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Research article

The efficacy and safety of the novel combination lenvatinib and pembrolizumab in endometrial cancer: A systematic review and single-arm meta-analysis

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ABSTRACT

Objective: Endometrial carcinoma is the most widespread gynecological cancer, with increasing morbidity and mortality. Pembrolizumab, a monoclonal antibody that targets PD1 receptor tumors, is approved for patients with microsatellite instability-high (MSI-H) solid tumors. Many clinical trials and observational studies have been conducted to assess the safety and efficacy of Lenvatinib and Pembrolizumab combination therapy in the setting of endometrial cancer. However, results have been inconsistent, and current data is based on a heterogeneous population. The primary objective was to assess the safety and efficacy of Lenvatinib plus Pembrolizumab for endometrial cancer.

Data sources: The search was conducted from inception from four databases; PubMed, Google Scholar, the Cochrane Library, and ClinicalTrials.gov. The electronic database search was conducted from inception to August 20, 2023.

Study eligibility criteria: We considered randomized controlled trials and single-arm observational studies, i.e. cohort, case-control and cross-sectional studies.

Methodology: We performed a single-arm meta-analysis, involving 7 studies having a total of 495 patients with endometrial cancer were eventually included which had the following outcomes: Complete response, Partial response, Progression-free survival, stable disease, progressive disease, safety outcomes, Adverse events, and the total number of deaths.

Results: Our results showed that 88.6 % of the patients were positive for non-MSI-H/pMMR tumors (95 % CI = 0.825–0.927) whereas 6.5 % (95 % CI = 3.8–9.8 %) of the patients for MSI-H/dMMR tumors. The pooled objective response of endometrial cancer patients treated with Lenvatinib and Pembrolizumab was 36.5 % (95 % CI = 0.258–0.471), the pooled estimate of complete and partial response was 47 % (95 % CI = 0.024–0.070) and 31.3 % (95 % CI = 0.230–0.396). 38.2 % patients had stable disease (95 % CI = 0.329–0.435) and 24.0 % patients had progressive disease (95 % CI = 0.103–0.378). The pooled median progression-free survival was 5.97 (95 % CI 5.43–7.63) months and, whereas the median overall survival was 17.19 months (95 % CI 15.34–19.31). All grade adverse events occurred in 85 % and Grade 3 or worse

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adverse events occurred in 39 % of patients during the therapy whereas death occurred in 23.8 % during the treatment.
Conclusion: The results of this meta-analysis concludes that although the combined treatment of a Lenvatinib and Pembrolizumab had a PFS and OS that was inferior to the standard therapy used to treat advanced and recurrent endometrial cancer, it is still a novel treatment and shows potential for further research with a greater sample size.

1. Introduction

Endometrial Carcinoma is the most widespread gynaecological cancer, which affects 25.7/100,000 women in the United States annually [1,2]. It is the only malignancy of gynaecology with substantially increasing morbidity and mortality [3]. Globally, endometrial cancer has accelerated by 132 % in the last 30 years [4]. In the upcoming year, endometrial carcinoma is anticipated to make up more than 90 % of 61,000 new cases of uterine corpus cancer, which will be responsible for claiming around 11,000 lives [2].

The American Cancer Society states that the standard first-line treatment option for endometrial cancer is surgery [5]. However, for advanced, recurrent and metastatic endometrial cancer, radiotherapy and chemo drugs such as Paclitaxel, Doxorubicin and either Carboplatin or Cisplatin are the standard adjuvant therapy [5–7]. Two other treatment regimens in the metastatic setting, namely Megestrol acetate and Pembrolizumab have been approved. Megestrol acetate is used for palliative treatment, and Pembrolizumab, a monoclonal antibody that targets Programmed death receptor-1 (PD1) tumors, is approved for patients with microsatellite instability-high (MSI-H)/mismatch repair deficient solid tumors that have first-line chemotherapy failure [8]. Pembrolizumab has shown little efficacy in Microsatellite stable tumors. Since VEGF activation and expression plays an essential role in pathogenesis and poor prognosis of endometrial cancer, Lenvatinib targeting VEGFR1–3, FGFR1–4, PDGFRα, and the oncogenes RET and KIT, is also seen being used alongside with Pembrolizumab in different clinical trials and observation studies [9,10].

