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Short Communication

Optimisation of second line antihormonal treatment for castration resistant metastatic prostate cancer

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Abstract

Background: The prognosis of castration resistant metastatic prostate cancer has been improved by several recently introduced therapeutic options, among others the second line antihormonal agents. Still, several questions related to the optimal use of these new drugs have remained open. The following ones were addressed in this paper. (1) Is the use of abiraterone + hydrocortisone inferior to abiraterone + prednisone in terms of overall survival? (2) Is the treatment up to prostate specific antigen (PSA) progression inferior to the treatment up to radiological progression in terms of overall survival? (3) Does the level of initial PSA decrease have a predictive value for the duration of response? **Methods**: As part of our self-assessment the dataset of 62 patients with castration resistant metastatic prostate cancer who started second line antihormonal therapy at our outpatient clinic before 31st of December 2019 was analysed. **Results**: 35 patients received abiraterone with prednisone substitution, 12 patients received abireterone with hydrocortisone substitution and 15 patients received enzalutamide. 39 patients were treated until clinical or radiological progression and 23 patients were treated until biological progression. (1) Median overall survival of patients substituted with hydrocortisone was not inferior as compared to patients substituted with prednisone (31 months vs. 17 months). (2) Median overall survival of patients treated until PSA progression was not inferior as compared to patients treated until radiological progression (32 months vs. 17 months). (3) Median overall survival of patients whose first control PSA level was below the normal value was 50% higher than median survival of patients whose first control PSA level was over the normal value (25 months vs. 17 months). Median overall survival of patients treated with abiraterone or enzalutamide was similar (21 months vs. 24 months). **Conclusions**: The combination of abiraterone + hydrocortisone is not inferior to the combination of abiraterone + prednisone and the treatment up to PSA progression is not inferior to the treatment up to radiological progression in terms of overall survival for patients with castration resistant metastatic prostate cancer.

Keywords: Prostate cancer; Abiraterone; Enzalutamide; Hydrocortisone; Biological progression

1. Introduction

The prognosis of castration resistant metastatic prostate cancer has been improved by several recently introduced therapeutic options, among others the second line antihormonal agents [1–4]. Two drugs with different mode of action but equal efficacy are counted to this group: abiraterone and enzalutamide. Both agents have gained broader indications for the treatment of locally non-controllable prostate cancer [5–9]. In addition, other drugs like apalutamide and darolutamide are approved for the treatment of non-metastatic castration resistant prostate cancer [10,11].

Designation of these new agents is controversial. The term androgen receptor-targeted agents (ARTA) has been proposed. However, abiraterone targets the steroid synthesis at the level of the 17α-hydroxylase and not the androgen receptors in turn bicalutamide, flutamide and nilutamide target the androgen receptors yet the term ARTA is not supposed to cover them. In this paper we propose the use of the term "second line antihormonal therapy", considering that a luteinising hormone releasing hormone (LHRH) agonist or antagonist stands in the first line.

Optimal use of the new agents is under investigation. In this paper we addressed only the metastatic castration resistant disease and the drugs were used with a few exceptions after docetaxel treatment. We tried to answer some questions that are out of the focus of large controlled trials: (1) Is the use of abiraterone + hydrocortisone inferior to abiraterone + prednisone in terms of overall survival? (2) Is the treatment up to PSA progression inferior to the treatment up to radiological progression in terms of overall survival? (3) Does the level of initial PSA decrease have a predictive value for the duration of response?

2. Methods

As part of our self-assessment the dataset of 62 male patients with castration resistant metastatic prostate cancer was analysed. Median age was 71 years (range: 44–86 years). The patients were treated with second line antihormonal therapy at our outpatient clinic between 2014 and

2019. The inclusion was stopped on the 31st of December 2019. The follow up was closed on the 31st of October 2021 for statistical analysis. At the moment of the closure 16 patients were alive and 6 patients had been still on antihormonal treatment for at least 22 months.

