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Disease Control after Androgen Deprivation Therapy Combined with Di Bella Multitherapy

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ABSTRACT

Purpose: *To describe the clinical response, disease control, and treatment safety in prostate cancer patients treated with androgen deprivation therapy (ADT) combined with Di Bella multitherapy (MDB) in patients with prostate cancer.*

Materials and Methods: *Consecutive evaluable patients with histologically confirmed prostate cancer treated with ADT plus MDB were retrospectively identified from institutional clinical records. Baseline demographic and clinicopathological characteristics were collected and clinical responses were assessed using radiological, biochemical, and clinical follow-up documentation. Disease control rate (DCR) was defined as remission or stable disease. Continuous variables are summarized as median and interquartile range (IQR) and categorical variables as frequencies and percentages. Exact binomial 95% confidence intervals (CI) were calculated, and exploratory comparisons between disease stages were performed using Fisher's exact test.*

Results: *A total of 109 consecutive evaluable patients were included, including 64 localized, 22 regional, and 23 distant stage cases. The median age at treatment initiation was 64 years (IQR: 56–68 years). Disease control was observed in 47 of 64 localized patients (73.4%; 95% CI 61.3–83.1), 16 of 22 regional patients (72.7%; 95% CI 49.8–89.3), and 9 of 23 distant-stage patients (39.1%; 95% CI 19.7–61.5). Disease stage was significantly associated with disease control (Fisher exact test, p=0.008). No grade 3–4 treatment-related toxicities or treatment discontinuations were documented.*

Conclusions: *ADT combined with MDB is associated with favorable and durable disease control and acceptable tolerability across disease stages. These findings should be considered exploratory and hypothesis-generating and require prospective validation.*

Keywords

Androgen deprivation therapy, Di Bella Method, Disease control rate, Growth hormone signaling, Prostate cancer.

Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men worldwide and is a leading cause of cancer-related mortality. Globally, PCa accounts for approximately 25% of all male malignancies and is characterized by a prolonged natural history and latency period that may range from 3 to 10 years [1].

Androgen deprivation therapy (ADT) is a standard systemic treatment for advanced recurrent metastatic prostate cancer. Its therapeutic effect is achieved through pharmacological or surgical suppression of androgen-dependent tumor proliferation, with maximum androgen blockade providing additional disease control in select patients [2].

Despite the established efficacy of ADT, disease progression and therapeutic resistance occur frequently during long-term treatment. Experimental evidence suggests that one of the mechanisms involved in treatment resistance is the progressive

activation of autocrine growth hormone (GH) signaling in prostate cancer cells. GH signaling has been implicated in tumor proliferation, angiogenesis, epithelial–mesenchymal transition, metastatic dissemination, and resistance to androgen receptor-targeted therapies [3]. Therefore, the inhibition of GH signaling and related endocrine, proliferative, oxidative, and epigenetic pathways may represent a complementary therapeutic strategy [4]. Somatostatin and its analogs directly inhibit GH secretion and exert antiproliferative activity through somatostatin receptors expressed in prostate cancer tissues [5,6]. The Di Bella method (MDB) combines somatostatin or octreotide, dopamine D2 receptor agonists (Bromocriptine and Cabergoline), melatonin, retinoids solubilized in vitamin E [7], vitamins D3 [8], C [9] and sodium butyrate [10], with the aim of simultaneously modulating multiple biological pathways involved in tumor progression. Retinoids regulate differentiation, apoptosis, and immune activation [11] and vitamin E contributes to the preservation of somatostatin receptor signalling [12]. Melatonin exerts antioxidant and antiproliferative effects [13,14], vitamin D modulates inflammatory and proliferative signaling [8], and sodium butyrate regulates histone deacetylase-dependent differentiation pathways [10].

The aim of this retrospective observational case series was to describe the clinical response, disease control, and treatment tolerability of patients with prostate cancer treated with ADT combined with MDB in routine clinical practice.

Materials and Methods

Study design

This retrospective, single-center, observational cohort study included consecutive evaluable patients with histologically confirmed prostate cancer treated with ADT combined with MDB.

