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Sequencing and Combining CRPC Therapies - What Does the Future Hold? – Charles Ryan

The European Association of Urology defines castration-resistant prostate cancer (CRPC) as serum testosterone < 50 ng/dL or < 1.7 nmol/L plus either biochemical progression (three consecutive rises in prostate-specific antigen [PSA] one week apart, resulting in two 50% increases over the nadir, and PSA > 2 ng/mL) or radiologic progression (at least two new bone scan lesions or a soft tissue lesion using Response Evaluation Criteria in Solid Tumors [RECIST]).[1] Symptomatic progression alone is not enough to diagnose CRPC; instead, it should trigger further investigation.

Since 2010, many new agents have joined our armamentarium for treating metastatic CRPC, raising the question of how best to sequence them. For men with newly diagnosed, presumably hormone-sensitive mPC, we usually start treatment with either abiraterone acetate or docetaxel. Therefore, although we have five or six approved treatments for mCRPC, not every patient should receive all of them. More lines of therapy may lead to better outcomes, but only if they are the right lines of therapy. Recommending a second line of therapy that will be ineffective based on resistance to first-line treatment makes no sense and will not help our patients. Instead, we need to consider predictors of response and resistance at each stage of treatment.

CONSIDERATIONS FOR EARLY THERAPY

When considering androgen receptor (AR)-directed strategies for hormone-sensitive prostate cancer (HSPC), we might ask what “early treatment” means. Most patients with high-volume HSPC are offered docetaxel, making them “post-chemotherapy” when they receive AR-targeted treatments. But is low-volume disease is less aggressive than high-volume disease, and if so, is it more sensitive to AR-targeted therapy? In the randomized, phase III CHAARTED trial, upfront docetaxel combined with androgen-deprivation therapy (ADT) conferred a statistically significant survival advantage compared with ADT alone in patients with high-volume PC (median overall survival [OS], 49.2 months vs. 32.2 months, respectively) (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.45 to 0.81; P < .001).[2]

However, all docetaxel recipients in CHAARTED eventually went on to develop CRPC requiring second-line therapy, and we know very little about the efficacy of non-chemotherapy options such as abiraterone and enzalutamide in the post-docetaxel setting. This is important because CRPC is a broad-spectrum disease in which morbidity and mortality correlate with multiple measurable factors such as hemoglobin, albumin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and Eastern Cooperative Oncology Group (ECOG) performance status.[3] Asymptomatic patients with CRPC who have low-volume disease and who lack these predictors of morbidity can live for years, while patients with high-risk, high-volume, highly symptomatic CRPC may die within months of diagnosis.[3,4,5]

Castration-resistant prostate cancer spans a broad prognostic spectrum even when it is chemoptherapy-naïve.[6,7] In a recent analysis of the abiraterone arm of the randomized, double-blind, phase III COU-302 Study of men with chemotherapy-naïve mCRPC,[8] patients who at baseline had no pain, normal ALP and LDH levels, and fewer than 10 bone metastases survived a median of 42.6 months[7] – a fairly good prognosis compared to a decade ago, when we had only docetaxel to treat chemotherapy-naïve CRPC. However, patients who had more risk factors for progression had significantly shorter median OS time —in some cases, even shorter than the 17-month OS we typically obtain with docetaxel monotherapy.[7,9,10]

When selecting therapy for early CRPC, it's also important to keep in mind that the National Comprehensive Cancer Network (NCCN) considers the onset of visceral disease to be a major fork in the road. [NCCN] Patients with liver metastases have especially poor outcomes. It remains unclear whether this is because of biological differences in the tumor or because of morbidity to the liver itself. In a recent study of more than 8,000 men with mCRPC who were enrolled in phase III trials, patients with lymph-node- only disease had the best OS (median, 31.6 months; 95% CI, 27.9 to 36.6 months), patients with lung and bone metastases had shorter and similar median OS (19.4 months [95% CI, 17.8 to 20.7 months] vs. 21.3 months [20.8 to 21.9], respectively), and patients with liver metastases the worst OS (median, 13.5 months; 95% CI, 12.7 to 14.4 months).[12]

Studies of bone marrow, transurethral resection of the prostate (TURP), and autopsy specimens indicate that CRPC is hypersensitive rather than resistant to ADT.[13,14,15,16] Treatment-mediated selection pressure during ADT causes the androgen receptor to amplify, and to avoid adding fuel to the fire, we continue ADT in the CRPC setting. Treatment-mediated selection pressure also continues throughout the life of a tumor, further intensifying the need to correctly sequence therapies.