Many clinical trials and observational studies have been conducted to assess the safety and efficacy of Lenvatinib and Pembrolizumab combination therapy in the setting of endometrial cancer. However, results have been inconsistent and current data is based on a heterogeneous population. Therefore, our meta-analysis's primary outcome assesses the safety and efficacy of Lenvatinib plus pembrolizumab for endometrial cancer.

2. Objective

The aim of this single-arm meta-analysis was to estimate the efficacy and safety of the novel combination therapy, Lenvatinib and Pembrolizumab in treating endometrial cancer (EC), and henceforth compare it with the current first-line treatment.

3. Materials and methods

3.1. Search strategy

We searched PubMed, Google Scholar, the Cochrane Library, and ClinicalTrials.gov for potentially eligible studies conducted from inception till August 20, 2023. The medical subject headings (MESH) terms used to formalize the search string were: "Endometrial cancer", "Lenvatinib," and "Pembrolizumab", and the search strategy in PubMed was as follows: (("lenvatinib" [Supplementary Concept]) AND "pembrolizumab" [Supplementary Concept]) AND "Endometrial Neoplasms" [Mesh]. This meta-analyses was preceded by a written protocol registered in the International Prospective Register of Systematic Reviews (reference number CRD42023453166). The meta-analysis followed the guidelines set by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). No limitations were placed on region, race, age or payment during the research and references to literature reviews and original research were analyzed to ensure no qualified study was missed.

3.2. Inclusion and exclusion criteria

The inclusion criteria were as follows [1]: The targeted population consisted of patients with confirmed endometrial cancer irrespective of subtype [2]; studies included patients being treated with a combination lenvatinib plus pembrolizumab [3]; the study designs include randomized controlled trials and single-arm observational studies, i.e. cohort, case-control and cross-sectional studies were integrated; and [4] studies reporting either efficacy and/or safety endpoints, including the overall response (OR), complete response (CR), partial response (PR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

All studies that did not meet pre-specified criteria or their study designs were classified as case reports, meta-analyses, reviews, conference abstracts, unpublished reports, animal studies, irrelevant outcomes and irrelevant populations were excluded. All the articles were retrieved from the systematic search were compiled and exported to Mendeley Desktop v1.19.8 where duplicates were assessed and removed. Relevant articles were evaluated by two independent reviewers (WS and TS) based on the pre-defined eligibility criteria. No study had missing summary statistics and we didn't have to convert data of any study. Any further discrepancies were resolved and cross checked by third investigator.

3.3. Quality assessment

Included non-randomized studies (single-group studies) were evaluated using the methodological index for non-randomized studies (MINORS) [11].The JBI Critical Appraisal Checklist for Case Series was used to assess the retrospective studies without a comparison group [12]. The Quality assessment was conducted by two independent reviewers (AS and SM) and any conflicts were discussed and resolved.

3.4. Data extraction

The following baseline characteristics of the included studies were recorded: authors, year of publication or results of the report, study design, country, age, therapeutic regimen, follow-up period, number of patients, age, duration of treatment and the type of endometrial cancers. Efficacy outcomes were recorded in self-designed original data sheets, including OR, CR, PR, PFS, stable disease, progressive disease, safety outcomes, AEs and the total number of deaths.

3.5. Statistical analysis

Statistical analysis of the pooled OR, CR, PR, stable disease, progressive disease, total number of deaths and AE results of patients with Endometrial cancer treated with Lenvatinib and Pembrolizumab was performed using OpenMeta[Analyst]. A 95 % CI represented the effect size of all pooled results with upper and lower limits. The pooled K-M curves were estimated and analyzed using the IPD-fromKM Shiny application based on the paper by Na Liu [13] and the pooled K-M graphs were derived via the R-Shiny Tool [14] using the multivariate methodology of DerSimonian and Laird [15] by an independent reviewer (SP). The heterogeneity across studies was examined using the Cochrane Q chi-square test and I2 statistic. The fixed-effects model was used for pooled results with low heterogeneity ($I2 \leq 50$ %); otherwise, the random-effects model was used for analysis. The subgroup analysis was performed by dividing the studies into two groups for the pooled results with high heterogeneity.

