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Metastatic Prostate Cancer under Androgen Deprivation Therapy: Factors Influencing Castration Resistance

Modou Ndiaye[1], Ousmane Sow[1*], Babacar Sine[1], Omar Gaye[1], Alioune Sarr[1], Abdoulaye Ndiath[1], Cyrille Ze Ondo[1], Amath Thiam[1], Ndeye Aissatou Bagayogo[1], Samba Thiapato Faye[1], Ndiaga Seck Ndour[1], Aboubacar Traore[2], Ngor Mack Thiam[1], El Hadj Malick Diaw[1], Yaya Sow[1], Boubacar Fall[2], Babacar Diao[1], Alain Khassim Ndoye[1]

[1]Urology-Andrology Department, Aristide Le Dantec Hospital, Dakar, Senegal
[2]Urology-Andrology Department, De la Paix Hospital, Ziguinchor, Senegal
Email: *sowman87@yahoo.fr

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Abstract

Objective: To evaluate the factors predicting the time to progression to castration-resistant in metastatic prostate cancer under Androgen Deprivation Therapy (ADT) in our center. **Patients and Methods:** This is a retrospective, descriptive, analytical study in a single center over a period of 2 years. It has interest patients followed for metastasized prostate cancer under ADT. The parameters studied were: epidemiological, clinical, paraclinical, prostate specific antigen (PSA) nadir, time to nadir (TTN) and their link with the castration resistance. **Results:** The frequency of castration resistant prostate cancer was 28 patients per year. The mean age was 70.4 ± 7.9 years. An ECOG score ≥ 3 was more common as was the cT2c stage. The median of the initial total PSA was 489.6 ng/ml (203.3; 1653.2). All patients had adenocarcinoma. The International Society of Urological Pathology (ISUP) 1 was more frequent. Bone metastases were more frequent. The medians of nadir, TTN and the castration resistance were 19.3 ng/ml (3.7; 102.1), 5.5 months (3; 9) and 11 months (6; 15.3), respectively. The Eastern Cooperative Oncology Group (ECOG) score, clinical stage, metastatic site, the nadir and its TTN influenced the DSR. Age, lymph node involvement, initial total PSA and Gleason score did not influence the castration resistance. **Conclusion:** ADT should be initiated as soon as possible before an attack of general and/or clinical stage advanced to delay resistance. A drilling should be associated with this hormone therapy as much as possible because of its gain on resistance.

Keywords

Cancer, Prostate, Androgen Deprivation Therapy, Resistance, Prognoses

1. Introduction

Prostate cancer is the most common cancer in older men, the second leading cause of cancer death after lung cancer and the fourth leading cause of cancer death in the general population [1]. In Senegal, most prostate cancers are diagnosed in locally advanced or metastatic stage [2] [3]. ADT the effects of which have been known for several years, is the cornerstone of the treatment of metastatic prostate cancer [4]. Bilateral pulpectomy remains the most common method in our context [2]. The hormone-sensitivity is limited in time and the biochemical progression usually takes place between 18 and 36 months after the start of hormone therapy [5]. Ten to 20% of prostate cancers progress to castration-resistant prostate cancer (CRPC) within 5 years of diagnosis, and more than 84% of newly diagnosed metastatic cancers would be CRPC [6]. The resistance to castration of metastatic prostate is now likely to be treated with new molecule. The CRPC poses a therapeutic problem in developing countries because of the accessibility and cost of these new molecules used at this stage. The objective of this study was to evaluate the factors predicting the time to progression to castration-resistant in metastatic prostate cancer under Androgen Deprivation Therapy (ADT) in our center.

2. Patients and Method

This is a retrospective, descriptive, analytical and single-center study, collecting the records of patients followed for metastasized prostate cancer between January 1, 2016 and December 31, 2017. ADT was: either medical, using analogues of luteinizing hormone-releasing hormone (Goserelin, triptorelin) or surgical, using bilateral testicular pulpectomy. A non-steroidal antiandrogen (bicalutamide) was used to complete the androgen blockade. The definition of CRPC in the CCAFU Oncology Recommendations 2016-2018 was used [7]. The general condition was evaluated by the ECOG (Eastern Cooperative Oncology Group) performance status score. Patients who had metastatic prostate cancer on hormone therapy with a complete history were included. Patients with metastatic prostate cancer receiving hormone therapy with an incomplete or unrecognized record and those with localized or metastatic prostate cancer without hormone therapy were not included. The parameters studied were: frequency, age, general condition, clinical T stage, initial total prostate specific antigen (PSA), International Society of Urological Pathology (ISUP) score 2014, lymph node involvement, metastatic sites, total PSA nadir and its TTN and their link with the castration resistance. IBM SPSS Statistics Viewer 20 software was used for statistical analysis. Prognostic factors were assessed by a multivariate analysis with the Chi-2 test

and the p value < 0.05 was considered to be statistically significant. The data were collected on a survey form from the files of patients followed in consultation or hospitalized in our department for metastatic prostate cancer under hormone therapy.