Both abiraterone and enzalutamide are highly active agents that have tremendous effects on progression-free survival (PFS), with a median of 17 months in recent trials comparing mono- therapy with prednisone or placebo.[8,17] However, it's crucial to remember these drugs only benefit patients who respond. A patient with CRPC who responds well to either therapy may survive without disease progression for 3 to 4 years, while someone who does not respond well is not benefiting and needs a change treatment. When I start a patient with early CRPC on abiraterone or enzalutamide, I

see him again in 12 weeks. If his PSA level has not decreased, I stop the drug. This patient will not benefit from more time on abiraterone or enzalutamide; he probably has a subset of CRPC that requires greater biological attention. In my experience, about 15% of patients who receive abiraterone or enzalutamide do not respond to treatment — their rising PSA continues unchecked. I stop treating these patients. About another 10% of patients have a modest (less than 50%) decline in PSA. I keep this latter group on treatment.

SEQUENCING: WHAT WE KNOW

Let's consider more data on sequencing therapies in CRPC. In a recent non-randomized retrospective study, researchers compared PFS, OS, and PSA responses from consecutive patients with chemotherapy-naïve mCRPC who received either abiraterone followed by enzalutamide (n=65) or enzalutamide followed by abiraterone (n=16).[18] The two groups were similar at baseline.

Initially, investigators observed a slight improvement in the patients who started with abiraterone and transitioned to enzalutamide. Median PFS was 19.5 months (15.5 to 22.3 months), vs. 13.0 months (95% CI, 10.3 to 21.2 months) among patients who received enzalutamide followed by abiraterone.[18] An expanded retrospective study made it clear that some patients responded to abiraterone but not enzalutamide, while others responded to enzalutamide but not abiraterone.[19] Nonetheless, the general trend persisted: Patients who started with abiraterone and then transitioned to enzalutamide had somewhat better PFS (median, 455 days [95% CI, 385 to 495 days]) than patients who started with enzalutamide and transitioned to abiraterone (median, 296 days; 95% CI, 235 to 358 days).[19] Overall survival did not significantly differ between groups.[19]

More compelling initial data come from an ongoing, randomized, phase II study comparing abiraterone vs. enzalutamide in patients with treatment-naïve mCRCP.[20] Patients crossed over to the other treatment arm when they first progressed. So far, median time to progression has been 7.4 months in each arm, suggesting that abiraterone and enzalutamide each offer one shot on goal.[20]

Therefore, I choose between abiraterone and enzalutamide based on the adverse effects I most want to avoid. Abiraterone is commonly associated with edema, so I avoid recommending it in patients with congestive heart failure.[8] Enzalutamide is more likely than abiraterone to cause central nervous system toxicity, which can lead to fatigue and may be poorly tolerated in older patients.[22] Thus, I tend to consider enzalutamide if patients have baseline edema or CHF, renal impairment, or diabetes, and abiraterone if patients are older, already are receiving multiple medications, or have substantial fatigue, a history of neurologic issues or falls, or mild pain that might benefit from low-dose steroids. Note that the norm with abiraterone is now once-daily treatment with 5 mg prednisone,[23] which is not a supraphysiologic dose and therefore should not affect treatment choice.