All patients had ongoing androgen deprivation therapy and most of them were pre-treated with docetaxel. The tumour board only approved the indication of the second line antihormonal therapy. The choice between abiraterone or enzalutamide was at the discretion of the specialists. The patients were randomly addressed by the urologists to one of the oncologists, but there was no official randomisation. The treatment was managed by three oncologists. Doctor 1 treated 32 patients, doctor 2 treated 7 patients and doctor 3 treated 23 patients. All of them used to prescribe both, abiraterone and enzalutamide. 47 patients received abiraterone and 15 patients received enzalutamide (The reason why more patients were treated with abiraterone than with enzalutamide is, that the former drug was introduced earlier in the country).

Two doctors (doctor 1 and doctor 2) followed the official recommendations, giving 5 mg of prednisone twice daily in association to abiraterone and continuing the therapy until clinical or radiological progression. One doctor (doctor 3) considered that two small changes regarding the official recommendations, namely giving 10 mg of hydrocortisone once daily in association to abiraterone and continuing the therapy until PSA progression may be clinically or financially beneficial without being taken for protocol violation.

Concerning the 47 patients treated with abiraterone, the subgroup of doctor 1 and 2 (35 patients) received 1000 mg of abiraterone oid and 5 mg of prednisone bid, the subgroup of doctor 3 (12 patients) received 1000 mg of abiraterone oid and 10 mg of hydrocortisone oid in the morning. Concerning patients treated with enzalutamide (15 patients) the subgroup of doctor 1 and 2 as well as the subgroup of doctor 3 received 160 mg of enzalutamide oid.

Concerning treatment duration, patients in the group of doctor 1 and 2 (39 patients) were treated until radiological progression independently whether they received abiraterone or enzalutamide. Patients in the group of doctor 3 (23 patients) were treated until biological progression independently whether they received abiraterone or enzalutamide. Biological progression was defined according to a modified Prostate Cancer Working Group 2 (PCWG2) model: 25% of PSA increase at two consecutive determinations of an interval of one month, even if the absolute PSA increase did not reach 2 ng/mL.

Patients in the group of doctor 3 were alerted at the first PSA increase that the disease seems escaping control. They were informed about the standard treatment duration and the reasons of stopping the medication upon biological progression. All of them were offered to continue the medication until radiological progression in case they change referent physician. At the second instance when PSA was further increasing none of them wanted to change doctor and all of them accepted stopping the treatment. The follow up was continued and when PSA was ranging between 20–100 ng/mL either a second line chemotherapy or in the absence of this possibility in the first period the initiation of bisphosphonates was offered.

Four different analyses were done, three of them to find an answer to the three questions of the study and a control analysis. All comparisons were based on the same dataset, but choosing different subgroups as follows: (1) Patients substituted with hydrocortisone were compared to patients substituted with prednisone within the group of patients who received abiraterone. (2) Patients of doctor 1 + 2 were compared to patients of doctor 3. (3) Patients presenting a deeper PSA drop (below 4 ng/mL) were compared to patients presenting a moderate PSA drop (over 4 ng/mL) at the first laboratory control after 2 months of treatment. In this assessment patients of all doctors were included.

As a control analysis patients treated with abiraterone were compared to patients treated with enzalutamide by either doctor. The two medications are known to have similar efficacy in terms of overall survival. We wished to see whether our data are in line with the international standards. The plan of the analyses is summarised in Fig. 1.

Bimonthly PSA and basic laboratory controls were done for all patients during the treatment. Hydrocortisone dose was doubled in some cases when hyponatraemia or hyperkalaemia were detected at a scheduled blood test. There was no clinical sign of adrenal insufficiency in any group. Thoraco-abdomino-pelvic computed tomography (CT) scans were done every three months.

26 patients received chemotherapy after progression on antihormonal therapy. 22 patients received cabazitaxel, 3 patients received docetaxel and 1 patient received a combination of cisplatin and etoposide. 18 out of the 26 patients received at least 4 cycles of chemotherapy. The same proportion of patients treated by doctor 1 and 2 as compared to doctor 3 received at least 4 cycles of chemotherapy.