This study was conducted in accordance with the Declaration of Helsinki and reported in accordance with the STROBE statement.

Written informed consent for treatment and retrospective data collection was obtained from all participants.

Patient selection

Consecutive evaluable patients were retrospectively identified from institutional clinical records.

Eligible patients met all the following inclusion criteria:

- Histologically confirmed prostate adenocarcinomas
- Measurable disease according to the RECIST 1.1
- Combined ADT and MDB treatment
- Availability of baseline clinical and pathological data
- Sufficient follow-up data for response assessment

A total of 109 consecutive evaluable cases met these criteria and were included in the final analysis (Figure 1).

Because the present study was based on retrospectively identifiable evaluable cases extracted from a longitudinal institutional archive, a complete screening log of all historical records was not available.

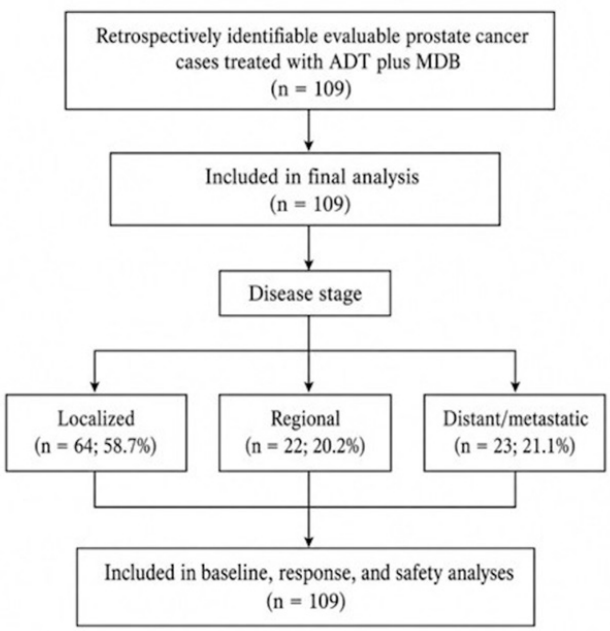

Figure 1: Patient flow diagram.

Baseline assessment

Baseline evaluation data included age at treatment initiation, serum prostate-specific antigen (PSA), Gleason score, disease stage, and previous oncologic treatments. The disease stage was classified as localized (n= 64), regional (n=22), or distant/metastatic (n=23).

Treatment protocol

All patients received standard ADT according to the disease stage and physician judgment, combined with MDB, as follows:

- somatostatin or octreotide
- dopamine D2 receptor agonists (bromocriptine and cabergoline)
- melatonin
- retinoids dissolved in vitamin E
- vitamins D3 and C
- sodium butyrate

Follow up and outcome assessment

Follow-up evaluations were performed according to routine clinical practice, and included clinical examination, laboratory testing, PSA measurements, and radiological reassessment when clinically indicated.

Because exact death dates and complete long-term vital statuses were not consistently available in retrospective records, survival analyses were not performed.

Study endpoints

The primary endpoint was disease control rate (DCR), defined as the proportion of patients achieving remission or stable disease.

Secondary endpoints included progression rate and treatment tolerability.

Outcome definitions

Treatment response was classified into three mutually exclusive categories based on retrospective clinical documentation.

Remission: Documented radiologic and/or biochemical improvement without evidence of progression.

Stable disease: absence of clinically documented progression during follow-up.

Progressive disease: Radiologic, biochemical, or clinical evidence of disease progression.

Statistical analysis

Continuous variables were summarized as median and interquartile range (IQR).

Categorical variables were summarized as frequencies and percentage.

Disease control, remission, and progression rates were calculated using exact binomial 95% confidence intervals (CI).

Exploratory comparison between diseases stages were performed using Fisher's exact test.

Because exact death dates and complete long-term vital status data were not consistently available in retrospective records, survival analyses were not performed.

Missing baseline values were not imputed, and analyses were performed using available case data. Statistical analyses were performed using Python version 3.11 with standard scientific libraries. Two-sided p values <0.05 were considered statistically significant.

