Acta Clin Croat (Suppl. 3) 2022; 61:51-56
doi: 10.20471/acc.2022.61.s3.7

Professional Paper

ROLE OF ANDROGEN RECEPTOR-TARGETED AGENTS IN LOCALIZED PROSTATE CANCER

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ABSTRACT: Anti-androgen therapy continues to be a basic pilar of treatment for both localized and metastatic prostate cancer. The advent of new generation of androgen receptor targeted agents (ARTA) transformed the care of patients with advanced disease. After such a success, the steps were taken to incorporate a new generation of ARTAs into the treatment landscape of localized prostate cancer. High-risk prostate cancer represents the most aggressive form of localized disease with significant metastatic potential and poor outcome. Here, the impact of novel therapies will likely be profound and transforming. This clinical space has already been a showcase for multidisciplinary treatment where the combination of local therapies with systemic treatment gradually improved patient outcomes and the chances of cure. The most recent step in redefining the treatment of localized disease is the adoption of novel ARTAs moving forward the multidisciplinary platform. In this narrative review, we discuss current clinical evidence supporting the use of novel ARTAs in patients with localized high-risk prostate cancer and cover recent developments in biomarker-driven strategies for treatment individualization in this clinical context.

Key words: *Radiotherapy (RT); prostate cancer; androgen deprivation therapy (ADT); abiraterone; enzalutamide; androgen receptor; androgen receptor targeted agents (ARTAs)*

Role of androgen deprivation therapy (ADT) in localized prostate cancer

Androgen deprivation therapy (ADT) has been a cornerstone of prostate cancer treatment across the whole disease spectrum for decades, expanding from localized and biochemically recurrent disease to the metastatic stage (1). Depletion of serum testosterone is the main goal of ADT, and it can be achieved either with surgical castration (e.g. orchiectomy) or by administration of chemical compounds which interfere with hypothalamus-pituitary-testis axis and centrally block production of testosterone (e.g. gonadotropin-releasing hormone (GnRH) agonists). However, despite castrate serum levels of testosterone, prostate cancer cells are able to maintain their local intracellular testosterone production under selective pressure of ADT using different adaptation and escape mechanisms especially those existent in castration-resistant disease, invariably leading to disease progression and poor outcome (2,3).

Additional and profound testosterone inhibition achieved either by using novel direct androgen receptor inhibitors/antagonist (like enzalutamide, darolutamide, apalutamide) or by using inhibitors of androgen biosynthesis (like abiraterone acetate) have proved beneficial in advanced disease and had gradually moved in earlier phases of disease (4–8)a phase 3, double-blind, randomized study. We evaluated the

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longer-term efficacy and safety of enzalutamide up to the prespecified number of deaths in the final analysis, which included an additional 20 mo of follow-up for investigator-assessed rPFS, 9 mo of follow-up for OS, and 4 mo of follow-up for safety. Enzalutamide reduced the risk of radiographic progression or death by 68% (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.28–0.37; $p < 0.0001$.

Nowadays, the standard of care of metastatic hormone sensitive prostate cancer is the combination therapy of ADT plus novel androgen inhibition, resulting in prolonged survival and less disease-related symptoms compared to the treatment with ADT alone (9).

On the heels of success of novel anti-androgen therapy in metastatic disease, the trials of such therapies in localized prostate cancer were performed or are currently ongoing and will be published in the near future.

Localized high-risk prostate cancer accounts for approximately 20% of total clinical disease presentation and represents the most concerning form of disease (10). Furthermore, the majority of men who nowadays succumb to prostate cancer have been initially diagnosed with localized tumor. Despite the advances in the treatment of prostate cancer, high-risk prostate cancer still has 35.5% cumulative mortality at 15 years (11).

Several randomized trials showed that the addition of ADT to radiotherapy improved overall survival of high-risk prostate cancer patients compared with radiotherapy alone (12–14).

The rationale for the combination of radiotherapy and ADT is to eradicate both the primary tumor and micrometastatic clones. NCCN guidelines sub-stratify high-risk prostate cancer into high-risk and very high-risk sub-categories, as these latter have poor oncological outcomes compared to regular high-risk patients (9). The patient is categorized into a very high-risk group if he has either: T3b-T4 stage, primary Gleason pattern 5, or more than 4 biopsy cores with Grade Group 4 or 5 prostate cancer. This stratification helps to identify candidates for more intense multimodal therapy.

