Abstract:

Objective

Patients with endometrial cancer who progress following first line therapy have improved survival outcomes with pembrolizumab and lenvatinib (pem/len) compared with standard of care chemotherapy, as demonstrated in KEYNOTE-775. This was in a group of trial patients with a good performance status and excluded those with carcinosarcoma histology. In KEYNOTE-775 pem/len was associated with significant toxicity leading to dose reductions, treatment cessation and patient morbidity. We set out to assess the tolerability, toxicity and outcomes following pem/len for patients with recurrent, advanced or metastatic endometrial cancer in a real-world setting.

Methods

UK centres treating patients with pem/len for advanced endometrial cancer within the compassionate access programme were approached. Retrospective data was analysed for those treated between May 2022 and June 2023. Data on patient demographics, treatment, toxicity and outcomes was extracted from medical records. Toxicity and tolerability were compared in those over and under the age of 70.

Results

7 centres returned data for 70 patients. Median age of patients was 68.5 years (range 45-85) with a performance status of 0-1 in 77.1% and of 2 in 22.9%. Histological subtypes included serous (34.3%), endometrioid (32.9%), carcinosarcoma (14.3%), clear cell (7.1%), mixed (2.9%) and other (8.6%). Grade ≥3 toxicity was reported in 55.7% with any-grade toxicity observed in 85.7%. In those aged ≥70 years (n=30) the rate of grade ≥3 toxicity was 60.0%. Rates of dose reduction of lenvatinib were 64.3% and toxicity-related treatment interruption 45.7%. The 6-month progression-free and overall survival rates were 54.0% (95%CI: 39.0-66.8) and 70.1% (95%CI:56.5-80.1) respectively.

Conclusion

This real-world, observational study of pem/len showed comparable tolerability, toxicity and outcomes to previously reported clinical trial data. Our cohort included patients with a poorer PS and a broader range of histological subtypes including carcinosarcoma.

KEYWORDS: Endometrial cancer; pembrolizumab; lenvatinib; toxicity; tolerability

Introduction

Endometrial cancer (EC) represents the sixth most common cancer in women globally [1] and the fourth most common cancer in women in the UK with around 9,700 new cases reported each year [2]. The management of recurrent, advanced or metastatic EC is palliative with treatment tailored individually for patients depending upon their extent of disease, molecular subtype, clinical symptoms, comorbidities, performance status (PS) and patient preference. Epidemiologically, racial disparity is observed with aggressive molecular subtypes indicating poorer outcomes seen more commonly in patients of black ethnicity [3].

Pembrolizumab is a humanised monoclonal antibody [4]. It binds to the programmed cell death-1 (PD-1) receptor, blocking interaction with PD-L1 and PD-L2. Pembrolizumab monotherapy has shown anti-tumour effects in EC with an objective response rate of 13% in patients with PD-L1 positive disease [5]. Lenvatinib is a tyrosine kinase inhibitor that inhibits the activities of vascular endothelial growth factor receptors, as well as other proangiogenic and oncogenic tyrosine kinase pathway-related receptors [6]. KEYNOTE-146 investigated pembrolizumab and lenvatinib (pem/len) in patients with EC [7]. The treatment was started at 200mg pembrolizumab intravenously 3-weekly and lenvatinib 20mg orally daily. No dose reductions for pembrolizumab were possible but a tiered dose reduction schedule for lenvatinib to 14mg, 10mg and 8mg was utilised according to toxicity. Once patients were deemed stable on treatment the regimen could be amended to pembrolizumab 400mg intravenously 6-weekly with daily lenvatinib continued. KEYNOTE-146~~It~~ demonstrated encouraging results in all patients, regardless of mismatch repair (MMR) status, but tolerability was a concern with 66.9% of patients experiencing a Common Terminology Criteria for Adverse Events (CTCAE) grade 3-4 treatment-related toxicity.

KEYNOTE-775 (KN-775) [8], published in February 2022, was a phase III, randomised clinical trial comparing pem/len and chemotherapy in patients with endometrial cancer who had previously received at least one platinum-based chemotherapy regimen. Patients with carcinosarcoma were excluded from the trial. The two primary end points were progression free survival (PFS) and overall survival (OS) and safety and tolerability were secondary endpoints. The endpoints were evaluated in patients with proficient MMR (pMMR) disease and all patients. Following the publication of KN-775, pem/len became available via a Compassionate Access Programme (CAP) in the UK for all patients with pMMR EC who had received treatment with a prior platinum-containing regimen. Subsequent to this, in June 2023 pem/len was approved by NICE for patients with advanced or recurrent EC who had progressed after platinum treatment and were not candidates for curative surgery or radiotherapy regardless of MMR status [9]. Of note patients with carcinosarcoma are not eligible for pem/len based on this approval [10].

