Review Article

2nd generation anti-androgens and radiotherapy for localized prostate cancer

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Abstract: Combining radiotherapy and androgen deprivation therapy is the current backbone of localized prostate cancer treatments. Recently, new agents have been used in the settings of metastatic and high risk prostate cancer, and more data is emerging showing promising results when combining these new drugs with radiotherapy.

Keywords: Radiotherapy (RT); prostate cancer; androgen deprivation therapy (ADT); abiraterone

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Introduction

Radiotherapy (RT) is one of the pillars of prostate cancer (PCa) treatments. Advanced in technology and clinical knowledge have allowed physicians to minimize treatments toxicity and improve clinical outcomes. Anti-testosterone treatments, commonly termed androgen deprivation therapy (ADT), are widely used in the treatment of both localized and metastatic PCa. ADT has proven to reduce tumor burden and improve clinically meaningful outcomes. Combining RT and ADT is the backbone of localized prostate cancer treatments in intermediate and high-risk disease; numerous prospective trials with long-term follow-up have demonstrated this combination to be superior to single modality therapy. In this review we will evaluate the role of Abiraterone and other 2nd generation anti-androgens in combination with RT.

Testosterone and prostate cancer

The two principal androgens in men are testosterone, produced by Leydig cells (located in the testis), and dihydrotestosterone (DHT), a testosterone derivative, produced in peripheral tissues by 5-α reductase. The close link between testosterone and prostate cancer has been observed in preclinical and clinical systems and the notion of androgen promotion of prostate tumorigenesis, known as the "androgen hypothesis", has been extensively studied (1-3). Interestingly, two large population based studies evaluating testosterone and DHT levels, showed no association between endogenous testosterone levels and PCa development (4,5), and a cause-and-effect relationship of serum testosterone and PCa remains controversial (6).

Because most of these studies evaluated circulating levels of testosterone, this inability to prove a substantial relationship between high levels of testosterone and PCa may reflect the relative importance of tumor microenvironment as opposed to systemic levels of the hormone. Recent data indicates that the actual levels of testosterone in the tumor remain high even in castrated patients (7). This maybe the result of tumor cells upregulated biosynthesis of androgens (8), mainly by increased CYP17A1 production, which is a key enzyme in the steroidogenic pathway of androgens, converting 17α-hydroxy-pregnenolone to dehydroepiandrosterone (DHEA). With that understanding, trials evaluating the role of Abiraterone acetate, which inhibits CYP17A1 showed positive results and will be discussed further in this review.

Traditional androgen deprivation therapy

Since their introduction into the clinics few decades ago, gonadotropin releasing hormone (GnRH) analogs and androgen receptor (AR) blocking agents have been the mainstay of therapy for locally advance or metastatic PCa. GnRH analogs exert their action by continuous stimulation of the pituitary gland, leading to down-regulation of type-I GnRH receptors and desensitization of pituitary gonadotrophs (9). This will result in reduced Luteinizing hormone (LH) secretion with negative effect on Leydig cell production of testosterone.

AR blocking agents, or AR antagonists, such as bicalutamide, inhibit binding of DHT, as they bind to AR and induce structural change (10), thus preventing AR from binding to coactivators and DNA, destabilizing it and rendering it non-functional (11). Enzalutamide, a newer AR antagonist, has both a higher receptor affinity and inhibits AR nuclear translocation (12). Even newer AR antagonists are being developed hoping to overcome mutated AR that leads to resistance to therapy (13).

While GnRH reduce serum testosterone, it may have little effect on intratumoral testosterone, so adding AR antagonists to achieve better testosterone deprivation of tumor cells seems logical with the aim of total androgen blockade. By administering unopposed GnRH analogs, a "flare up" phenomenon might occur in which the sudden stimulation of the anterior pituitary leads to LH surge followed by up to a two-fold increase in testosterone (14). Prophylactically blocking the AR may reduce the effect of testosterone surge, which was reported to cause worsening of clinical conditions such as pain (15), however, it is not clear if this affects patients' survival (16).

GnRH agonists and RT

The primary mechanism by which RT eradicates prostate cancer cells is via direct and indirect DNA damage (17). The resultant genotoxic stress inhibits proliferation and ultimately leads to cell death. These properties of radiation have been known for many years and led to development and utilization of external beam radiation, brachytherapy and proton beam radiation in the treatment of PCa. Preclinical data demonstrated that ADT could induce tumor cell death by apoptosis (18) and reduce a preset cellular adaptation to oxidative stress (19) and potentiate the effects of radiation therapy.

These effects were also clearly demonstrated in the clinic. The results of large phase III randomized control trials evaluating the role of ADT addition to RT in in intermediate risk (20) and high risk (21,22) PCa show improvement in disease specific survival and overall survival. This led for guidelines recommending the addition of 4–6 months of ADT for intermediate risk PCa and 24–36 months of ADT for high risk PCa (23).

Abiraterone acetate and RT

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme, as mentioned earlier, is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes two sequential reactions: (I) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and (II) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals (24).