The rationale for the combination trials in localized high-risk disease lies in the fact that the advances in single-treatment modalities (e.g. radiotherapy, radical prostatectomy) are limited by the tolerability of extended surgery or radiotherapy dose-limiting toxicity but also due to the presence of subclinical metastasis. The latter is evidenced by the metabolic imaging using novel PSMA tracer, where up to 25% of high-risk patients are found to have distant metastases not previously seen on conventional imaging (15).

In order to reach better outcomes, a treatment could be optimized using multimodality approach in three different ways: applying novel therapeutic strategies, using treatment intensification, and to treat both the primary tumor and possible micrometastatic disease. ADT plus RT has become the standard of care in men presenting with high-risk prostate cancer. It is well established that extended ADT duration improves overall survival. However, the optimal duration of ADT when given in conjunction with RT has not been firmly established. It is clear that ADT duration beyond 18 months is beneficial, however, it remains a subject of debate whether it is 24 months or 36 months.

In RTOG 92-02 and DART 01/05 GICOR trial, the periods of 4 months vs 28 months of ADT were compared (16,17). EORTC 22961 investigated the ADT duration of 6 months vs 36 months (18).

All three trials demonstrated the improvements in overall survival with prolonged ADT. Nabid et al. investigated ADT duration of 18 months vs 36 months of ADT. Although 36 months period was not superior to 18 months of ADT, the trial was not designed as superiority trial, therefore the equivalency cannot be established (19).

Combination of novel anti-androgen therapy and ADT in high-risk disease managed with radiotherapy

In localized prostate cancer the role for novel androgen receptor pathway inhibitors in patients receiving primary radiotherapy has been studied in ATLAS trial (apalutamide), ENZARAD trial (enzalutamide), STAMPEDE trial (abiraterone), and DASL-HiCaP study (darolutamide). There are few single-institution studies of novel antiandrogen therapy in combination with radical prostatectomy. Here, complete pathologic response and minimal residual disease at final pathology are the primary endpoints. PROTEUS trial combined apalutamide with surgery and provided more relevant oncologic data.

In STAMPEDE trial addition of abiraterone to ADT was tested in newly diagnosed hormone sensitive prostate cancer (20). This study included a heterogenous group of patients, including 27% with newly diagnosed node-negative, nonmetastatic prostate can-

cer. These patients received abiraterone plus ADT vs ADT alone for 2 years and were mandated to receive definitive radiation therapy (21).

Clinical question tested in STAMPEDE trial was to determine whether abiraterone acetate is effective for men with high-risk prostate cancer and no metastases on CT and bone scan. Trial protocol was amended in 2019 to allow differential reporting for M1 and M0 disease. Standard treatment arm consisted of 3 years of ADT + standard of care radiotherapy (SOC). Experimental arm consisted of SOC plus 2 years of abiraterone acetate + prednisone (AAP) (randomization 2011-2013) and of SOC plus 2 years of abiraterone acetate + prednisone + enzalutamide (randomization 2014-2015). For purpose of trial analysis authors combined these two arms and results were presented on ESMO 2021 Meeting. Trial primary endpoint was metastasis-free survival. After median follow-up of 6 years, patients randomized to ADT + AAP ± Enzalutamide had 6-years metastasis-free survival 82% compared to 69% for patients randomized to SOC (HR 0.53, 95%CI 0.44-0.64). In both experimental arms patients had improved metastasis-free survival (ADT+AAP HR 0.54, ADT+AAP+Enzalutamide HR 0.53). 6-year overall survival was also improved from 77% to 86% for patients receiving ADT + AAP ± Enzalutamide (HR 0.6) compared to SOC 3 years of ADT + primary radiotherapy. Other secondary endpoint such as prostate cancer-specific survival and progression-free survival were also improved in ADT+AAP±Enzalutamide arms, with 6-year prostate cancer-specific survival improvement from 85% to 93%.

Taken together, 2 years of AAP-based therapy significantly improved metastasis-free and overall survival of high-risk M0 prostate cancer starting ADT and should be considered as the new standard of care. However, it seems that adding enzalutamide to AAP increase toxicity but had no discernible effect on efficacy (21).

