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COMBINING ENZALUTAMIDE AND RADIOTHERAPY IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER: A REVIEW OF CURRENT EVIDENCE

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ABSTRACT

Background: prostate cancer is the second most frequent cancer worldwide, with a very high rate of progression despite treatment. The most aggressive form of the disease is known as castration-resistant prostate cancer, which carries a poor prognosis. Castration resistant prostate cancer (PC) patients are a niche of patients affected by progressive prostate cancer despite androgen deprivation therapy (ADT) and a serum testosterone value < 50 mg/dl. Androgen receptor targeted therapy (ARTT) as it has been shown for Enzalutamide and Abiraterone in phase III clinical trials, has high efficacy in patients with metastatic castration resistant prostate cancer (mCRPC), leading to improved overall survival. **Methods:** we reviewed available literature regarding the combination of enzalutamide antihormonal drug and ablative radiation therapy for the treatment of metastatic castration-resistant prostate cancer. This combination treatment is safe and effective, with few adverse events. This dual treatment may enhance the effects of second-line hormonal therapy, as radiotherapy renders cancer cells more prone to immune-mediated cytotoxicity. Moreover, radiotherapy exerts its effect both on directly irradiated cells and on other distant tissues, with an abscopal effect, already demonstrated in other solid tumors. **Results:** in the available literature, the combination of radiation therapy and enzalutamide has prolonged both overall survival and progression-free survival, with a positive impact also on locoregional recurrence and distant metastases.

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INTRODUCTION

Prostate cancer is the most common solid cancer and the second most common cause of cancer-related death in men Systemic therapy based on androgen deprivation is the standard primary treatment strategy in patients with advanced prostate cancer (1). Despite adequate therapy, the disease eventually progresses to mCRPC (2). While docetaxel has long been the only agent with level 1 evidence for improved overall survival (OS) mCRPC), the advent of novel drugs/treatments, such as enzalutamide, abiraterone acetate, cabazitaxel, sipuleucel-T, and radium-223 has revolutionized therapeutic strategies (3,4). Many patients who initially respond to enzalutamide will experience disease progression on therapy, indicating acquired resistance.

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The androgen receptor (AR) controls transcription of key DNA repair genes important in mediating radioresistance in PC. Indeed, AR inhibition increases DNA damage in tumors, improving radiosensitivity and decreasing survival of PC cells This suggests that ADT and AR inhibition may act synergistically with radiation (5,6). Enzalutamide is an AR antagonist that not only blocks androgen binding to its receptor, but also inhibits nuclear translocation and DNA binding, and there are preclinical data suggesting that enzalutamide may be a better radiosensitizer than ADT. Some patients treated with ARTT may present an oligoprogression that, probably, does not represent a systemic drug resistance. The irradiation of lesions progressing on ARTT would likely be effective as resistant lesions are ablated, while continuing ARTT keeps responsive or stable lesions suppressed (7,8). In castrate-sensitive PC, the ARCHES and ENZAMET trials have also demonstrated improved survival with enzalutamide added to ADT (9). Thus, earlier treatment with AR-targeted agents may be beneficial, particularly as a radiosensitizing agent.

We conducted a systematic review of all clinical trials assessing treatment combinate with next-generation androgen receptor inhibitors for mCRPC as enzalutamide and the radiotherapy.

Effect of enzalutamide combined to radiotherapy: Published data useful for the review were identified by a PubMed search, performed with combinations of the following search terms: "metastatic prostatic cancer" and "enzalutamide", and "oligoprogressive disease" and stereotactic radiotherapy". Only articles written in English were considered. Abstracts presented between 2016 and 2021 at the main international meetings also were searched. Treating metastatic prostate cancer patients is an ongoing challenge. Treatment of men with PC after radical prostatectomy has evolved considerably over the past 10 years, particularly with the incorporation of hormonal therapy and early salvage radiotherapy (RT) to the prostate bed (10). Retrospective series suggest that salvage RT reduces distant metastases and PC mortality, especially when given at a PSA level of at least 0.5 ng/ml. Multi-institutional studies suggest improved long-term survival and freedom from metastases with earlier utilization of salvage RT (11).