Abiraterone has demonstrated its capacity to dramatically reduce circulating levels of testosterone and thus more effectively suppress the androgen axis (25). Taplin *et al.* recently reported on their outcomes with the use of neoadjuvant abiraterone in combination with leuprolide in the up-front, high risk setting prior to prostatectomy (26). Patients were initially randomized to either leuprolide alone for 12 weeks or leuprolide in combination with abiraterone; all patients then received an additional 12 weeks of combination therapy until radical prostatectomy; biopsies were conducted at week 12 of the study. Compared to leuprolide alone, there were statistically significant decreases at 12 weeks in intra-tumoral levels of DHT and DHEA in the group treated with both leuprolide and abiraterone ($P<0.0001$). Similar decreases were seen with androstenedione and testosterone. A PSA nadir of ≤0.2 ng/mL at 12 weeks was achieved in 90% of the patients in the combination arm versus only 4% in the leuprolide alone arm ($P<0.0001$). At the time of prostatectomy, those who had undergone 24 weeks of combined therapy versus those who had undergone only 12 weeks had a nearly significantly higher rate of near pathological complete response (CR) or total CR, 34% versus 15%, respectively ($P=0.09$). The data from Taplin *et al.* makes clear that, even in the high-risk, locally advanced setting, there are

clonogens capable of escaping chemical castration with LHRH agonists only. This cohort of patients may thus benefit from added Abiraterone.

Abiraterone is now approved by the FDA for use in metastatic, castrate sensitive disease (27). The approval resulted from the reports of 2 phase III trials: LATITUDE (ClinicalTrials.gov Identifier NCT01715285) and STAMPEDE (ClinicalTrials.gov identifier NCT00268476). In LATITUDE (28), patients with metastatic prostate cancer, not previously treated with ADT, were randomized receive to Abiraterone or placebo, combined with ADT. With a median follow up of 30.4, median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached *vs.* 34.7 months) [hazard ratio for death, 0.62; 95% confidence interval (CI), 0.51 to 0.76; P<0.001]. Other endpoints (median length of radiographic progression-free survival, time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and PSA progression, time to next symptomatic skeletal event) were all significantly better for the Abiraterone group. In STAMPEDE (29), patients were also randomized to ADT with or without Abiraterone; however, 28% of accrued patients had node-negative, non-metastatic disease. This group of patients were treated with local RT. Overall survival was superior in the combination group, with a 3-year survival of 83% as compared with 76% in the ADT-alone group. While subgroup analysis of the non-metastatic group failed to show a statistically significant overall survival benefit, it did demonstrate an improvement in failure-free survival in all subgroups.

It is clear from the above, that combination of radiation and Abiraterone needs further evaluation in the locally advance disease. The PEACE 1 trial (ClinicalTrials.gov Identifier NCT01957436), which will randomize patients to 4 arms and evaluate the role of combined ADT, Docetaxel, Abiraterone and RT in metastatic patients, will also help understand the role of the combination on Abiraterone and RT.

New medications and RT

Enzalutamide

Enzalutamide is an oral AR antagonist with a binding affinity five to eight times that of bicalutamide. Enzalutamide's binding to the C-terminal portion of the AR inhibits nuclear translocation, DNA binding, and coactivator peptide recruitment (30). This potent antagonism of AR led to a phase III trial demonstrating that enzalutamide conferred an OS benefit on post-docetaxel treated patients (31). Another approach, of combining Abiraterone and Enzalutamide was reported in a recent phase I/II, showing a favorable toxicity profile for bone metastatic CRPC patients treated with this combination (32). This strategy is being actively pursued in the Alliance for Clinical Trials in Oncology (Alliance) Trial A031201 in the metastatic CRPC setting (ClinicalTrials.gov Identifier NCT01949337).

Combining Enzalutamide with RT in the locally advanced prostate is also being actively investigated. A phase II trial at Duke University evaluating the combination of 6 months of abiraterone and Lupron with definitive, conventionally dose radiation (75–80 Gy) to the prostate and seminal vesicles alone (NCT01717053) was recently reported out at GU ASCO. In addition, both the Dana-Farber Cancer Center (NCT02028988) and the University of Texas-Southwestern Medical Center (NCT02064582) are conducting phase II trials of enzalutamide (one in combination with leuprolide) with conventionally dosed radiation therapy in intermediate and high-risk prostate cancer patients. The ENZARAD trial—an open label, randomized, stratified, 2-arm multicenter phase 3 clinical trial—is studying Enzalutamide in ADT with radiation therapy for high risk, clinically localized, prostate cancer (33).

Apalutamide

The most recently designed AR antagonist, Apalutamide (ARN-509), demonstrated *in vitro* potency superior to even enzalutamide, a potential property that can only increase its therapeutic index (34). Indeed, in a recently reported, first-in-human phase I trial of Apalutamide in metastatic CRPC patients, Apalutamide demonstrated maximal AR inhibition at doses well below the maximum tolerated dose (MTD); 60% of patients had a ≥50% decline in PSA as compared with baseline, and of those, six (20%) had a ≥90% decline. No patients on that trial experienced seizures, a potentially limiting toxicity of Enzalutamide (35). In an additional, phase II trial, looking at the sub-group of patients with non-metastatic CRPC (n=47), at 12 weeks, PSA response was 91% and the median time to progression had not yet been reached (36).

ATLAS: a randomized, double-blind, placebo-controlled, phase 3 trial of Apalutamide in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy is currently recruiting (ClinicalTrials.gov Identifier NCT02531516) (37); in this trial, patients will be randomized

to receive either Apalutamide (240 mg/day) for overall 30 months, or bicalutamide, for 4 months from randomization (placebo controlled). All participants will be treated with GnRH agonist for 30 months from randomization, with radiation therapy to the prostate starting at 8 weeks post randomization. And AASUR, a phase 2 trial of Apalutamide, Abiraterone, and Lupron for 6 months combined with five-fraction, stereotactic body RT for patients with very high risk, node negative prostate cancer is also recruiting at multiple institutions, including our own (NCT02772588).

Conclusions

RT and ADT have been proven to be effective combination in the treatment of prostate cancer. Newer medications, that have either a higher affinity to the AR or act on reducing testosterone on multiple levels, show promising results in small phase I/II trials and are now being evaluated for localized disease when combined with radiotherapy.

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Footnote

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