ATLAS trial is large phase III randomized trial that investigate addition of apalutamide to radiotherapy management of high-risk prostate cancer. Apalutamide is given neoadjuvantly/ prior to radiotherapy, concomitant with radiotherapy and adjuvantly for 2 years post radiotherapy. Primary endpoint is metastasis-free survival. The first results will be released in 2023 and hopefully will corroborate results of abiraterone seen in STAMPEDE trial (22).

Next trial in high-risk localized prostate cancer space is ENZARAD trial, an open label, randomized, phase III trial, taking place in Australia, New Zealand, USA, UK, Ireland, and Europe. All participants receive LHRH antagonist for 24 months (2 years), and radiotherapy is starting about week 16. Prescribed radiotherapy dose is 78 Gy in 39 fractions, or 46 Gy in 23 fractions plus brachytherapy boost. Elective nodal radiotherapy is optional for N0 patients and mandatory for N1 patients. Per randomization enzalutamide is given in the standard daily dose of 160 mg for 24 months, alternatively patients are given older non-steroidal anti-androgen. The trial primary endpoint is metastasis-free survival (23)during and after radiotherapy (RT.

Trials of novel anti-androgen therapy combined with surgical approach

After radical prostatectomy 20-50% of patients with localized high-risk prostate cancer experience disease progression (24).

Neoadjuvant studies with next-generation androgen receptor inhibitors have shown that 6 months of profound androgen blockade may improve local disease control at the time of radical prostatectomy (example ADT with or without abiraterone) (25,26)but not by concomitant ADT with surgery. Luteinizing hormone–releasing hormone agonist (LHRHa; leuprolide acetate.

Other studies have investigated neoadjuvant enzalutamide and apalutamide in patients with localized high-risk prostate cancer undergoing radical prostatectomy.

Systemic therapy regimens were different and varied significantly (leuprolide × 6 months + abiraterone × 3 vs. 6 months (NCT00924469); enzalutamide vs. enzalutamide + dutasteride + leuprolide × 6 months (NCT015472990; enzalutamide + leuprolide with or without abiraterone (NCT02268175) (27).

Based on these premises, large phase III randomized trial (PROTEUS) was designed to determine if treatment with apalutamide plus ADT before and after radical prostatectomy in patients with localized high-risk or locally advanced prostate cancer results in an improvement in pathologic complete response rate and metastasis-free survival compared with placebo plus ADT. Patients receive 6 treatment cycles of apalutamide or placebo, followed by radical prostatectomy, followed by an additional 6 cycles of apalutamide or placebo. Dual primary end points are pathologic complete response and metastasis-free survival. Secondary endpoint as usual are PSA-free survival and progres-

sion-free survival. Approximately 2000 pts are to be enrolled globally. The study started in June 2019, and final analysis of the trial is expected in late 2026 (28).

There was an effort to look at the role of ARTA in patients with localized prostate cancer undergoing active surveillance. The ENACT trial (NCT02799745) is an open label, phase 2 trial which randomized 230 patients with clinically localized low- or intermediate-risk prostate cancer to receive enzalutamide monotherapy or just observation per active surveillance protocol. The results of the study were presented during the 2021 AUA Annual Meeting when primary end point of time to pathological or therapeutic prostate cancer progression was met. Patients who received enzalutamide had a 46% reduction in the risk of prostate cancer progression compared with patients undergoing active surveillance. Enzalutamide treatment was associated with higher likelihood of having a negative biopsy at one year post treatment, and as well as with statistically significant reduction in the mean percentage of cancer-positive cores at 1 year (29).

While it is not clear what the benefit of enzalutamide would be in patients undergoing active surveillance, this study does show the role of single ARTA in patients with localized prostate cancer which certainly will be further evaluated.

Genomic-based approaches to guide ARTA in localized disease treated by surgery or primary radiotherapy

There has been significant interest in looking at biomarker-based strategy of therapy individualization in prostate cancer, particularly in the applied genomics area. Genomic biomarkers have potential to improve risk stratification of localized prostate cancer and might influence therapeutic decision making (30). The 2020 NCCN guidelines recommended use of Decipher and Prolaris tumor-based molecular assays in men with high-risk prostate cancer and life-expectancy of more than 10 years (9). Furthermore, Decipher, a 22-gene genomic classifier, improved the estimation of risk to develop distant metastases, compared to NCCN risk groups only (31). Decipher is also confirmed to be independent predictor of metastasis in high-risk prostate cancer following local therapy (32).

