tumors. Second-line ORR was 18.5%. CBR was 35.8%, but was significantly associated with timing of stable disease assessments in first- and second-line. Meta-regression performed in mixed and second-line studies showed an association between previous HT and greater ORR (β 0.561; $p = 0.024$), suggesting potential confounding by indication (re-treatment of good responders to first-line HT).

Conclusion. HT is associated with modest ORR in advanced EC, and is greatest in HR+ tumors. Response rates in second-line are likely dependent on response to previous HT.

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1. Introduction

Hormonal therapy (HT) is used frequently in the treatment of advanced endometrial cancer (EC), particularly in patients with low-grade or estrogen receptor (ER) and/or progesterone receptor (PgR) positive disease. Commonly used agents include progestins, aromatase inhibitors (AIs), and selective estrogen receptor modulators (SERMs). However, high-level evidence to support and direct their use in this setting is lacking. A 2010 Cochrane Systematic Review examining the use of HT in EC did not find evidence that HT improves survival in this population [1]. However, this review focused on randomized clinical trials reporting survival outcomes, and did not include earlier phase trials or observational studies. Further, due to insufficient and heterogeneous data, authors were not able to pool outcomes, and meta-analysis was not performed. Additionally, their role in hormone receptor (HR) positive patients could not be explored, despite ER status having been shown previously to predict for response to HT. [2].

In this study, we aimed to quantify the median objective response rate (ORR) and survival outcomes associated with the use of HT in women with advanced EC, including in subgroups based on HR status. In order to minimize heterogeneity, we focused on the use of HT alone or in combination, and studies of HT combined with targeted or chemotherapy agents were not included. We also examined the effect of clinico-pathologic factors on response and survival outcomes.

2. Methods

2.1. Data sources and searches

This analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3]. An electronic search of the following databases was performed from 1946 to July 1st, 2016: Medline (host: OVID), Medline in Process, Medline Epub Ahead of Print (host: OVID), EMBASE (host: OVID), and Cochrane Database of Systematic Review. Search terms included "endometrial neoplasms", "antineoplastic agents, hormonal", "estrogen receptor modulators", "estrogen antagonists", "progestins", "aromatases inhibitors", "gonadotropin-releasing hormone" and synonymous terms, including specific drug terms. Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. The full search strategy is described in Appendix 1.

2.2. Study selection

The following eligibility criteria were utilized: 1) studies of adult women with advanced or recurrent EC; 2) examining the use of progestins, AIs, SERMs, fulvestrant or gonadotropin-releasing hormone (GnRH) agonists alone or in combination; 3) reporting median ORR, clinical benefit rate (CBR), complete response (CR), partial response (PR), stable disease (SD), progression-free survival (PFS) and/or overall survival (OS); 4) available as full-text publication; 5) clinical trials or cohort or case-control studies; and 6) English language publication. ORR was defined as the percentage of patients with CR or PR, whereas CBR included those who achieved CR, PR or SD. Studies of combination HT were included, while those examining HT combined with chemotherapy or other targeted therapies were excluded. Studies were considered as clinical trials where treatments were prospectively assigned. Case reports, conference proceedings and letters to editors were excluded. All titles identified by the search were evaluated, and all potentially relevant publications were retrieved in full. Two reviewers (JE and DD) reviewed independently the full articles for eligibility based on inclusion criteria and data extraction, and disagreements were resolved by consensus.

2.3. Data extraction

The following details were extracted from included studies using predesigned data abstraction forms: name of first author, year of publication, journal, study design, number of patients included in analysis, median or mean age, recurrent or advanced disease, patients with each histologic subtype and tumor grade, number of patients with ER and PgR positive or negative disease, details of previous treatments received, and median ORR, PFS and/or OS. Where available, subgroup data for ER and/or PgR positive and negative patients were collected. Criteria for tumor response or stability and cut-offs for determining positive ER and PgR expression were defined as reported in individual studies.

2.4. Statistical analyses

Extracted data from all included studies were weighted by individual study sample size and pooled in a meta-analysis for each of the endpoints of interest. ORR and CBR were calculated from CR, PR and/or SD where not provided. Studies of first- and second-line HT were analyzed independently. Data from mixed studies were included if subgroup data based on previous HT exposure were provided. Individual treatment arms of randomized studies were analyzed separately. Where outcome data were available for only a subset of patients, response rates were calculated based on the whole study population (intention to treat analysis). The primary outcome of interest was median ORR. Meta-regression was performed to evaluate the influence of factors such as histologic

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