As seen in other studies with this treatment regimen, high rates of adverse events (AEs) were noted in KN-775. Almost all patients in the treatment groups had AEs (>99%) and AEs of grade 3 or higher occurred in 88.9% of the patients who received pem/len. The most commonly occurring toxicity with pem/len was hypertension (any-grade 64.0%, grade≥3 37.9%) attributable to the lenvatinib.

Our study aimed to establish the real-world tolerability of pem/len in patients with advanced, recurrent or metastatic pMMR EC treated in the United Kingdom (UK).

Methods

We performed a multicentre retrospective observational review to document outcomes from patients with advanced, recurrent or metastatic EC treated with pem/len within the limited-time CAP in the UK. Centres enrolled within the CAP were informed of this project by the pharmaceutical company running the CAP (Merck & Co., Inc., Rahway, NJ., U.S.A.). Centres willing to contribute contacted the study team and were subsequently sent the data collection sheet (Appendix 1).

Data Collection

Approval for data sharing and analysis was sought within each centre from the Caldicott Guardian and all data was anonymised. Data was collected retrospectively from the electronic notes within each individual participating centre for patients treated prior to 30th June 2023. Demographic data included patient age, body mass index (BMI), ethnicity and PS. Disease characteristics included histological subtype and disease stage at diagnosis. Dates and type of previous and subsequent lines of treatment as well as the start date of pem/len were collected. Treatment outcome data included date of treatment interruption (and reason), date of dose reduction and date of last review (or patient death). For each cycle of treatment the toxicity experienced with CTCAE v5.0 grade was documented.

Assessment of Outcome Measures

The primary objective was to investigate the tolerability of pem/len in patients with advanced endometrial cancer within the CAP and as such the rates of toxicity was the primary outcome measured. The secondary outcome measures aimed to establish how these toxicities were managed including rates of dose reduction and treatment interruption. For all toxicity and tolerability outcomes, participating centres recorded each outcome for each cycle per patient. These were available to record for each of the adverse-events reported with a frequency ≥ 25% in KN-775 with a further option to add additional toxicities not otherwise specified.

Survival data was also analysed as a secondary outcome measure. Time on treatment (censoring those still on treatment at last review), progression-free survival (censoring those still on treatment at last

review or that came off treatment for reasons other than disease progression or death) and overall survival (censoring those still alive at last review) from start of pem/len were also secondary outcome measures. In exploratory analyses, we compared safety and tolerability data in those over the age of 70 years to those younger than 70 years, and time-to-event outcomes within the carcinosarcoma subgroup.

Descriptive statistical analyses were performed using Microsoft Excel version 2308. Analyses of time-to-event endpoints were performed using IBM SPSS Statistics for Windows version 28 (IBM Corp., Armonk, NY, USA) and Graphpad Prism version 6 (GraphPad Software, La Jolla, CA, USA). 95% Confidence intervals are provided for information, all analyses are descriptive in nature.

Results

Seven UK centres provided data for a total of 70 patients. The median age of patients at the start of treatment with pem/len was 68.5 years (range 45-85), with a PS of 0-1 in 77.1% and 2 in 22.9%. Thirty patients were aged over 70 years (42.9%). The mean BMI of patients was 27.8 (range 24.5-45.7). Clinician reported ethnicity data revealed that 68.6% of patients were white, 17.1% black and 12.9% Asian. Histological subtypes and other patient and disease related details are shown in Table 1.

Any-grade toxicity was reported in 60 patients (85.7%), with grade ≥3 toxicity reported in 39 patients (55.7%). Of the any-grade toxicities, fatigue was the most common (68.6%) followed by hypertension (55.7%) and hypothyroidism (42.9%).

Grade ≥3 toxicity was reported in 39 patients (55.7%). Of these, hypertension was most frequently reported (28.6%), followed by proteinuria (10.0%) and fatigue (8.6%). The toxicity which occurred with the most frequency outside of those commonly reported in KN-775 was mucositis in 13 patients (any grade, 18.6%). There was one episode of grade 5 toxicity (pneumonitis). Table 2 shows the reported toxicity rates.

In those aged ≥70 years the rate of grade ≥3 toxicity was 60.0%, with any grade toxicity observed at a rate of 86.7%. In those with a PS of 2, any grade toxicity was reported in 75.0% and grade ≥3 in 37.5%.

The incidence with each cycle for the three most commonly reported (in KN-775) toxicities is shown in figure 1.

