

# Somatostatin analogs in the treatment of castrate-resistant prostate cancer: efficacy and tolerability

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*Castrate-resistant prostate cancer (CRPC) is one of the most complex and currently completely unsolved problems of oncurology. Possible novel treatment of CRPC is administration of Octreotide Long, long-acting somatostatin analogue.*

*In this paper we have shown an experience of treatment with Octreotide Long 30 mg and dexamethasone in 69 CRPC patients from February 2014 to March 2016. We have assessed an efficacy and safety of the therapy. Age of patients ranged from 56 to 89 years, all patients had continued androgen deprivation. Response to the treatment was assessed clinically by the following factors: change in the level of prostate specific antigen (PSA) in serum, dynamics of indicators of general and biochemical blood tests, the level of pain syndrome and improvement in the patient's quality of life. Total response to reduction and stabilization of PSA level was achieved in 70.9 % of patients. In general, the best results were observed in the group of patients treated with Octreotide Long before first-line chemotherapy with docetaxel. Tolerability of Octreotide Long in combination with dexamethasone in all cases was good. No significant side effects — neither hematological, nor clinical were noted. We also did not register any cases of drug discontinuation due to its intolerance.*

**Keywords:** prostate cancer, morbidity, methods of treatment, hormonal therapy, castration resistance, survival rate, somatostatin analogues, Octreotide Long, effectiveness of treatment, side effects

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## Introduction

Morbidity of prostate cancer (PC) in Russia continues to grow. In 2014, more than 34,000 new cases were registered, and morbidity increase in the last 10 years was 157.78 %, the highest value among malignant tumors. PC is one of the most pressing problems in oncology, both because of high (and increasing) morbidity and often unsatisfactory treatment outcomes [1–4].

Despite the developed and available PC diagnostics algorithm and widespread implementation of testing for prostate-specific antigen (PSA) level in men after 50, in 49.6 % of patients with newly diagnosed PC, a locally advanced and metastatic disease is diagnosed [1].

Hormone therapy of locally advanced and metastatic forms of PC, aimed at blocking testosterone synthesis and elimination of androgen stimulation of the tumor, is widely used for primary hormone-sensitive forms of PC, as well as recurrences after local treatments (radical prostatectomy and beam therapy). However, its effectiveness is time-limited, and sooner or later (on average, after 2 years) castration resistance develops in the majority of patients [4–9]. Prescription of steroid and non-steroid antiandrogens, estrogens, chemotherapy, radiopharmaceuticals, some of which are rather toxic, demonstrates a short-lived effect [4].

A particular problem in cancer urology is posed by castration-resistant prostate cancer (CRPC), which severely worsens disease prognosis. Several new options have appeared in recent years (abiraterone, enzalutamide, apalrinadine, docetaxel, and cabazitaxel chemotherapy), but treatment outcomes are still unsatisfactory, duration of response to these medications is short, selection of the most rational

strategy is difficult. Therefore, the search for additional therapy opportunities remains vitally important [7–10]. One of the directions in CRPC treatment may be prescription of long acting somatostatin analogs (Octreotide-long) in combination with dexamethasone and continued androgen deprivation [5, 10].

Antitumor activity of somatostatin is associated with inhibition of cell growth and neoangiogenesis, increased intensity of apoptosis in cancer cells. The level of inhibition depends on the level of somatostatin receptors' expression [4].

The idea of using somatostatin analogs is based on cell heterogeneity of PC: along with androgen-dependent cells, it contains, though in a smaller amount, cells with neuroendocrine differentiation expressing somatostatin receptors. These cells are potential targets for PC treatment [4, 5, 11, 12]. The existence of these cells was confirmed by immunohistochemistry: PC expresses a marker of neuroendocrine differentiation chromogranin A [12, 13], though its role as a predictor of response to somatostatin analogs in PC treatment is not yet definite.

In recent years in Russia, results of several clinical trials were published demonstrating effectiveness and safety of somatostatin analogs (Octreotide-long in 20 and 30 mg doses) in combination with dexamethasone and continued drug or surgical castration in patients with CRPC [14–21]. A positive effect in the forms of decreased PSA level was achieved in 60 % of patients, lack of progression for 8 months in 88 % of patients, decreased pain syndrome in 80 %, and positive overall objective clinical response in 85 % [4, 5, 11, 14]. In these studies, the most effective dose of Octreotide-long for treatment of CRPC was 30 mg

once in 28 days. The treatment is tolerable, and the best results were achieved for prescription of Octreotide-long before chemical therapy.

**The study objective** is to evaluate effectiveness and safety of a depot form of somatostatin analog Octreotide-long at 30 mg dose in combination with dexamethasone and castration therapy before cytotoxic therapy and after docetaxel use for treatment of patients with CRPC.

### Materials and methods

Between February and May of 2014 in the outpatient facility of the Moscow City Oncological Hospital # 62, a clinical study of effectiveness and safety of a depot form of Octreotide-long at 30 mg dose in combination with dexamethasone in patients with CRPC was performed. Since Octreotide-long has shown positive results of treatment and safety assessment, it is now used in routine clinical practice. Until March of 2016, we had treated 69 CRPC patients using Octreotide-long, and the results are presented below.

Patient age varied from 54 to 89 years (mean age 69.2 years). More than a half (58.0 %) of men were aged 60–69, 19 (27.5 %) were younger than 60, the rest (14.5 %) were above 70. In all patients, adenocarcinoma of the prostate was histologically verified. Predominantly, it was moderately and poorly differentiated per the Gleason grading system (Table 1).