Median overall survival was the endpoint for every analysis. With regard to the low number of cases confidence intervals and significance were not calculated. Kaplan-Meyer survival curves were constituted.

3. Results

35 patients received abiraterone with prednisone substitution, 12 patients received abiraterone with hydrocortisone substitution and 15 patients received enzalutamide. 39 patients were treated until clinical and radiological progression and 23 patients were treated until biological progression. Patients treated by doctor 1 and 2 were slightly younger than those treated by doctor 3. There was no difference between the two groups regarding the most relevant laboratory findings. The patients' baseline characteristics are summarised in Table 1.

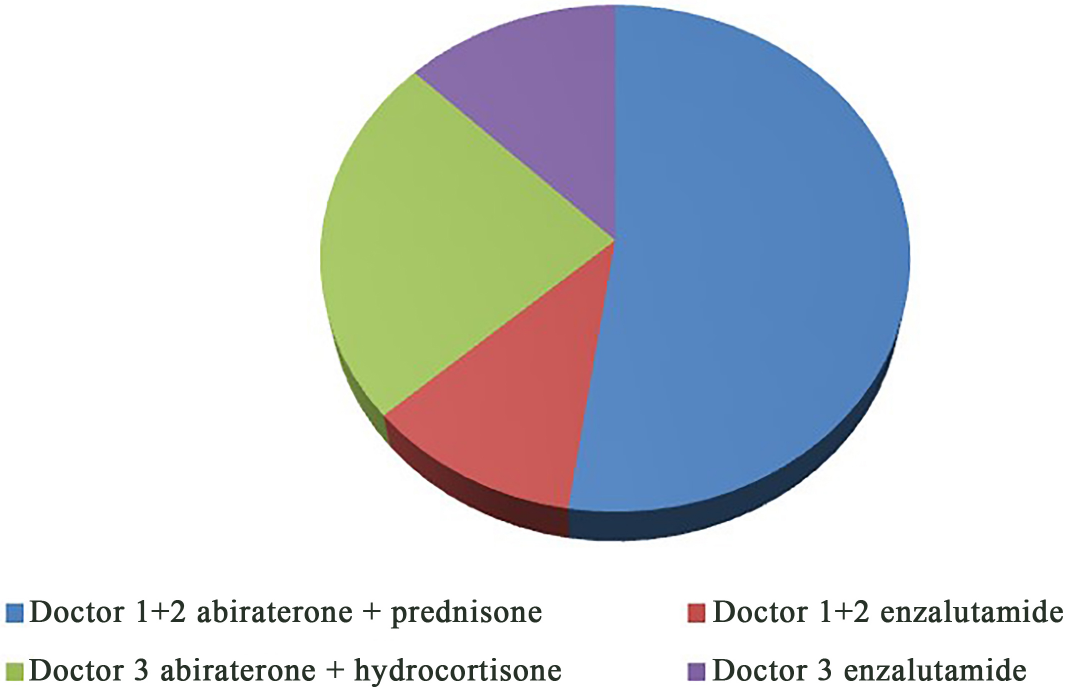

Fig. 1. Plan of the analyses. The sectors are proportional with the patient numbers. (1) Doctor 1 + 2 abiraterone + prednisone vs. Doctor 3 abiraterone + hydrocortisone, (2) Doctor 1 + 2 vs. Doctor 3, (3) Deep PSA drop vs. moderate PSA drop (not indicated on the figure). "Control": Doctor 1 + 2 and 3 abiraterone vs. Doctor 1 + 2 and 3 enzalutamide.

Table 1. Patients' characteristics at baseline.

	doctor 1 + 2	doctor 3
number	39	23
age	68 (44–83)	72 (61–86)
PS	0.33 (0–2)	0.30 (0–2)
PSA	206 (3–1000)	189 (2–927)
HGB	135 (82–158)	128 (85–155)
ALP	388 (58–2740)	392 (145–1113)
≥4 cycles CT	11 (28%)	7 (30%)

PS, performance status; PSA, prostate specific antigen; HGB, haemoglobin; ALP, alkaline phosphatase; CT, chemotherapy.