Results

Patient characteristics

A total of 109 consecutive evaluable patients were included, including 64 localized (58.7%), 22 regional (20.2%), and 23 distant (21.1%) stage cases. The baseline demographic and clinicopathological characteristics of the patients are summarized in (Table 1).

Baseline characteristics

Baseline demographic and clinicopathologic characteristics are summarized in Table 1.

Median age at treatment initiation was 64 years (IQR 56-68). Baseline PSA values were available for 99 of 109 patients.

Clinical response

Clinical response according to disease stage is reported in Table 2.

Table 2: Clinical response according to disease stage.

Response	Localized	Regional	Distant
Remission	47	16	5
Stable disease	0	0	4
Disease control	47	16	9
Progressive disease	17	6	14

Disease control was observed in 47 of 64 localized patients (73.4%; 95% CI 61.3-83.1), 16 of 22 regional patients (72.7%; 95% CI 49.8-89.3), and 9 of 23 distant-stage patients (39.1%; 95% CI 19.7-61.5).

Disease control rates with exact binomial 95% confidence intervals are shown in Table 3.

Table 3: Disease control rate with exact binomial 95% confidence intervals.

Stage	Disease control	95% CI
Localized	73.4%	61.3–83.1
Regional	72.7%	49.8–89.3
Distant	39.1%	19.7–61.5

Progressive disease was observed in 17 of 64 localized patients (26.6%), 6 of 22 regional patients (27.3%), and 14 of 23 distant stage patients (60.9%).

Exploratory analysis demonstrated a significant association between disease stage and disease control (Fisher exact test, p= 0.008). Table 4 presents an exploratory comparison of these results.

Table 4: Exploratory comparison of disease control across disease stages.

Test	p
Fisher exact test	0.008

Table 1: Baseline characteristics of the study population according to disease stage.

Variable	Overall (n=109)	Localized (n=64)	Regional (n=22)	Distant (n=23)
Age, years, median (IQR)	64.0 (56.0–68.0)	63.5 (54.0–69.0)	65.5 (59.0–68.0)	62.0 (57.5–66.0)
Baseline PSA, ng/mL median (IQR)*	10.24 (5.31–27.0)	7.25 (4.95–12.0)	13.68 (6.0–23.0)	114.0 (26.0–194.0)
Gleason ≤ 6	25	22	2	1
Gleason 7	35	21	10	4
Gleason ≥ 8	35	11	7	17
Gleason missing	14	10	3	1
Prior surgery	24	11	9	4

* PSA available in 99/109 patients.

Safety

No grade 3-4 treatment-related toxicity or treatment discontinuation was documented in clinical records.

Safety outcomes are summarized in Table 5.

Table 5: Safety outcomes.

Variable	Value
Grade 3–4 toxicity	0
Treatment discontinuation	0

Discussion

In this retrospective case series, ADT combined with MDB was associated with favorable disease control in localized and regional diseases, with lower but measurable disease control in distant-stage cases.

The observed stage-dependent differences are biologically consistent with an increasing tumor burden, higher baseline PSA values, and greater prevalence of high-grade disease in advance-stage patients.

The biological rationale of MDB is supported by experimental evidence demonstrating the role of autocrine GH signalling in prostate cancer progression and therapeutic resistance [3,4], as well as by studies documenting antiproliferative effects of somatostatin analogs [5], retinoids [11], melatonin [13,14], vitamin D [8] and sodium butyrate [10].

The present findings should be interpreted within the limitations of retrospective observational data and should not be interpreted as evidence of comparative efficacy.

Limitations

This study had several limitations, including its retrospective design, single-center setting, absence of an internal comparator, incomplete long-term survival data, potential selection bias, and limited ability to reconstruct a complete screening log from historical archival records.

Conclusions

In this retrospective observational case series, ADT combined with MDB was associated with favorable disease control and acceptable tolerability across disease stages. These findings should be considered exploratory and hypothesis generating. Therefore, prospective controlled studies are required.

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