WHEN TO START THERAPY

The next question is when to start therapy. Among early-stage CRPC patients in the COU-302 Study whose PSA was less than 80 ng/mL, Brief Pain Inventory score was 0-1, and Gleason score was less than 8, those who received abiraterone typically survived almost 1 year longer than those who received placebo (median OS, 53.6 months vs. 41.8 months, respectively) (HR, 0.61; 95% CI, 0.43 to 0.87; P = .006).[24] Thus, early-stage CRPC patients not only had a better prognosis than did patients with later-stage disease, they did better on abiraterone.

Among COU-302 patients with asymptomatic or mildly symptomatic mCRPC, baseline PSA < 15.6 ng/mL also was associated with a significantly lower hazard of progression (HR, 0.58; 95% CI, 0.46 to 0.74), death (HR, 0.53; 0.39 to 0.72), and time to PSA progression (HR, 0.63; 0.50 to 0.78) compared with baseline PSA >106.2 ng/mL (P < .001).[26] Abiraterone also led to a faster rate and a greater degree of PSA decline than placebo.[26]

On the flip side, in an exploratory analysis of the randomized phase III COU-301 Study, abiraterone improved median OS to 13.9 months among patients with post-docetaxel mCRPC who had lung metastases, a 6-month improvement compared with prednisone alone.[25] Abiraterone also improved median OS in patients with liver metastases, although prognosis remained poor overall (median OS, 7.3 months vs. 4.0 months with prednisone alone).[25]

This data addresses questions that come up all the time in the clinic: We see patients with mCRPC who look and feel fine, and we're considering copayments and morbidities and wondering whether to start them on abiraterone now or wait until they develop pain or progression. To date, all data suggests that waiting is not an advantageous choice for these patients.[24,26] I do sometimes wait 1-2 months to start abiraterone in order to see how quickly PSA is rising, but I don't wait until patients develop pain or other symptoms.

STOPPING, SWITCHING, AND STACKING

Another important question is when to stop treatment. Among individual patients who receive AR-directed therapy, percent change in PSA kinetics falls into three categories: non-responders, whose PSA continues to rise sharply after starting treatment, drifters, whose PSA declines and then drifts upward, and sustained or consecutive responders, who experience a durable decline in baseline PSA.[28]

A sustained response clearly merits staying on treatment. For non-responders, I stop treatment at 12 weeks and consider other therapeutic options. For drifters, however, treatment decisions become a bit more complex. Consider the reported case of a patient with CRPC who started abiraterone and had an excellent response.[27] After 9 months, his PSA began drifting upward and continued on that trajectory for 43 months

before he developed symptomatic progression — in this case, bone metastases requiring palliative radiation.[27] Had this patient's physician stopped abiraterone when his PSA began drifting up, he might have cycled through many therapies with their various morbidities. Many experts hypothesize that both abiraterone and enzalutamide continue to suppress growth of PC even after PSA begins drifting up after an initial response.[27] I agree, and I do not automatically stop abiraterone or enzalutamide in these patients.

It's also helpful to consider sequencing data from the PLATO trial (NCT01995513). In this phase IV, 16-week, double-blind, placebo-controlled study, 509 patients with chemotherapy-naïve mCRPC initiated enzalutamide and then were randomly assigned to add or switch to abiraterone after PSA progression.[29] Staying on enzalutamide and adding abiraterone did not improve median PFS (5.7 months; 95% CI, 4.6 to 8.1 months) compared to stopping enzalutamide and switching to abiraterone (5.6 months; 95% CI, 4.5 to 7.3 months) (HR, 0.83; 95% CI, 0.61 to 1.12; P = 0.2). Median time to PSA progression was 2.8 months in both arms, and all patients progressed rapidly. Thus, "stacking" these two drugs may have little benefit.

When we consider sequencing, is there a "typical" chemotherapy-naïve CRPC patient? In the COU-302 Study, patients tended to had a PSA of about 40 ng/mL, bone metastases, and no pain, but the cohort covered a broad spectrum of disease.[30] We've gotten to the point where we don't really view chemotherapy as central to the life of a patient with CRPC. Abiraterone and enzalutamide were first developed post-chemotherapy because of regulatory factors, not biology or clinical insight. Both drugs were subsequently developed for the pre-chemotherapy setting, and therefore, it's becoming moot to talk about "chemotherapy-naïve CRPC."