4. Results

4.1. Literature search results

The electronic search yielded 304 results from four databases, Pub-Med, Cochrane, Google scholar and ClinicalTrials.gov, out of which 29 were assessed for eligibility. After the screening and de-duplication procedure, 7 studies [9,10,16–20] involving a total of 495 patients with endometrial cancer were eventually included in this meta-analysis. No such studies that might appear to meet inclusion criteria but were excluded were found. The summary and results of literature search are given in (Supplementary data 1; Fig. 1).

4.2. Study characteristics

Table 1 provides baseline characteristics of the selected articles (Supplementary File 1; Table 1). All the eligible studies including two retrospective cohort studies and five single-arm RCTs, utilized the same intervention, Lenvatinib (20 mg) + Pembrolizumab (200 mg). The patients included in the study were either previously treated with endometrial cancer (EC), recurrent EC, advanced EC, or treatment-naïve EC. 88.6 % of the patients were positive for non-MSI-H/PMMR tumors (95 % CI = 0.825–0.927) whereas 6.5 % (95 % CI = 3.8–9.8 %) of the patients were positive for MSI-H/DMMR tumors (Supplementary File 1; Figs. 3–4).

4.3. Publication bias

Evaluation of publication bias could not be done visually in funnel plots as less than 10 studies were included [21].

4.4. Quality assessment

Five single-arm studies were assessed using the MINORS index scored 14, and hence were acceptable for the present meta-analysis. Two retrospective studies without comparison were included after they were assessed using the JBI Critical Appraisal Checklist for Case Series (Supplementary data 1; Table 2 A,B).

4.5. Efficacy

1. Objective Response (OR):

Out of the 7 studies analyzed in the forest plot, 5 studies [9,10,16,18,19] indicate a positive effect and two studies [16,17] indicated a significant decrease in response rate. The pooled objective response (OR) of endometrial cancer patients treated with lenvatinib and pembrolizumab was 36.5 % [(95 % CI = 0.258–0.471), $I^2 = 80.15$ % ($p < 0.001$)] (Supplementary data 1; Fig. 4).

2. Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD):

In this forest plot, a total of 4 studies [9,10,18,19] exhibited a positive treatment effect while 3 studies [16,17] did not exhibit a significant improvement in CR. The p-value of 0.259 for CR and that of 0.004 for PR for the observed heterogeneity indicates it to be non-significant. In terms of Complete Response (CR) and Partial Response (PR), the forest plot indicates a mixed pattern of response rate across studies, with a pooled estimate of 47 % (95 % CI = 0.024–0.070) heterogeneity $I^2 = 22.26$ % (p = 0.259) and 31.3 % (95 % CI = 0.230–0.396) heterogeneity $I^2 = 68.4$ % (p = 0.004). (Supplementary data 1; Fig. 5A and B).

In terms of Stable Disease (SD) and Progressive Disease (PD), the pooled estimates showed 38.2 % patients had stable disease (95 % CI = 0.329–0.435, $I^2 = 17.06$ %) and 24.0 % patients have progressive disease (95 % CI = 0.103–0.378, $I^2 = 91.39$ %) (Supplementary data 1; Fig. 5C and D).

3. Progression-Free Survival (PFS) and Overall Survival (OS):

Four included studies reported complete PFS K-M curves model [10,17,18,20]; the pooled PFS and 95 % CI curved were analyzed using the fixed effects (Supplementary data 1; Fig. 6A). The cumulative PFS curves show that the median PFS was 5.97 (95 % CI 5.43–7.63) months, 6-month PFS was 44.6 %, 12-month PFS was 26.5 % and 18 month PFS was 23.4 %.

The Overall Survival KM curves were reported in two studies [18,20]; the pooled median OS was that was calculated using the fixed effects model was 17.19 months (95 % CI 15.34–19.31)(Supplementary data 1; Fig. 6B). The overall 6 month, 12 month and 18 month survival rate was 91.1 %, 63.2 % and 43.5 % respectively.

