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Treatment with Galeterone in An Elderly Man with Castration-Resistant Prostate Cancer: A Case Report

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Introduction

The fastest growing population in the United States is composed of individuals over the age of 65 years. Prostate cancer (PC) disproportionately affects the elderly, with the highest incidence rates seen in those 70 to 80 years of age.¹ Owing in part to the aging population and long natural history of the disease, approximately 54% of men who die of PC are older than 80 years of age.¹

Despite the increasing age of the population and increasing cancer incidence, elderly patients are unrepresented in clinical trials. Although 61% of new cancer cases occur in the elderly, this population comprises only 25% of cancer clinical trials participants.^{2, 3} Elderly patients more frequently experienced delays in treatment and dose reductions related to adverse events compared to younger patients, possibly reducing the efficacy of therapy.⁴ Additionally, this population is particularly susceptible to toxicity from antineoplastic therapies secondary to age-related changes in pharmacodynamics and pharmacokinetics, polypharmacy, underlying comorbidities, and reduced functional status.⁵

Men with high-risk localized PC, have significant disease-related morbidity. Data on the natural history of untreated PC indicates that men with high-risk disease over the age of 70 have a 10-year PC-specific mortality of 70%.⁶ Furthermore, men with castration-resistant prostate cancer (CRPC) have a poor prognosis with fewer than 20% of patients surviving beyond three years.⁷ Consequently, the optimal management of PC in elderly men, particularly octogenarians and older individuals, poses a unique clinical challenge. It requires the careful assessment of multiple factors, in addition to chronological age. Furthermore, there exists a need for more efficacious therapies with less toxicity for CRPC.

Our understanding of androgen receptor (AR) signaling in the pathogenesis of advanced PC has heralded the approval of new therapeutic agents. Abiraterone acetate is an irreversible inhibitor of CYP17, a key enzyme in cortisol and androgen biosynthesis.⁸ Given abiraterone's selectivity for 17 α -hydroxylase and risk of mineralocorticoid excess, it is administered with prednisone.⁸ Enzalutamide is a competitive antagonist of the AR, with downstream effects on AR nuclear translocation and association with DNA.⁹ Despite improvements in survival with these agents, 20–40% of patients have no response to therapy and the majority of patients with an initial response develop secondary resistance.^{8, 10, 11} Furthermore, cross-resistance is commonly observed when these agents are used in sequence.^{12, 13} Thus, new therapies are needed to overcome resistance and provide durable responses.

Galeterone (TOK-001) is a novel, selective, rationally-designed, semi-synthetic steroid analogue currently under investigation for the treatment of PC. Galeterone inhibits PC growth via: 1) irreversible and selective CYP17,20-lyase inhibition, 2) competitive antagonism of the AR with associated downstream effects on AR-mediated transcription, and 3) AR protein degradation, thus inhibiting androgen signaling within PC cells.¹⁴ Galeterone does not require concomitant steroids and has demonstrated a favorable safety profile in phase I/II trials.^{15, 16} To encourage the inclusion of elderly patients in trials, we describe a nonagenarian with non-metastatic CRPC treated with galeterone in a phase I trial.

Case Report

Our patient is a 90 year old man who presented in 3/2007 with symptoms of urinary frequency, poor urinary flow, and nocturia. His prostate specific antigen (PSA) was elevated at 30.9 ng/mL (Figure 1). Rectal examination revealed bilateral prostate nodules. Prostate biopsy demonstrated Gleason 5+4=9/10 prostatic adenocarcinoma with evidence of extraprostatic extension in the right apex and 9/12 cores positive for tumor. Bone scan was negative for metastases. He had a history of hypertension, psoriasis, glaucoma, and osteoarthritis. His performance status was ECOG 0.

Given his age and the high-risk of micrometastatic disease, he did not receive definitive local therapy and was initiated on treatment with leuprolide alone in 4/2007. On leuprolide his PSA nadir was suboptimal at 3.4 ng/mL.¹⁷ In 7/2008, bicalutamide was added given PSA increase. He demonstrated an initial PSA response; however, in 11/2009, bicalutamide was discontinued. He did not have an anti-androgen withdrawal response and PSA continued to rise. Imaging did not show metastases.

In 4/2010, at age 87, PSA of 9.84 ng/mL (3.5-month doubling time) and non-metastatic CRPC, he was enrolled on ARMOR1 (Androgen Receptor Modulation Optimized for Response, NCT00959959), a phase I, open-label, dose-escalation trial of galeterone for the treatment of chemotherapy-naïve CRPC (PSA measurements collected locally are documented). Galeterone capsules (micronized powder, 325 mg) were administered orally in 8 dose cohorts ranging from 650–2600 mg/day. Our patient received galeterone 1,300 mg orally daily. His course was complicated by the development of minimal fatigue and weight loss. The weight loss developed in the context of depression after the death of his wife and

was felt to be unrelated to therapy. Additionally, he developed a maculopapular rash on his trunk and back in the setting of phototherapy for psoriasis. This prompted galeterone interruption for two weeks in 4/2011. In 11/2011, he developed a recurrent rash with associated pruritis and conjunctivitis. Skin biopsy was consistent with a hypersensitivity reaction. Given such, galeterone was permanently discontinued in 11/2011 at a time when his PSA was slowly rising and no metastases were present. Ten months after discontinuation of galeterone an identical rash recurred, and in retrospect the rash was unlikely a consequence of galeterone.