One study recently validated the prognostic value of Decipher genomic test in patient samples from the RTOG 9601 trial. In this trail patients with PSA recurrences after surgery were randomized to radiation alone or in combination with 2 years of 150 mg of older generation anti-androgen, bicalutamide (33). This study by Feng et al. found that only patients with intermediate to high Decipher scores had benefit from the antiandrogen therapy, while patients with low Decipher scores did not (34). These results gave impetus for number of other trials where Decipher test was incorporated to select patients at high risk post prostatectomy, who could potentially benefit from additional adjuvant therapies. Examples of such trials are NRG-GU002 RADD randomized trial (NCT03070886), which is investigating the addition of adjuvant docetaxel to radiation and ADT for patients with persistently elevated PSAs after prostatectomy, ECOG ERADICATE trial, in which patients who had a prostatectomy with high Decipher scores were randomly assigned to 12 months of ADT with or without 12 months of darolutamide (27).

Another genetic biomarker, PAM50, is also being prospectively tested in the NRG GU006 BALANCE trial (NCT03371719). PAM50 has been previously validated for breast cancer molecular subtyping (35), while in prostate cancer showed ability to distinguish which patients benefit from ADT in retrospective study (36). In BALANCE trial patients with PSA recurrences after prostatectomy are being randomized to salvage radiotherapy alone or in combination with 6 months of apalutamide (27).

On a further note, in patients with intact prostate cancer treated with RT-based approach, an NRG trial was design to investigate the potential of Decipher genomic assay to optimize treatment decisions particularly for high-risk prostate cancer where the potential of such impact would be the greatest. The PREDICT-RT (NRG GU009) trial was designed as phase III trial where all eligible patients undergo diagnostic prostate biopsy tissue testing with Decipher assay. Basically, trial compares less or more intense hormone therapy approach in addition to standard-of-care radiation therapy in NCCN high-risk prostate cancer patients with either lower or higher genomic risk. More precisely, patients with high Decipher scores will be randomized to either standard of care (definitive radiotherapy + 2 years of ADT) or standard of care + treatment intensification with apalutamide. Conversely, patients with low or intermediate Decipher scores will be randomized to either standard of care (definitive RT + 2 years of ADT) or definitive RT + 1 year of ADT (treatment deintensification) (37).

Concluding thoughts

Eradication of occult metastatic disease is a key factor for treatment success in patients with high-risk prostate cancer. Multimodal treatment strategies that involve surgery, radiotherapy, and systemic therapy have the potential to cure patients with high-risk disease. Ongoing biomarker-based clinical trials will inform us which patient population will likely benefit the most from treatment intensification ushering the era of precision medicine to the forefront of care in prostate cancer.

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Sažetak

ULOGA MODERNE ANTI-ANDROGENE TERAPIJE U LIJEČENJU LOKALIZIRANOG RAKA PROSTATE

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SAŽETAK: Anti-androgena terapija je temelj liječenja lokaliziranog i uznapredovalog raka prostate. Dolazak nove generacije lijekova koji inhibiraju androgenu osovinu preobrazila je liječenje bolesnika sa uznapredovalim rakom prostate. Temeljem uspjeha u uznapredovaloj bolesti, u tijeku su napori da se nova generacija anti-androgenih lijekova inkorporira u liječenje lokalizirane bolesti. Visokorizičan rak prostate predstavlja najagresivniji oblik lokalizirane bolesti sa značajnim metastatskim potencijalom. Za očekivati je da će u ovom stadiju utjecaj novih terapija biti preobražavajući. Lokalizirani visokorizični rak prostate se liječi multidisciplinarno. Tu su kombinacije lokalnog liječenja i sustavne terapije postepeno popravljale ishode liječenja i omogućavale priliku za izliječenje. Zadnji napor predstavlja usvajanje novih anti-androgenih terapija. U ovom preglednom članku razmatramo kliničke dokaze za upotrebu nove generacije anti-adrogene terapije u bolesnika sa lokaliziranim visokorizičnim rakom prostate i dajemo pregled zadnjih strategija za personalizaciju liječenja.

Ključne riječi: *Radioterapija, rak prostate, androgen deprivirajuća terapija, abirateron, enzalutamid, androgeni receptor, lijekovi koji ciljaju androgeni receptor*