4.6. Safety

Treatment-related Adverse Events (AEs) were reported in all of the seven studies [9,10,16–19]. The number of patients being treated with Lenvatinib and/or Pembrolizumab who faced dose interruptions or reductions was 68.5 % and 59 % respectively, and 17.3 % patients discontinued the treatment due to the AEs. All grade AEs occurred in 85 % and Grade 3 or worse AEs occurred in 39 % % of patients during the therapy (Supplementary data 1; Figs. 7 and 8). In addition, death occurred in 23.8 % during the treatment (Supplementary data 1; Fig. 9).

The most common all grade AEs included hypertension (61.5 %), fatigue (54.3 %), diarrhea (53.5 %), decreased appetite (47.7 %), hypothyroidism (45.2 %), and nausea (40.6 %) (Supplementary data 1; Table 3) (Supplementary Data 3; Figs. 1–14) (Supplementary Data 4; Figs. 1–11).

Arthralgia, Headache, Proteinuria, PPE, Dysphonia, weight loss and GI related AE's such as Diarrhea, nausea and vomiting occurred in more than 20 % patients. Incidence of grade 3 or worse hypertension was found in an astounding 38 % patients, whereas the rest of the Grade 3 greater than or equal to AEs fell below 10 % (Supplementary data 1; Table 3).

4.7. Sensitivity analysis

To further explain the high heterogeneity of the results, sensitivity analysis was performed to calculate the influence of individual studies on pooled ORR, and PR. Kim et al. [17] was the source of heterogeneity in both ORR and PR. Exclusion of this study significantly reduced the heterogeneity and the pooled estimate for ORR and PR was recalculated to 41 % (95 % CI = 0.360–0.460, I2 = 0 %, p = 0.661) and 35.2 % (95 % CI = 0.304–0.401), I2 = 0 % (p = 0.440) respectively. (Supplementary data 2).

To resolve heterogeneity in any grade AEs, we performed a subgroup analysis on the basis of type of study (clinical trial vs observational studies) that resulted in reduced heterogeneity in both subgroups (Heterogeneity in pooled result of Observation studies I2 = 43.19 %; Heterogeneity in pooled result of clinical trials I2 = 0 %) (Supplementary Data 2).

5. Discussion

Our study is novel in evaluating the efficacy and safety of Lenvatinib and Pembrolizumab in patients with Endometrial Cancer. With most of clinical studies being single-arm, phase I, or phase II with small sample size, the LEN + PEMBRO-included arm data on tumor response, survival, and safety were extracted and analyzed.

Despite the therapy regimen, disease status, and subtypes, the pooled OR and PR of patients with Advanced or Recurrent Endometrial Cancer treated with LEN + PEMBRO were 36.5 % and 31.3 % respectively, which seemed to be not very optimistic compared with 62 % and 41 % OR, CR and PR in Paclitaxel and carboplatin (PC), and 51–59 % in patients who were treated with PC + bevacizumab/temsirolimus [22,23]. PC regimen resulted in a CR of 21 %, which was lower than that of LEN + PEMBRO i.e 47 % [23].

With TAP and TC therapy, the median PFS was 14 months and 13 months respectively, compared to the pooled median PFS remained around 6 months with LEN + PEMBRO therapy.

The median overall survival for the patients receiving TAP was 41 months and 37 months for patients receiving TC, whereas it was 17 months for patients treated with LEN + PEMBRO, leading to no improvement in the survival of patients with advanced or recurrent endometrial cancer [7].

From the safety perspective, 39 % of patients developed ≥ grade 3 AEs with LEN + PEMBRO treatment, which were lower than TC + bevacizumab/temsirolimus, 40.2 % and 44.2 %. All Grade AEs developed in 85 % patients with LEN + PEMBRO treatment, whereas in TC + bevacizumab/temsirolimus, they developed in 100 % of the patient population. Death during active treatment with TAP was

reported in 3 % of TAP-treated patients and 2 % of TC-treated patients, which is staggeringly low as compared to the 23.8 % deaths which occurred in patients treated with LEN + PEMBRO [7,22].