3. Results

Seventy-eight patients were included. Among them, 56 patients had CRPC. The frequency of CRPC was 28 per year. The mean age was 70.4 ± 7.9 years. The most common age groups were those between 60 and 70 and those between 70 and 80. A deterioration of the general condition with a higher ECOG score ≥ 3 was observed in 59% of patients. The clinical T stage of the tumor classified cT2c was more common, found in 55% of the patients followed by the stage cT4 observed in 36%. The median total PSA rate before treatment was 489.6 ng/ml (203.3 and 1653.2 ng/mL). Eighty-six percent (86%) of patients had a total PSA greater than 100 ng/ml. An adenocarcinoma was objectified in all patients and the ISUP score 1 was more common, found in 33% of patients. Fifty-one percent (61%) of patients did not have a regional lymph node assessment and regional lymph node involvement observed in 38% of thoracoabdominal-Computed Tomography (CT) patients. Bone metastases were more frequent, objectified in 43.6% of patients with bone scintigraphy. The median total PSA nadir was 19.3 ng/ml (3.7 and 102.1 ng/ml). The median TTN was 5.5 months (3 and 9 months). The median of the castration resistance was 11 months (6 and 15.3). Eighty-seven percent of the patients had surgical castration. This surgical castration was associated with a drilling in 19% of patients. The patients, who had surgical castration associated with drilling, had less resistance compared to the other patients (**Table 1**). This type of treatment influenced significantly (p 0.003) the castration resistance. The deterioration in general condition with an ECOG ≥ 3, total PSA nadir and its TTN, Metastatic sites and Clinical stage T influenced the castration resistance with significant p (**Table 1** and **Table 2**). The patients classified CT4 were 3 times more likely to develop resistance than others with odds ration of 3.4 and a confidence interval 1.0 to 11.3. Patient age (p = 0.120), lymph node involvement (p = 0.14), initial total PSA rate, ISUP score did not affect the castration resistance with p which were not significant (**Table 3**).

4. Discussion

The frequency of castration resistant cancer is high in our center. This high frequency can be explained by the fact that our patients often come for consultation only at the late stage, therefore already metastasized [2] [3] [8]. In the literature, almost all prostate cancers progress to castration resistance to increasing serum PSA despite castrate levels of testosterone and progress to metastases [6]. Ten to 20% of prostate cancers progress to CRPC within 5 years of diagnosis, and more than 84% of newly diagnosed metastatic cancers are thought to be CRPC [5] [9]. The epidemiological profile of CRPC is difficult to determine due to the lack of

Table 1. Distribution of the type of treatment, the Gleason score and clinical stage based the castration resistance.

		Slice at castration resistance				Total	p
		Not resistant	<5	5 - 10	>10		
Type of treatment	Medical castration	4	1	0	4	**9**	**0.003**
	Surgical castration	9	3	27	15	**54**	
	Surgical castration + drilling	9	2	3	1	**15**	
	Total	22	6	30	20	**78**	
Score ECOG	0	0	0	1	0	**1**	**0.010**
	1.0	9	0	3	1	**13**	
	2.0	8	1	5	4	**18**	
	3.0	5	4	13	7	**29**	
	4.0	0	1	8	8	**17**	
	Total	22	6	30	20	**78**	
Clinical T stage	cT2b	0	0	0	4	**4**	**0.019**
	cT2c	16	3	8	16	**43**	
	cT3c	2	1	0	0	**3**	
	cT4	4	2	12	10	**28**	
	Total	22	6	20	30	**78**	

Table 2. Distribution of metastatic sites according to castration resistance.

