Incidence of Adverse Events with Pembrolizumab in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC): A Systematic Review of Literature

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Presenters: Abey Pandaplakkal John[1], Sandeep Mahapatra[1], Deepak Singla[2]
Affiliation: [1]Evalueserve, Bangalore, Karnataka, India, [2]Evalueserve, Gurugram, Haryana, India.

INTRODUCTION

Prostate cancer (PC) is the second most common cancer, and the fifth most common cause of cancer-related mortality among male patients, worldwide. In Europe and Japan, the incidence of PC in male in 2020 exceeded that of lung cancer [1]. Findings suggest that the number of new cases annually will rise from 1·4 million in 2020 to 2·9 million by 2040 [2]. mCRPC remains a significant medical challenge, even with recent advancements in diagnosis and treatment. To improve patient outcomes, it is important to understand the underlying mechanisms of resistance to treatments and develop new therapeutic approaches. Multiple drugs are now approved as the standard of care treatments for patients with mCRPC that have been shown to prolong survival. [3,4]}

OBJECTIVE

We aimed to evaluate the rate of adverse events (AEs) with pembrolizumab either alone or as combination therapy in patients with mCRPC.

METHODS

Search Strategy

We conducted a comprehensive search using MeSH terms combined with Boolean operators based on PICOS criteria (Table 1). Any additional keywords were also identified both for drug and disease through open searches. The search was run through online database (PubMed) between 2018-2023 with no limitation to language. The search strategy was peer-reviewed and utilized a combination of controlled vocabulary.

Table 1:PICOS Criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	• Patients with mCRPC	• Others
Intervention/Comparator	• Pembrolizumab	• Others
Outcome	• Any	• No exclusion based on outcome
Study Design	• Clinical trials • Observational studies	• Editorials, notes, comments, letters • Case reports, case series • Preclinical studies • Non-English

Steps in the research cycle: The steps undertaken in conducting the review is enumerated below:

Search Strategy

- This systematic literature review was conducted according to the preferred reporting initiative for systematic reviews and meta-analyses (PRISMA) guidelines
- We search the biomedical databases (PubMed) clinical trials (EudraCT, and clinicaltrials.gov.) including searches on grey literature as well, for the identification of clinical trials and observational studies
- The keywords used were Keytruda, lambrolizumab, MK-3475, pembrolizumab, SCH-900475, prostatic cancer, mCRPC, prostate neoplasm, etc.

Screening and Data Extraction

- First, title/abstract screening (first pass screening) of the studies was done followed by a full text- review (second pass screening) of shortlisted studies
- Back references of relevant studies for additional results were checked
- Titles and abstracts identified from this search were screened for full-publication review by two independent reviewers. Any disagreement was resolved by a third senior researcher. Reasons for exclusion of all the studies were also documented

RESULTS

Out of 118 studies identified from the literature, a total of 12 studies were included after full text screening (Figure 1). Most of the included studies were phase 2 trials (n=4), followed by phase ½ trials (n=3), observational studies (n=2), phase 1 and phase 3 trial (n=1 each). Our findings also reported data for one pilot trial.

A total of eight studies reported data for pembrolizumab in combination with other drug and five studies reported data for pembrolizumab as monotherapy. However, one study reported data for both monotherapy as well as combination therapy. The most common combination used with pembrolizumab was olaparib and enzalutamide (2 studies each).

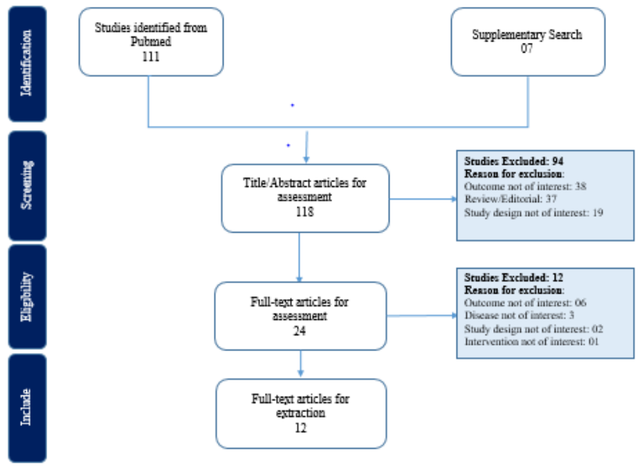

Figure 1: PRISMA Chart

Safety

Among the 12 included studies >250 different types of AEs were reported in mCRPC patients regardless of study design and monotherapy or combination therapy. The most common treatment related AEs (TRAEs) reported in the literature were grade 3-5 anemia (27% and 19.6%), febrile neutropenia (12%), fatigue (5.9%), and any grade chills (89.2%), pyrexia (54.1%), anemia (46%), nausea (45.9%). Immune related AEs (IrAEs) reported were any grade hypothyroidism (10.7% and 4.9%), colitis and myositis (7.1% each), hyperthyroidism (3.6%). Grade 3-5 IrAEs were severe skin reactions (1.6%), colitis (1.2%), hyperthyroidism (<1%). Any grade serious AEs reported in the literature were febrile neutropenia (10.6%), anemia (6.9% and 3.4%), and colitis, pneumonitis, pneumonia (2.9% each). Treatment emergent AEs reported were grade 3 asthenia, fatigue, peripheral neuropathy (4.3% each) and grade 4 increased lipase levels (4.3%).

A total of nine studies reported data for treatment discontinuation and five studies reported data for death due to AEs. The AEs were acceptable in most of the cases with very less treatment related discontinuation (~10-15%) and death (<1%). Overall, most widely reported AEs were fatigue (n=11), nausea (n=9), diarrhea (n=8) etc. All other most reported AEs (>4 studies) are depicted in the figure 2.

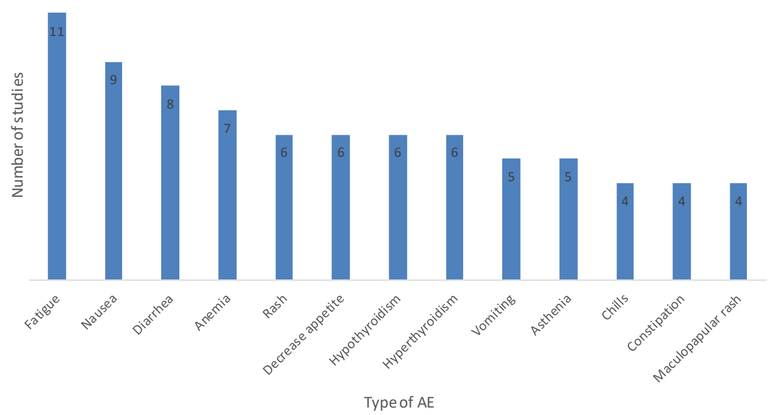

Figure 2: No. of studies with >4 AEs

CONCLUSION

Pembrolizumab was associated with a significant incidence of AEs, although most of the AEs were of mild to severe grades (grade 1-3). Fatigue, nausea and diarrhea were among the commonly reported AE. Careful clinical observation can be effective in handling these AEs without further harms. The AEs were tolerable in most cases and did not require hospitalization or treatment discontinuation

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