EFFICACY AND SAFETY OF NILUTAMIDE IN METASTATIC PROSTATE CANCER PATIENTS WHO UNDERWENT ORCHIECTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

- Prostate cancer (PCa) is the sixth primary cause of cancer death and the second most common cancer in men across the world.[1]
- By 2030, PCa burden is expected to be 1.7 million new cases and 499000 new deaths.[1]
- The annual incidence of metastatic prostate cancer (mPCa) in 2013 was 72% more than that of 2004.[2]
- Surgical or medical castration is the first-line choice for the newly diagnosed, hormone naive, mPCa[3].
- Combined androgen blockade, which includes a non-steroidal antiandrogen along with orchiectomy or other agents, appears to be a standard treatment modality for advanced PCa.[4]
- Nilutamide can attain a significantly constant prostate specific antigen response with a favourable toxicity profile when it is used as a second line agent.[5]
- The combination of nilutamide with orchiectomy has been shown to be significantly effective when compared with orchiectomy and placebo in the management of mPCa.[4]

OBJECTIVE

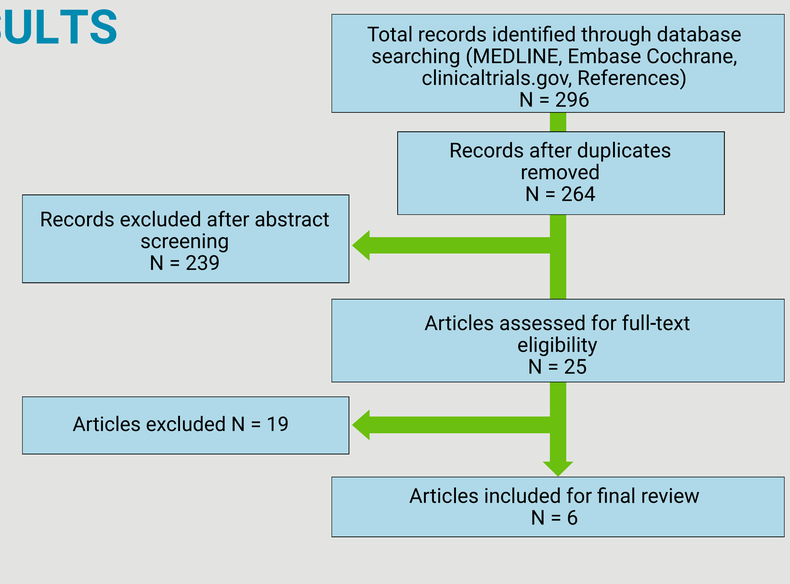
- To evaluate the efficacy and safety of nilutamide in metastatic prostate cancer patients who underwent orchiectomy.

MATERIALS AND METHODS

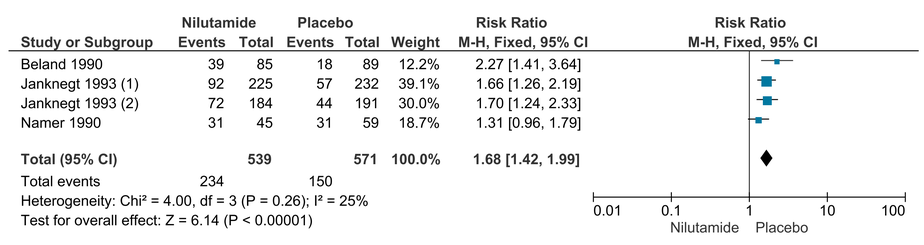
- Literature searches were conducted in MEDLINE, Embase, the Cochrane Library, and clinicaltrials.gov. No language or date restrictions were imposed.
- In addition, references of included studies were searched for relevant studies.
- All randomized controlled trials (RCTs) comparing nilutamide versus placebo in metastatic stages of prostate cancer patients who underwent orchiectomy were included.
- Outcomes:
  - Primary: Overall survival (OS), progression free survival (PFS) and response rate (RR).
  - Secondary: Complete response (CR), stable disease (SD), progressive disease (PD), disease control, and adverse events (tolerability) .
- Two authors independently selected papers, extracted data and assessed quality and disagreements were resolved through discussion.

  Study quality of included trials were assessed using the Cochrane Risk of Bias Tool.