		Slice at castration resistance				Total	P
		Not resistant	<5	5 - 10	>10		
Metastasis	M1a	0	0	0	1	**1**	**0.04**
	M1b	5	3	14	12	**34**	
	M1c	12	3	6	2	**23**	
	MX	5	0	10	5	**20**	
	Total	22	6	30	20	**78**	

Table 3. Distribution of the total PSA slice before treatment, the total PSA nadir tranche and the TTN according to castration resistance.

		Slice at castration resistance				Total	P
		Not resistant	<5	5 - 10	>10		
Slice total PSA	PSA < 100	1	0	4	3	**8**	**0.500**
	PSA ≥ 100	21	6	26	17	**70**	
	Total	22	6	30	20	**78**	
Slice total PSA nadir	<5	11	0	8	3	**22**	**0.030**
	5 - 10	11	6	22	17	**56**	
	Total	22	6	20	30	**78**	
Slice TTN	<2	1	3	1	1	**6**	**0.000**
	[2 - 5]	10	3	6	14	**33**	
	>5	11	0	23	5	**39**	
	Total	22	6	30	20	**78**	

standardized diagnostic models, reporting methods for CRPC and inconsistent terminology [10]. The average age of our series was similar to the average age of 73.3 ± 9.3 years found by Rigaud J *et al.* [11] when setting up their hormone therapy. Age was not a prognostic factor for the resistance that occurred in our series, which was consistent with the results of Mulders *et al.* [12]. However, Emrich *et al.* [13] found that age was a prognostic factor in their series. A deterioration in the general condition with an ECOG score of 3 more frequently objectified in our series could be explained by the fact that, this cancer is characterized in our regions by its diagnosis most often late, at a locally advanced or metastatic stage [3] [14]. This deterioration of the general condition was a prognostic factor in our series, as it was in most of the major series in the literature in single or multivariate analysis [15] [16] [17] [18]. Several African authors have also shown that this deterioration of the general condition with an ECOG score greater than or equal to 2 decreases survival [3] [14]. The clinical stage T2c was more frequent in our series which confirms that the tumor was advanced at diagnosis. The clinical stage of the tumor was an important prognostic factor, which was comparable to the results of Emrich *et al.* [13]. However Rigaud *et al.* [11] and Mulders *et al.* [12] had concluded that the clinical stage T of the primary tumor was not a prognostic factor. The level of total PSA before treatment did not influence the castration resistance as shown by Rigaud *et al.* [11]. In contrary, the results of Robinson *et al.* [19] showed that this pre-treatment total PSA level was a prognostic factor in patients treated with androgen suppression for prostate cancer. ISUP score has a disputed prognostic value in the case of advanced prostate cancer treated with hormone therapy. For some, the ISUP score has no influence on survival [12] [13] [18] but for others, a low ISUP score was a factor of good prognosis on survival in uni and multivariate analysis [17] [20]. The high Gleason (ISUP 4 and 5) score is a factor in the poor prognosis of prostate cancer in a study by Sine *et al.* [21] in Senegal and Gagnat *et al.* [22] in France. Indeed this hypothesis is confirmed by our series where the Gleason score (ISUP score) influenced the castration resistance. There was no significant difference between whether or not there was regional lymph node involvement, unlike Halabi *et al.* [23] who found in their study influence. The absence of regional lymph node assessment in our series could be explained by the fact that the patients were seen at an advanced stage with an impairment of renal function probably due to an invasion of the ureteral meatus making difficult the extension assessment by a thoraco-abdominal CT. It could also be explained by the lack of financial means of some patients in our regions.

An impact of the metastatic site on the castration resistance in our series has been proven by several authors in the literature [22] [23].

The PSA nadir was a significant influence on the castration resistance in our series that has been confirmed by several authors in the literature [9] [19] [22] [24] [25]. The median TTN in our series was short compared to those found in the literature. In effect Gagnat *et al.* [22] reported a median of TTN to 13.1

months. Most of the patients in our series had a prostate cancer already metastasized castration resistant which could explain this short time observed in our series. The study by Choueiri *et al.* [24] showed for the first time that the TTN was a significant prognostic factor for overall survival in metastatic prostate which complies our results. Currently in the literature several authors confirmed this impact on the occurrence of resistance [22] [26].

5. Conclusion

At the metastatic stage, ADT should be started as soon as possible before general involvement and/or an advanced clinical stage to delay resistance. Drilling for a cytoreduction must also be done as much as possible because of its gain on the occurrence of resistance to castration of metastatic prostate cancer under ADT.

Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

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