Recent data support the rationale for observation and early salvage RT in most men even with positive margins or high-risk features (12). The current National Comprehensive Cancer Network (NCCN) guidelines to consider 6–24 mo of hormonal therapy with salvage RT in this setting. Very important is that factors to consider in the description of oligometastatic disease include the distinction of synchronous versus metachronous metastases, the number and location of lesions, the imaging method and whether the patient is castration-naive or resistant to castration. Numerous studies have proposed different definitions tbut the cut-off of lesions cannot yet be defined. The term "oligoprogression" indicates a clinical condition in which the systemic disease is still controlled by systemic therapy except for a defined number of relapse sites. (13). In oligometastatic patient therapy is not enough but he could benefit from local treatment. The addition of RT to ongoing ARTT has a strong biological rationale. Radiotherapy induces cell death by disrupting various parameters of cell biology necessary for survival, stimulates the dying cells to release a range of molecules (often termed "danger signals") that in turn could render cancer cells more susceptible to an immune-mediated cytotoxic environment and could prevent to metastasis seeding (14, 15). The concept of continuing therapy beyond progression is that systemic treatment is effective, but one or only a few sites progressed or some new lesions developed. In this case, local therapy such as radiation therapy could possibly control new sites or progression sites maintaining systemic treatment. Then, this strategy could allow to delay the change of therapeutic strategy. The role and the efficacy of radiotherapy as well of 3DCRT as of SBRT in oligometastatic or oligoprogressive mPCa patients has already been demonstrated in the castration sensitive and castration resistant disease. It is irrefutable that SBRT, whenever possible, is the standard for the treatment of oligo-relapsing or oligoprogressive lesions, but also 3DCRT could represent a valid alternative in cases not elegibility for SBRT (16). A recent declaration of consent from the Italian Association of Radiotherapy and Clinical Oncology (AIRO) confirms hypothesis on the role of local treatment, such as radiotherapy, to progressive disease sites such as alternative to systemic treatment change, in asymptomatic or minimally symptomatic oligoprogressive patients (17).

The logic of delaying the initiation of a new line of treatment is to lengthen OS in patients with slowly progressing disease. Recently in a single-arm phase II trial, the Authors investigated safety and efficacy of enzalutamide combined to RT and ADT recovery (18). The study was run in men with Gleason 7-10 PC and PSA relapse within 4 years of RP between 0.2 and 4.0 ng / dl, no previous hormone therapy and no radiographic evidence of metastases. Thirty-seven patients completed treatment of ADT, 6 months of enzalutamide 160 mg / day and 66 Gy RT al prostate bed. The primary endpoint was 2-year progression-free survival (PFS) improvement compared to historical controls. Secondary goals included 3-year PFS, patient-reported safety, and quality of life (QOL).

The primary endpoint of PFS at 2 years was 65% versus 51% (in a study of men treated with rescue RT and adjuvant docetaxel) and 3-year PFS 53%. Eleven (29%) men experienced G3 toxicity and no G4-5 or unexpected toxicity was found. Quality of life data suggests modest deterioration of the intestinal, bladder and hormones symptoms at 3 months, with recovery within 24 months in the majority of patients. Therefore, adding oral enzalutamide for 6 months per day to the standard rescue radiotherapy and hormone therapy showed to be safe and can improve cancer remission. Some patients treated with ARTT may have an oligoprogression that is probably not systemic drug resistance. A recent analysis showed that the treatment of oligoprogressive sites with radiotherapy can extend the life of the ARTT. The Authors analyzed survival, progression-free survival and prognostic factors in order to characterize the patients who can benefit from this approach. From September 2015 they started treating mCRPC patients pharmacologically subjected to the androgen receptor targeted therapy in oligoprogression (1-3 new metastasis) with ablative or palliative radiotherapy. Until February 2018, 37 injuries were treated in 29 consecutive cases. The ARTT consisted of Abiraterone in 21 cases (72.4%) and enzalutamide in 8 cases (27.6%).