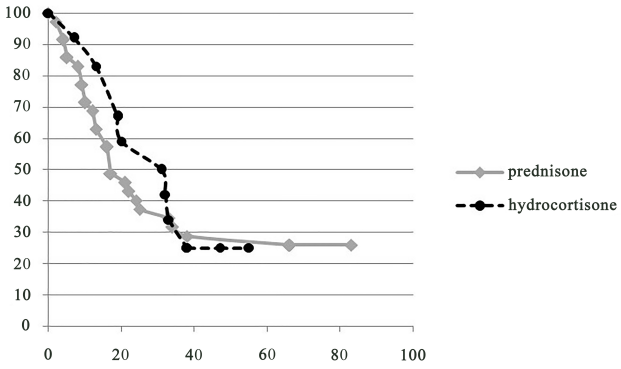

Fig. 2. Overall survival (in months) of patients treated with abiraterone.

(1) Concerning patients treated with abiraterone, the median overall survival with abiraterone + hydrocortisone was not inferior as compared to abiraterone + prednisone (31 months vs. 17 months, Fig. 2).

(2) Concerning treatment duration, the median overall survival of patients treated until PSA progression was not inferior as compared to patients treated until radiological progression (32 months vs. 17 months, Fig. 3).

(3) Concerning the duration of response, the median overall survival of patients whose first control PSA level was below normal value was 25 months (range: 10–55 months). The median overall survival of patients whose first control PSA level was over normal value was 17 months (range: 4–83 months).

The median overall survival of patient treated with abiraterone or enzalutamide was similar (21 months vs. 24 months).

4. Discussion

Three questions with regard to the optimisation of the second line antihormonal therapy for castration resistant metastatic prostate cancer were addressed.

(1) The use of prednisone in the treatment of metastatic prostate cancer is of historical origin. The disease was for a long time considered as chemoresistant. Mitoxantrone, the first efficacious agent was validated in ad-

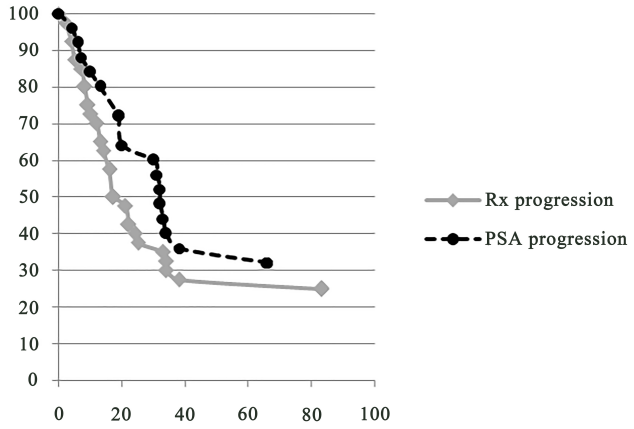

Fig. 3. Overall survival (in months) of patients whose second line antihormonal treatment was stopped at radiological (Rx) vs. biological (PSA) progression.

dition to prednisone while the control arm received prednisone alone. Prednisone was later associated to docetaxel as well [12]. In our clinical routine we do not systematically use steroids with docetaxel except a single dose of premedication on the day of the chemotherapy. We never observed any inconvenience with this strategy. We wonder the reasons why prednisone was chosen in the validation study as substituent to abiraterone. There are observations of PSA decrease after the change of prednisone to dexamethasone when PSA had been rising beside the previous drug still the use of dexamethasone has not become the standard of care [13]. Being internist and wishing the minimisation of side effects we tried the use of the absolutely physiological hydrocortisone. Our results suggest that the decision seems reasonable.