45 patients (64.3%) required a dose reduction of lenvatinib (71.9% in those aged ≥70) and toxicity-related treatment interruption was reported in 32 (45.7%) patients (40.6% in those aged ≥70). Of the 45 patients requiring a dose reduction of lenvatinib, 26 (57.8%) required their first dose reduction in the first three cycles of treatment. Of the 45 patients who required a dose reduction the modal final dose was 10mg (range 8-14mg).

The median follow-up on patients in our study was 8.0 months, time-to-event outcomes are shown in Figure 2. The median time on treatment for all patients was 4.9 months (95% CI: 3.6-7.4) with a 6-month rate of 40.5% (95% CI: 28.0-52.7). Median PFS was 9.0 months (95% CI: 4.9-12.1) with a 6-month rate of 54.0% (95% CI: 39.0-66.8). The 6-month OS rate was 70.1% (95% CI: 56.5-80.1), the median was not estimable due to the short duration of follow-up. Eleven patients (15.7%) went on to receive a further line of systemic therapy (5 patients with weekly paclitaxel, 4 with platinum-based regimens and 2 other treatments). Ten patients (14.3%) had the histological subtype of carcinosarcoma, time-to-event outcomes are show in Figure 3.

Discussion

This real-world cohort study of recurrent, advanced or metastatic endometrial cancer patients treated with pem/len within the CAP shows that this combination is tolerable with similar toxicity and patient outcomes to the KN-775 trial. This is particular notable given that the cohort was older and with more advanced PS than in the clinical trial. The pem/len arm of KN-775 had a median age of 64 years and only PS 0-1 patients were eligible, whereas the cohort had a median age of 68.5 years and we can see that in the real-world this treatment regimen is being used in patients with a more advanced PS (22.9% PS 2) despite not being eligible for pem/len on this approval. We postulate that these patients were borderline fit but thought to be symptomatic from their cancer and therefore likely to be PS 1 if gaining response to treatment. These patients did not show higher rates of toxicity. Our data also included more patients of black ethnicity than in the pem/len arm of KN-775, with 17.1% versus 4.1%. This is of particular importance given the poorer outcomes in this patient group as we have discussed.

In addition, our population included a higher proportion of less frequently observed histological subtypes. Serous cancers were the most frequently reported tumour type despite endometrioid being the subtype found with the most frequency in patients with EC and in KN-775. One explanation may be that these less frequently observed subtypes are typically more aggressive and therefore more expected in a population of patients with advanced, recurrent, or metastatic disease. It may also be that these patients are less likely to delay treatment start to complete screening for clinical trials and are therefore underrepresented within the KN-775. Another reason for this may also be the increased frequency of pMMR status seen in the non-endometrioid subtypes.

Since this is a retrospective analysis of patient notes we would expect the rates of toxicity reporting to be lower than in phase III trials which adhere to more rigorous reporting methodology. However, toxicity rates were still high in our patient population with any-grade toxicity rates of 85.7% and grade ≥3 toxicity rates of 55.7%. In patients with few oncological treatment options toxicity and quality of

life (QoL) are exceedingly important. Toxicity leads to treatment interruptions and delays which may be detrimental to disease response as well as impacting on patients' QoL.

High rates of hypertension have been seen in the KN-775 and were also demonstrated in our population. Any-grade hypertension was observed in 55.7% with grade ≥3 observed in 28.6%. The incidence of hypertension was not related to any specific time point in treatment and was observed in patients throughout treatment, although it should be note there were fewer patients receiving treatment in the later cycles. Hypertension may pre-exist in this patient cohort due to increased number of comorbidities including obesity, but we do not have this data for our cohort. What can be ascertained is that there is a need to manage those with high blood pressure from the start of, if not prior to, the commencement of treatment.

Fewer cases of hypothyroidism were observed in our population compared to KN-775, but a significant proportion were still affected (42.9%, any-grade). The incidence of hypothyroidism (as shown in fig. 1) also appeared to increase with longer duration on treatment. Few cases of hypothyroidism grade ≥3 toxicity were seen (2.9% of patients). Whilst the symptoms of hypothyroidism such as cold intolerance and mood changes can be troublesome and may (such as in the case of fatigue) contribute towards higher rates of other toxicity observed, the mitigation of this toxicity can be managed appropriately in the outpatient environment with the addition of medications such as levothyroxine.

The two toxicities which occurred with higher frequency in our population compared to KN-775 were fatigue (68.6% any-grade and 8.6% grade ≥3) and proteinuria (34.3% any-grade and 10.0% grade ≥3). This may be because our population included older patients who may have had increased co-morbidities including pre-existing renal dysfunction. Proteinuria as a toxicity may be harder to manage leading to dose reductions, treatment interruptions or discontinuation. It is important to recognise the onset of proteinuria in patients on pem/len and react with changes such as dose reductions early.