The median age of patients was 72 years (range 53-91 years) and the median time between the onset of androgens deprivation therapy and the initiation of ARTT was 48.1 months (12.1–123.3 months). Most did not receive chemotherapy due to bad clinical conditions. Seventeen (65.5%) patients received ARTT as first-line treatment, 10 (34.5%) as second-line (after docetaxel) and only 2 (6.9%) as third-line. Six lesions (16.2%) were treated with stereotactic body radiotherapy (SBRT) and 31 (83.8%) with conformal palliative radiotherapy (3DCRT). Lesions with a volume under 15 cm3 and, in case of bone lesions without involvement of posterior wall of vertebral body, were treated with SBRT, whereas the others with 3D conformal radiotherapy. The treated lesions were the only apparent site of disease for all patients. All patients presented rising PSA level during treatment with ARTT and were submitted to F-Choline PET-TC scan that revealed an oligo-progressive pathological uptake. Among patients treated with SBRT, 22 (75.9%) received single target treatment, 6 (20.7%) presented 2 lesions and 1 (3.4%) 3 lesions. Thirty-one (83%) out of 37 treated lesions were located in the bone, which represented the majority of the metastatic sites, 2 (5.5%) in lung, 2 (5.5%) in prostatic bed and 2 (5.5%) lymph nodes (lumbar-aortic and internal iliac stations). (Table 1). All patients underwent a pre-treatment planning CT (2.5 mm slice thickness) in the supine position with feet rests. Planning CT images were fused with

Table 1. Characteristics of patients (N=29)

Age Median (range)	1years 72 (53–91)
Time between ADT and ARTT Median (range)	2months 48.1 (12.1–123.3)
RT techniques	3DRT 24 (82.7%) - SBRT 5 (17.3%)
ARTT Abiraterone Enzalutamide	3 421 (72.4%) 58 (27.6%)
Treatment line I: 17 II-III:12	6 7(58.6%) 8(41.4%)
PSA after 1 month from the start of ARTT Median (range), ng/ml 3.02 (0.02–100)	≤50% reduction 5 (17.2%) > 50% reduction 24 (82.8%)
RT timing respect the start of ARTT	< 6 months 15 (51.7%) > 6 months 14 (48.3%)
RT sites Lesions (%)	Bones 31 (83%) Lung 2 (5.5%) Lymphnodes 2 (5.5%) Prostatic Bed 2 (5.5%)

MR images and/or F-Choline TC-PET using automatic matching to help gross target volume (GTV) delineation. For patients treated with SBRT the GTV was expanded of 5 mm in all direction isometricly to obtain PTV. For patients treated with palliative radiotherapy the GTV encompassed the bone or lymph-nodal lesion. Clinical target volume (CTV) encompassed GTV plus 5 mm margin and, Planning Target Volume (PTV) was generated by adding a 5 mm isometric margin to CTV. Treatment was delivered by a linear accelerator using 6–15 MV photons. Thus, the PTV received 27 Gy in 3 fractions (9 Gy per fraction) in bone lesions treated with SBRT, 54 Gy in 3 fractions (18 Gy for fraction) for lung lesions and 20–30 Gy in 5–10 fractions in patients treated with palliative dosage. The mean value of isodose line covering PTV was 94% (range 90–98%). After radiation treatment patients continued ARTT with a first PSA assessment after 1 month and then every 3 months. Patients with PSA reduction continued follow up until PSA rising and/or appearance of new symptoms. Then, patients underwent a new FCholine TC-PET and in case of appearance of new lesions were shifted to other therapy. Toxicities were assessed at each follow up according to the Radiation Therapy Oncology Group (RTOG) scale for acute and late adverse effects. The median follow-up for surviving patients was 36.3 months (range 12.9-68.9 months). The overall median duration of ARTT treatment was 14.8 months (range 4.4-45.3 months) and median duration of ARTT after radiotherapy was 4.6 months (range 1-33.8 months). Patients with <50% and> 50% PSA reduction 4 weeks after initiation of ARTT had a median PFS of 26.0 months (range 5.5-30.1 months) and 14.2 months (range 4.3–45.3 months), respectively (p = 0.872). The median PFS for SBRT-treated patients was 20.4 months (range 6.3-30 months) and 11.6 months (range 4.3–45.3 months) for those treated with 3DCRT (p = 0.765). Patients undergoing radiotherapy <6 and> 6 months after initiation of ARTT had a median PFS of 7.9 months (range 4.3-26 months) and 27.7 months (range 10.4–45.3 months), respectively (p < 0.001) (Fig. 2). Before radiotherapy 28 out 29 patients (96.5%) presented pain (median Numerical Rating Scale value 7, range 2–9) versus 14 out 29 patients (48.3%) (median NRS value of 2, range 2–4) after radiation treatment. No toxicities were observed. ADT Androgen deprivation therapy, ARTT Androgen receptor targeted therapy. RT Radiotherapy, 3DRT Conformal radiotherapy, SBRT Stereotactic body Radiation therapy, PSA Prostatic specific antigene