(2) The treatment up to radiological progression as determined by the RECIST criteria is the standard of care for every solid tumour. However, prostate cancer is exceptional from two aspects. First, it disposes a highly sensitive biological marker, the PSA. Second, it usually exclusively gives bone metastases. In contrast to visceral lesions, bone metastases do not show regression in parallel with disease control. In case a medical treatment is effective, PSA decreases while the radiological image of the modified bone structure remains the same. Once the disease becomes resistant to the treatment PSA should return to the initial value before any radiological progression will be detectable. Nevertheless, this may take several months if not years. The pursuit of a treatment with low efficacy but high cost has the more concern the budget of the country is more restricted.

(3) The prediction of efficacy at the beginning of the second line antihormonal treatment is partially also of financial interest. Abiraterone and enzalutamide target the androgenic pathway at different points, but interestingly the efficacy of the two agents is equal in terms of benefit in progression free survival [2,3]. This is true in statistical level. Whether any difference may exist in personal level is not known. Moreover, the sequential use of the two agents has little additional benefit. Although some data suggest that the order abiraterone $\rightarrow$ enzalutamide is more favourable as compared to the order enzalutamide $\rightarrow$ abiraterone [14], currently there is no recommendation either for the choice between the two drugs or for the sequential use of them. Still, what about the proportion of patients who would potentially better respond to one of the therapies or the crossover treatment? In countries with less strict social security limitation the crossover treatment is frequently tried. In Hungary there is no possibility for a crossover after progression on the agent of first choice. If the difference in personal benefit exists, the possibility of crossover at the moment of the first laboratory control—when patients are in regression—might allow a chance to get the more suitable drug for every patient. The crossover could be recommended in case the PSA does not drop below a predefined level.

As expected, abiraterone and enzalutamide provide the same benefit in overall survival. This fact serves as control and comforts our other results. Interestingly these results are somewhat even better than the overall survival data of the registration trials (14.8 months for abiraterone and 18.4 months for enzalutamide [2,3]).

The proportion of patients who received chemotherapy was equilibrated between the subgroups. Anyway, given that the majority of patients did not receive any chemotherapy the reception of chemotherapy did not influence the median overall survival. The relatively small number of patients who received cabazitaxel is due to the late introduction of this agent in our country.

The weakness of our study is the low number of cases. Nevertheless, it has to be recognised that the questions addressed in this work will never put into the focus of a randomised multicenter trial. Although the topics are not of interest for the manufacturers they may be of interest for clinicians and for financing organisations. We believe that by this way even a study with small numbers may have an impact on clinical routine.

An important goal of the management of metastatic prostate cancer patients is that possibly all patients receive the available two lines of antihormonal- as well as the two lines of chemotherapy. This strategy allows the longest survival benefit. For doing so it is essential to start every treatment line by relatively low PSA level. In our routine we try to stay between 20–100 ng/mL. Patients in progression even at low levels of PSA may do a pause before starting the next line. These pauses have no risk provided that regular PSA controls and physical examinations are going on beside the LHRH agonist or antagonist treatment. Just in contrary, pauses are comfortable for patients and doctors as well. The potential benefit of the combined use of several treatment modalities from the beginning on is currently under investigation.

In case our results are confirmed in larger populations, hydrocortisone could replace prednisone as steroid substituent associated to abiraterone and second line antihormonal therapy could be stopped at biological progression. The alternative treatment strategies could provide more comfortable tolerance and better cost-efficiency.

5. Conclusions

The combination of abiraterone + hydrocortisone is not inferior to the combination of abiraterone + prednisone and the treatment up to PSA progression is not inferior to the treatment up to radiological progression in terms of overall survival for patients with castration resistant metastatic prostate cancer.

Author contributions

All authors participated in the treatment of the patients. KT prepared the manuscript. KK, AA, KN, HÁ and SZ contributed with data collection and critical remarks. All co-authors accepted the final version.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. KT is serving as one of the Guest editors of this journal. We declare that KT had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AN.

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