Hypertension was one of the most concerned AEs for patients on LEN + PEMBRO, and 38.2 % of patients developed hypertension grade 3 events or worse, which was obviously higher than 16.1 % and 2.1 % in TC + bevacizumab/temsirolimus. Similarly, 4.4 % to 5.5.% patients developed grade 3 or greater proteinuria in TC + bevacizumab treated patients, compared 3.1 % patients in LEN + PEMBRO treated patients, whereas grade 3 or worse fatigue developed in 12.5 % TAC-treated and 9.6 % TC treated patients, as compared to 6.3 % in LEN + PEMBRO patients [7,22].

Nevertheless, similar to other pharmaceutical substances, lenvatinib and pembrolizumab may elicit adverse effects as well, encompassing undesired or detrimental reactions to these medications. Histologically identifiable pre-neoplastic lesions of atypia, known as endometrial intraepithelial neoplasia, may undergo transformation into endometrial carcinoma by KRAS2 mutation, near diploid karyotype, PTEN mutation and mismatch repair defects leading to microsatellite instability [2]. Although microsatellite instability or mismatch repair deficiency has been found in 30 % of primary surgical cases of endometrial carcinoma, microsatellite-stable tumors comprise about 70 % of recurrent cases [10]. The recommended dosage for lenvatinib and pembrolizumab in the treatment of endometrial cancer is 20 mg and 200 mg, respectively. However, it is important to note that individual variations in patient condition and treatment response may necessitate adjustments to these dosages [24]. In relation to adverse events (AEs), the combined estimation of any-grade AEs at 85.0 % suggests a substantial occurrence of treatment-associated unpleasant effects in our study while on grade 3/4 adverse events (AEs) are consistent with the comprehensive safety evaluation, demonstrating a significant incidence rate of 39.0 %. The prevailing adverse effects associated with lenvatinib and pembrolizumab in the context of endometrial cancer encompass hypertension, hypothyroidism, diarrhea, decreased appetite, rash, and nausea. Conversely, less frequently observed symptoms comprise hepatotoxicity, nephrotoxicity, hemorrhagic events, and immune-related infections [25–27].

6. Limitations

The potential of utilizing the combined treatment approach involving Lenvatinib and Pembrolizumab shows promise in the management of endometrial cancer, as indicated by substantial tumor response rates and extended progression-free survival. Nevertheless, it is imperative to recognize the limitations of the study. The risk for bias arises from the small number of research (only 7) included and the inherent variety in study designs and patient demographics. It is important to proceed with caution when interpreting the results due to the substantial heterogeneity seen across multiple outcomes. We were able to resolve the heterogeneity of almost all the outcomes by sensitivity analysis but of grade 3–4 AEs and death. The duration of the response could not be analyzed, due to lack of sufficient data. Moreover, the retrospective and observational design of the study limits the ability to establish causal relationships and introduces potential issues related to selection bias and confounding variables. The potential for publication bias may be introduced due to the dependence on solely published literature.

7. Conclusion

The results of this meta-analysis concludes that although the combined treatment of a Lenvatinib and Pembrolizumab had a PFS and OS that was inferior to the standard therapy used to treat advanced and recurrent endometrial cancer, it is still a novel treatment and shows potential for more research. Further studies with large sample size and control groups are expected to confirm the efficacy and safety of this combination and provide stronger evidence to promote Len + Pembro as possible regimen for EC.

Ethical approval

No Ethical Approval was required for this research.

Financial statement

No funding was undertaken for this meta-analysis.

Prospero registration

Our meta-analysis was registered with PROSPERO on August 21, 2023 under the registration number: CRD42023453166.

Declaration of generative AI in scientific writing

The authors did not use any AI software or tool in this manuscript.

Data availability statement

Data included in article/supplementary material/referenced in article. The data associated with this study has been deposited into a publicly available repository. All the data associated to our study is freely available to the public.

CRediT authorship contribution statement

Wania Sultan: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tasmiyah Siddiqui:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Sanila Mughal:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ayman Sultan:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Shubram Pandey:** Software, Project administration, Methodology, Investigation, Data curation. **Mirza Mehmood Ali Baig:** Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30257.

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