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Advanced Androgen Blockage in Nonmetastatic Castration-resistant Prostate Cancer: An Indirect Comparison of Apalutamide and Enzalutamide

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Abstract

Patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) have historically had few treatment options. Recently, randomized controlled trials have examined the benefit of apalutamide and enzalutamide in these patients. We sought to perform an indirect treatment comparison using a network meta-analysis approach to compare the relative efficacy and toxicity of these two agents. The primary outcome of this analysis was metastasis-free survival (MFS) while secondary outcomes were time to prostate-specific antigen progression, overall survival, and adverse events. The Bucher technique for indirect comparison was used to compare apalutamide and enzalutamide using the common placebo comparator. We found no evidence of a significant difference in MFS (hazard ratio 1.04, 95% confidence interval 0.78–1.37) between enzalutamide and apalutamide. Similarly, there were no differences for any of the secondary outcomes. While indirect comparisons cannot supplant direct comparative data, this analysis suggests that apalutamide and enzalutamide are similarly effective in delaying metastases for patients with nmCRPC.

Patient summary: Historically, there have been few treatment options for prostate cancer patients receiving androgen deprivation therapy who have rising prostate-specific antigen levels without obvious recurrence of cancer. Recent randomized controlled trials demonstrated that treatment with enzalutamide and apalutamide delayed the development of metastatic cancer. This study demonstrates through an indirect comparison that both medications are likely to have similar efficacy and side-effect profiles.

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Approximately 40% of men initially diagnosed with localized prostate cancer will experience disease recurrence after undergoing surgery or radiation [1]. Early administration of androgen deprivation therapy (ADT) for patients with biochemical progression after initial treatment improves metastasis-free survival, symptoms from metastatic disease, and prostate cancer–specific mortality [2]. However, many patients eventually develop resistance to ADT and progress to castration-resistant prostate cancer (CRPC) [3]. In many cases, these patients have no evidence of metastasis, a state referred to as nonmetastatic CRPC (nmCRPC).

Patients with nmCRPC generally have poor prognosis, with one-third of patients developing metastatic disease, one-fifth dying, and 42% experiencing one of these two events within 2 yr [4]. However, to date these patients are often managed expectantly. It has been shown that novel androgen axis inhibitors improve survival in men with metastatic castration-sensitive prostate cancer [5], in chemotherapy-naïve CPRC, and in postchemotherapy CRPC. However, only recently have such therapies been tested in nmCRPC.

Data recently presented by Hussain et al. [6] and Small et al. [7] demonstrated that enzalutamide (PROSPER) and apalutamide (SPARTAN), respectively, improved metastasis-free survival (MFS) compared to placebo among patients continuing ADT for nmCRPC. However, despite the importance in guiding prescribing practices, the comparative efficacy of these two agents remains unclear. As no direct comparative trials exist, we performed an indirect treatment comparison.

We identified available phase 3 randomized controlled trials (RCTs) examining novel androgen axis inhibitors in patients with nmCRPC using a search of conference proceedings of relevant medical societies and of PubMed on February 9, 2018. Observational studies, editorials, commentaries, review articles, and those not subject to peer review were excluded. To facilitate indirect treatment comparisons, all studies had to include a control arm comprising treatment with placebo and ADT, in addition to an active treatment arm.

The primary outcome of interest was investigator-adjudicated MFS. Secondary outcomes included time to prostate-specific antigen (PSA) progression, overall survival (OS), any adverse events (AEs), serious (grade 3 or 4) AEs, AEs leading to treatment discontinuation, and mortality due to AE. We performed indirect treatment comparisons of the novel androgen axis inhibitors using placebo plus ADT as the common comparator arm. We used the investigator-reported hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for efficacy-related endpoints and calculated odds ratios (with 95% CI) using the raw data presented for toxicity-related endpoints. We performed indirect treatment comparison using the method of Bucher et al. [8]. This methodology has been used for analyses of both HRs and odds ratios [9]. This approach has been identified as the most appropriate method for performing indirect treatment comparisons of RCTs [9,10]. The indirect treatment comparison was performed using Excel 2016 (Microsoft, Richmond, WA, USA) with a previously published macro [5].

We identified two relevant RCTs. Together, they report on 2608 patients, of whom 806 received apalutamide, 933 received enzalutamide, and 869 received placebo, in addition to ongoing ADT. Study methodology and inclusion criteria were similar between the studies although, PROSPER required serum PSA $\geq$2 ng/ml, while no such requirement was mandated in the SPARTAN trial. In addition, SPARTAN included patients with N1 disease (Table 1). As PROSPER has not yet been published as a complete manuscript, further comparison of the demographics of the two study cohorts is not possible.

Both apalutamide (HR 0.28, 95% CI 0.23–0.35) and enzalutamide (HR 0.29, 95% CI 0.24–0.35) demonstrated significant improvements in MFS compared to placebo. Indirect comparison of enzalutamide and apalutamide failed to demonstrate a significant difference in MFS between the two agents (HR 1.04, 95% CI 0.78–1.37). We performed a sensitivity analysis restricted to patients with N0 disease. Results were similar to the primary analysis (HR 0.89, 95% CI 0.65–1.18), consistent with no significant difference between the two agents. Similarly, there were no significant differences in time to PSA progression, OS, any AEs, serious AEs, AEs leading to treatment discontinuation, or mortality due to AEs (Table 2).

Novel androgen axis inhibitors have moved sequentially earlier in the disease process from the postchemotherapy space to prechemotherapy mCRPC and, in the case of abiraterone, to metastatic castration-sensitive prostate cancer. Notably, the absolute benefit in median OS has increased as abiraterone has been tested earlier in the disease continuum. In the SPARTAN trial, the investigators assessed the time from randomization to progression during the first subsequent treatment for mCRPC. On protocol, patients were offered secondary treatment at the discretion of their treating physician or offered abiraterone on the development of metastases: 165 men in the apalutamide arm and 217 men in the placebo arm received subsequent therapy for mCRPC. Secondary PFS was significantly longer for men who had been initially treated with apalutamide than placebo (HR 0.49, 95% CI 0.36–0.66).

While indirect treatment comparison analyses have been used and validated for comparing outcomes for RCTs, this approach is a surrogate for a head-to-head treatment comparison. Furthermore, the validity of such an approach relies on the comparability of the study cohorts. While the study inclusion criteria differed somewhat, with a minimum serum PSA of 2 ng/ml in PROSPER and no minimum in SPARTAN, as well as inclusion of patients with N1 disease in SPARTAN, the patients in the two study cohorts appear to have similarly aggressive disease characteristics, with median PSA doubling time in both studies between 3 and 5 mo. However, the novel androgen axis inhibitors abiraterone and enzalutamide, and most recently apalutamide, have received approval in disease spaces without direct comparison. Future clinical trials for nmCRPC patients should consider apalutamide or enzalutamide

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