DISCUSSION

The AR controls transcription of key DNA repair genes important in mediating radioresistance in PC. Indeed, AR inhibition increases DNA damage in tumors, improving radiosensitivity and decreasing survival of PC cells (19). This suggests that ADTand AR inhibition may act synergistically with radiation. Enzalutamide is an AR antagonist that not only blocks androgen binding to its receptor, but also inhibits nuclear translocation and DNA binding, and there are preclinical data suggesting that enzalutamide may be a better radiosensitizer than ADT. Enzalutamide was approved for treatment of mCRPC in 2013 and recently found to be effective in non-metastatic CRPC (20). In contrast to first generation anti-androgen agents - flutamide and bicalutamide - enzalutamide has a higher affinity to the androgen receptor a superior response in the castrate-resistant setting (21). Multiple phase 3 studies showed significant benefits with enzalutamide treatment in men with castrate-resistant PC (12–14).

In castrate-sensitive PC, the ARCHES and ENZAMET trials have also demonstrated improved survival with enzalutamide added to ADT (22). Thus, earlier treatment with AR-targeted agents may be beneficial, particularly as a radiosensitizing agent (23,24). Based on these data, AR inhibition added to standard salvage RT with ADT will further prolong or prevent progression, and improve the success of salvage radiation therapy We already know that rescue external beam RT with androgen deprivation therapy improves survival compared to RT in men with prostate cancer and increased prostate specific antigen levels after RP. Moreover, radiotherapy exerts its effect both on directly irradiated cells and on other distant tissues, with an abscopal effect, already demonstrated in other solid tumors (25, 26). The first phase II data and analysis represent a proof of concept for the role of enzalutamide combined to local radiotherapy for oligoprogressive mCRPC.

CONCLUSION

- Radiation therapy of oligoprogressive sites can prolong the duration of disease control under
- ARTT in mCRPC patients with a possible delay in starting a new line treatment. Patients who
- progressed within 6 months later the initiation of ARTT did not benefit from this approach.
- Further studies are needed to confirm or not the results of the early clinical observation and
- studies. In particular it's important to recognize other prognostic factors in order to better
- select oligoprogressive patients who could have a benefit from local treatment without
- interruption of the ARTT compared to those that need an immediate change of therapeutic
- systemic strategy. Phase randomized trials on this issue are welcome.

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Glossary of abbreviations

Androgen deprivation therapy (ADT)
Androgen receptor (AR)
Androgen receptor targeted therapy (ARTT)
Castration resistant prostate cancer (mCRPC)
Conformal palliative radiotherapy (3DCRT).
Italian Association of Radiotherapy and Clinical Oncology (AIRO)
National Comprehensive Cancer Network (NCCN)
Overall survival (OS)
Planning Target Volume (PTV)
Prostate cancer (PC)
Prostate-specific antigen (PSA)
Quality of life (QOL).
Radiation Therapy Oncology Group (RTOG)
Radical prostatectomy (RP)
Radiotherapy (RT)
Stereotactic body radiotherapy (SBRT)

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