Following discontinuation of galeterone, his PSA continued to rise, and in 9/2012 was 134.8 ng/mL. Imaging did not show metastases. He was initiated on abiraterone 1000 mg daily. After four weeks, his PSA decreased to 89.3 ng/mL. Treatment with abiraterone (no steroids were initially given) was complicated by fatigue requiring hospitalization and dose reduction to abiraterone 500 mg daily with the addition of prednisone. His PSA continued to decline to 65.2 ng/mL after four months of abiraterone, however given progressive failure to thrive requiring re-hospitalization, therapy was discontinued.

Discussion

Though historically, castrate-resistant tumors were thought to have little reliance on androgen signaling, it is now recognized that the AR axis continues to play a critical role in PC progression.^{18, 19} Though abiraterone and enzalutamide represent advances in PC therapy, responses to these agents are not durable and progressive disease ultimately develops.^{8, 10, 11, 20} Emerging evidence indicates that AR splice variants may be key drivers of resistance in CRPC.^{21, 22} A possible approach to overcome this mechanism of resistance is to target the non-ligand binding domain of the AR or induce AR degradation. Galeterone is a compound which *in vivo* has demonstrated AR antagonism and CYP17 inhibition, and also appears to cause AR degradation of full-length and variant AR, setting it apart from other AR targeting agents.¹⁴

The ARMOR1 trial evaluated the safety and efficacy of galeterone in metastatic and non-metastatic chemotherapy-naïve CRPC. This trial enrolled 49 patients, 16 of whom were ≥ 80 years of age. Patients ≥ 80 years of age experienced 174 treatment emergent adverse events (TEAEs), 90% of which were grade 1 or 2, similar to the overall cohort grade 1–2 TEAE rate of 90%. The ARMOR2 trial (NCT01709734) is a two-part phase II study designed to confirm the dose of reformulated galeterone and assess safety and efficacy of the confirmed optimal dose (2,550 mg) in four CRPC cohorts (treatment-naïve non-metastatic, treatment-naïve metastatic, metastatic post abiraterone, metastatic post enzalutamide).¹⁵ The median age in ARMOR2 was 71 years (range 48–94). There were 20 patients aged 80–89 years and two patients ≥ 90 years of age. Of the 22 patients ≥ 80 years of age, 15 were in the treatment-naïve arm, 71% of whom experienced a ≥ 50% PSA decline from baseline. Seven patients received treatment post-abiraterone or enzalutamide, of whom two had some minor decline in PSA. With regard to overall TEAEs, patients ≥ 80 years of age, experienced 196 TEAEs of which 84% were grade 1 or 2 compared to 90% for the overall cohort. Overall, PSA reductions were seen in 100% (n=21/21) of treatment-naïve non-metastatic CRPC and 90% (n=35/39) of treatment-naïve metastatic CRPC. Thirty-five percent, (n=13/37) of

metastatic CRPC refractory to abiraterone, and 56% (n=5/9) metastatic CRPC refractory to enzalutamide experienced PSA reductions. The most common TEAEs (>10%) were nausea (36%), fatigue (35%), pruritis (30%), anorexia (21%), hypokalemia (15%), and vomiting (14%).

As illustrated by our case report, galeterone therapy was feasible and associated with minimal toxicity in our 90-year old patient with non-metastatic CRPC. Treatment resulted in a durable clinical response of nearly 20 months without evidence of radiographic progression at therapy discontinuation. Though data are promising, additional long term safety and efficacy data will need to be investigated in phase III testing. Furthermore, our patient experienced a positive response to abiraterone following galeterone therapy suggesting ongoing AR related cancer growth and lack of absolute cross-resistance. As numerous therapeutic agents enter the treatment landscape, the optimal sequencing or combination of agents remains an important question. The activity of galeterone will be further explored in a prospective, biomarker-based trial in patients with CRPC harboring AR variants.

Conclusion

Elderly men warrant special consideration in the context of therapy for advanced PC and should be given opportunities to participate in clinical trials if eligibility criteria are met. Given the palliative nature of therapies for CRPC, opportunities exist for improvement in efficacy, toxicity, and quality of life. The new generation AR targeting agents hold promise as well-tolerated, effective treatment for the growing population of elderly men with CRPC.

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Clinical Practice Points

- Elderly men with castration-resistant prostate cancer warrant special consideration in the context of cancer therapy.
- Galeterone inhibits prostate cancer growth via CYP17 inhibition, competitive inhibition of the androgen receptor, and degradation of the androgen receptor.
- Galeterone is currently under investigation for the treatment of castration-resistant prostate cancer and a specific sub-population with splice variant AR.

Figure 1.
PSA response throughout course of treatment.