A patient who is undergoing treatment for PC enters a worse prognostic category when his performance status declines or he develops new symptoms, a skeletal event, or visceral metastases. All these are signs that resistance has developed and that it's time to change the treatment plan.

TUMOR BIOLOGY

Another key point is that as PC progresses, its biology evolves. We've known about non-adenocarcinoma PC for a long time, but now we're realizing that it's actually quite common, and we're getting some data on its prognostic implications. In a histologic study of 124 evaluable biopsies from patients with PC that was resistant to abiraterone or enzalutamide, only 35% of patients still had pure adenocarcinomas, while 13% had small cell neuroendocrine carcinomas, 26% had intermediate atypical carcinomas, and 26% had mixed histologies.[31] Disease evolves in response to treatment, and patients with non-adenocarcinoma PC have a much worse prognosis (median OS, 8.9 months) than patients with adenocarcinoma PC (median OS, not reached; P = .004).[31]

Genomics will further disrupt the sequencing question. Genomic studies clearly indicate that it's not just about tumor histology or treatment history, that a range of mutations drives disease biology and treatment selection. The frequency of genetic

alterations increases as PC progresses.[32,33] Additionally, in a recent prospective study, whole-exome and transcriptome sequencing of bone or soft tissue tumor biopsies from 150 patients with mCRPC showed that 22.7% of tumors harbored aberrations in the DNA repair pathway.[32]

As these results suggest, the DNA repair pathway is the leading candidate for targeted therapy in PC. There's reason for that: The androgen receptor is involved in DNA repair, and the presence of a defect in the DNA repair pathway may explain not only why a patient has prognostically worse PC, but also why certain therapies may be effective.[34] For example, in a cross-over study comparing abiraterone vs. enzalutamide in mCRPC, patients with truncating mutations or rearrangements in BRCA2 or ATM had a statistically significant five-fold higher hazard of progression compared with patients who lacked defects in these DNA repair genes ($P < .0001$).[20]

However, DNA repair alterations also may predict a better response to abiraterone. In a recent randomized study of 72 mCRPC patients who received abiraterone with or without veliparib, the 25% who had DNA repair-deficient tumors had significantly better and more durable responses compared with patients who had DNA wild-type tumors.[35] Median PFS was 13.8 months (95% CI, 8.1 months to not reached) among patients with DNA repair-deficient tumors and 7.8 months (5.4 to 13.3 months) among patients with wild-type tumors ($P = .01$).

Measurable disease and PSA response rates also were significantly better in patients with DNA repair-deficient tumors than in patients with wild-type tumors, with P-values of .009 and .02, respectively. Although this was a small trial, meaningful differences existed in both treatments arms.[35] We can conclude that knowing the DNA repair mutation status of a patient with CRPC may be helpful before starting abiraterone.

Finally, let's consider luminal and basal subtyping, a useful approach to molecular subtyping that has been used for years in breast cancer. The PAM50 gene classification set is a group of genes that cluster breast cancer specimens into luminal A (LumA), luminal B (LumB), and basal subtypes, and PC specimens cluster very similarly.[36] In a large study of pooled cohorts of patients who received hormone therapy and radiation for PC, hierarchical gene clustering and Kaplan-Meier curves showed that PAM50 gene clusters differed based on biochemical recurrence-free survival, distant metastasis-free survival, PC-specific survival, and OS.[36] I predict that in the future, we will be able treat patients with PC based on the molecular and genomic "buckets" their cancers fall into.

CONCLUSIONS

Seven years of experience with AR targeting in men with CRPC show that it provides an opportunity for clinical benefit with low morbidity. Patterns of treatment resistance differ and may be driven by tumor biology. In the future, biopsies of metastases or circulating tumor DNA will be standard ways to understand disease biology and make treatment decisions. For now, proactive, risk-adapted treatment of CRPC is personalized medicine.

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