In our patient population 64.3% patients required a dose reduction of lenvatinib during treatment which is consistent with the findings of KN-775 where 66.5% of the trial drug population required a dose reduction. Toxicity-related treatment interruption was reported in 45.7% of patients which was fewer than in KN-775 (69.2%).

We had a significant proportion of patients aged over 70 years old (30 patients, 42.9%). Within this population similar rates of any-grade toxicity were observed in both the older and younger age categories (any-grade toxicity 86.7% in those over 70 years vs 85.% in those younger than 70 years) but with a small increase in grade ≥3 toxicity in those aged greater than 70 years old (grade ≥3 toxicity

60.0% in those over 70 year vs. 52.5 % in those younger than 70). This could aid clinicians when making treatment decisions in this patient cohort with a minimal impact of age on toxicity noted in our results.

Median PFS was longer than the 6.6 months observed in KN-775 (9.0 months, 95% CI 4.9-12.1). Due to our small patient population and short follow-up we cannot state any statistical comparison, but we can conclude that our data is comparable with no major variation in PFS despite our older population with a poorer PS and rarer histological subtypes. Owing to the shorter follow-up period and subsequent small number of events observed, it is not possible to draw strong conclusions about OS but this does appear to markedly better or worse than KN-775. We did not collect radiological detail with regards to treatment response and progression. Analysis of this would be impacted by variations of imaging timing and lack of standardised reporting and is beyond the remit of this manuscript.

One of the main limitations of our study is that it involved retrospective data entry from patient notes. There may potentially be inaccuracies in this regard and outcomes such as toxicity are likely to be less stringently reported than in clinical trials. Due to this being a single arm, non-randomised study we are unable to draw direct comparisons between this and trial data. Real-world data is more subject to bias than prospective randomised-controlled trials, on which decisions such as those to implement guidance change are made. Despite this the importance of reporting this data, as well as the impact it has on in the healthcare setting, and seeing the impact of this treatment regimen in a more diverse real-world population is paramount as a useful adjunct to clinical trial data.

Due to the retrospective nature of our study, and the fact that it was multi-centre, there was no standardisation of the frequency and type of toxicity assessment, however all participating centres follow edthe monitoring regimen as per KN-775 and all patients were reviewed with BP, bloods and urine dipstick prior to every cycle. We collected individual data for each cycle of treatment per patient to ensure all data was captured.

Another limitation of our study is that we were unable to attribute the causality of the reported toxicity to pem/len. Whilst this is an important factor to be considered in randomised controlled trials, the implications of these events are limited in retrospective data analysis, as are likely to have the same impact on the patient and healthcare provider (e.g. dose reductions, increased monitoring, etc.) This is inherent in the set-up of a retrospective analysis where causality at the time of reporting is not documented.

Endometrial carcinosarcoma is responsible for 15% of deaths from uterine malignancies with limited treatment options for those with advanced disease [11]. The US Food and Drug Administration (FDA)

and the European Medicines Agency (EMA) approved the use of pem/len for endometrial cancer recurring after platinum-based chemotherapy, regardless of the histological subtype. In the UK, NICE approval was only granted for those without the carcinosarcoma subtype. The analysis of data from patients who accessed pem/len on the CAP enables us to review the data for those with this disease. Whilst our numbers are small (n=10) we can see from our survival curves that there are a proportion of these patients who have a sustained response beyond 6 months. This is not in keeping with previously published data indicating a lack of response in this cohort of patients (albeit with a smaller, single-institution population) [12]. Our data shows that there is a subgroup of patients with this aggressive subtype who respond, and more work is needed to identify therapeutic ways of targeting this cancer.

Conclusions

Within the limitations of this retrospective observational study, pem/len is tolerable in the real-world setting with comparable PFS and toxicity rates to phase-III trial data. Our real-world data included patients who were older and with a poorer PS, as well as those with carcinosarcoma (not included in KN-775 or recent UK Cancer Drug Fund criteria). This would indicate that it may be appropriate to consider pem/len in these patient populations. Many of the toxicities observed with a high frequency (e.g. hypertension and hypothyroidism) can be proactively managed to reduce the need for dose reductions or treatment interruption or cessation. There was a minimal increase in grade ≥3 toxicity observed in those over 70 years compared to KN-775, and comparable any-grade toxicity. Further work is required to find treatment strategies for patients with aggressive subtypes of the disease such as carcinosarcoma particularly as this may help to overcome the observed racial disparities in outcomes.

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