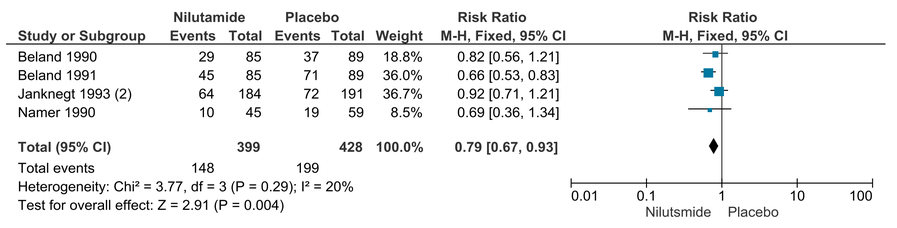
RESULTS

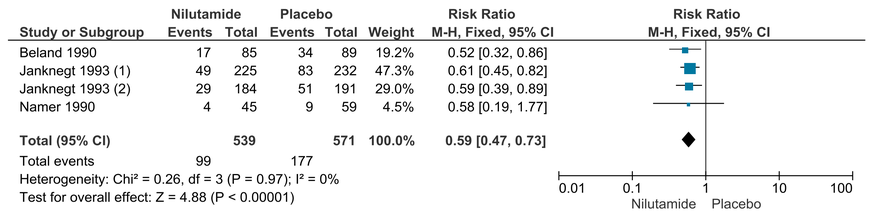


- A total of 6 RCTs involving a total of 1855 patients were included in this meta-analysis.
- A total of 912 patients received nilutamide followed by orchiectomy, and a total of 943 patients received placebo.
- Review suggests that , addition of nilutamide to the orchiectomy significantly improves the OS, PFS, RR, CR and PD when compared to placebo in patients with mPCa. However; stable disease was observed to be better with placebo than the nilutamide group.
- Overall, the risk of bias of included trials was low (n=4) to moderate (n=2).
- Most common adverse events reported with nilutamide include delayed adaptability to darkness or blurred vision, alcohol intolerance and hot flash.

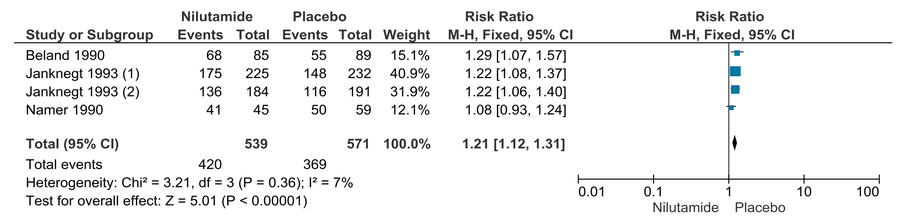


The **objective response** was higher with nilutamide group than the placebo (RR=1.68; 95%CI 1.42 to 1.99, 4 studies)
The **complete response** was higher with nilutamide group than the placebo (RR=2.03; 95%CI 1.35 to 3.06, 3 studies)

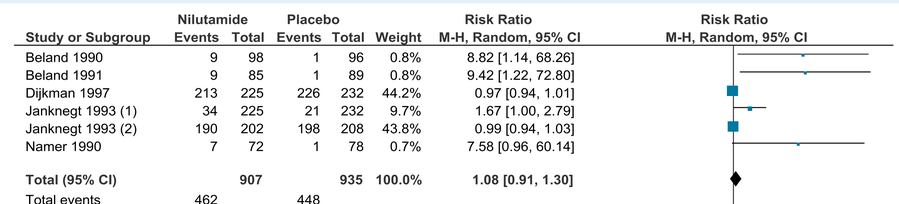




The **stable disease** was lower with nilutamide group than the placebo (RR=0.79; 95%CI 0.67 to 0.93, 4 studies)
The **progressive disease** was lower with nilutamide group than the placebo (RR=0.59; 95%CI 0.47 to 0.73, 4 studies)



The **disease control** rate was better with nilutamide group than the placebo (RR=1.21; 95%CI 1.12 to 1.31, 4 studies)



The **treatment discontinuation (Tolerability)** was comparable between nilutamide group and the placebo (RR=1.08; 95%CI 0.91 to 1.30, 6 studies)

OS and PFS

- A total of 3 studies with 1037 participants reported the OS. The median OS was significantly longer in nilutamide group (Range - 24.3 to 27.3 months) when compared to placebo group (Range - 18.9 to 24.2 months).
- Two studies with 867 partcipants reported the PFS. Significantly prolonged median PFS was observed with nilutamide group as compared to placebo group [Study I: 21.2 vs 14.7 months (p=0.002), Study II: 20.8 vs 14.7 months (p= 0.0041) respectively].

DISCUSSION

- Despite advances in the treatment of mPCa, most patients have a poor prognosis.
- Since many patients may not prefer, or are not candidates for aggressive treatment regimens, efforts should be put to identify efficacious but less toxic chemotherapeutic regimens.
- Nilutamide is a high-affinity non-steroidal anti-androgen which acts on the androgen receptors ligand binding and blocks the transcription of androgen response elements.[5]
- One RCT with 193 participants demonstrated that continuous androgen deprivation therapy with 300mg of nilutamide was better when compared to the intermittent therapy in terms of efficacy and quality of life outcomes.[6]
- When given as a part of CAB along with the orchiectomy or other surgical castration techniques, nilutamide has shown good activity, and its ADRs are not serious enough to lower QoL.[7]

CONCLUSIONS

- Nilutamide in combination with orchiectomy shows significant improvement in OS, PFS, response rate and clinical benefit when compared to orchiectomy with placebo in patients with mPCa

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