Prior to development of castration resistance, patients received different types of PC treatment: only hormonal therapy – 41 (59.4 %) patients; radical prostatectomy – 11 (15.9 %) patients including patients with subsequent recurrence and disease progression; prostate beam therapy (usually in combination with hormone therapy) – 17 (24.6 %) patients including patients with subsequent disease progression at different times, among them 2 patients received brachytherapy.

At the time of Octreotide-long treatment, all patients had metastatic CRPC. Distant metastases were mostly presented by bone deposits confirmed by bone scintigraphy, magnetic resonance imaging, or spiral computed tomography, with the number of bone lesions from 1 to superscan. Metastases in distant lymph nodes and parenchymal organs (mostly, in combination with bone lesions) were diagnosed only in 8 (11.6 %) patients. PSA level prior to Octreotide-long prescription was 50 ng/ml or higher in the majority of patients in the context of generalized oncological process.

**Table 1.** Histological characteristics of the tumor

| Total Gleason score | Number of patients, n (%) |
|---------------------|---------------------------|
| 6                   | 22 (31.9)                 |
| 7–8                 | 39 (56.5)                 |
| 9–10                | 8 (11.6)                  |

Patients were randomized into 2 groups: The 1st group ( $n = 31$ ) received treatment before chemotherapy (after completion of a course of antiandrogens), the 2nd ( $n = 38$ ) group included patients with progressive CRPC after the 1st line chemotherapy with docetaxel.

The depot form of Octreotide-long was injected intramuscularly at dose 30 mg every 28 days in combination with oral use of dexamethasone: 4 mg for 1 month, 2 mg for the next 2 weeks, and 1 mg as a maintenance dose until the end of the Octreotide-long treatment. All patients continued to receive androgen-deprivation therapy with confirmed blood castrate level of testosterone for the whole duration of the Octreotide-long treatment. Determination of serum testosterone has shown that in all patients it was at the castrate level: mean value 10.2 ng/dl, and only in 6 patients it was higher than 20.0 ng/dl.

Effectiveness of the drug treatment was evaluated before every injection of Octreotide-long using the serum PSA level, dynamics of performance status per the Karnofsky scale, quality of life, and pain syndrome per the World Health Organization Scale. Hematological control was regularly performed.

Prior to the Octreotide-long treatment, performance status per the Karnofsky scale was 80–100 % in 18 (26 %) patients, 60–70 % in 31 (45 %) patients, and 50–60 % in 20 (29 %) patients. It should be noted that patients after chemotherapy treatment initially had worse somatic status. Pain syndrome was absent in 5 (7.2 %) patients; in the majority of patients some pain was present, and only 9 (14.0 %) patients didn't require pain relievers. Twenty nine (29, 45.3 %) patients non-regularly took non-narcotic analgesics, 13 (20.3 %) took narcotic analgesics periodically to relieve pain, and 13 (20.3 %) required constant administration of opioid drugs.

The result of Octreotide-long treatment was considered positive if the serum PSA level decreased, complete blood count and comprehensive metabolic panel showed positive dynamics, pain syndrome decreased, and quality of life improved. Treatment continued until clinical progression or a significant (more than 50 % of the previous level) increase in the PSA level in 2 months, or an increase in the size of metastatic lesions by more than 20 %, or development of new lesions.

### Results and discussion

Analysis of the results of CRPC treatment with the depot form of Octreotide-long in combination with dexamethasone has shown that in both groups the majority of patients responded to treatment, though the duration of response without progression was longer in the prior-to-chemotherapy group. The number of cycles in the 1st group was between 2 and 25 (mean 6.8), in the 2nd – between 2 and 14 (mean 5.1).

Positive dynamics of the PSA level 3 months after the start of treatment were observed in 61.2 % of patients

in the prior-to-chemotherapy group and 36.8 % in the after-chemotherapy group. In the 1st group, a decrease in the PSA level by more than 50 % was reported in 41.9 % of patients, in the 2nd group in 28.9 % of patients. A decrease in the PSA level by more than 80 % in the 1st group was observed in 19.3 % of cases, in the 2nd – in 7.9 % of cases. Stabilization of the PSA level was reported in 9.8 % of patients in the 1st group and 23.7 % of patients in the 2nd group. In summary, overall response in respect to the PSA level (decrease + stabilization) was achieved in 70.9 % of patients receiving the Octreotide-long therapy before cytotoxic therapy and in 23.7 % of patients receiving the Octreotide-long therapy after chemotherapy (Table 2).

In the rest of observations (29.1 % in the 1st group and 39.5 % in the 2nd), no response to treatment in respect to the PSA level was observed. Disease progression was reported, and Octreotide-long was cancelled after 2 cycles. Response to treatment in respect to improved activity and performance status is presented in Table 3.

Objective and self-reported positive changes in the performance status were observed in 8 (25.8 %) patients in the 1st group and in 8 (21.0 %) patients in the 2nd group. Dynamics of pain syndrome in the course of treatment with Octreotide-long is presented in Table 4.

The presented data show that a decrease in pain syndrome in the course of treatment with Octreotide-long which plays a large part in improving the quality of life, was

**Table 2.** Dynamics of the level of prostatic-specific antigen in the course of Octreotide-long therapy

| Characteristic   | Octreotide-long prior to chemo-therapy (n = 31) |      | Octreotide-long after chemotherap (n = 38) |      |
|--|---|------|--|------|
|  | n   | %    | n  | %    |
| Overall response                                       | 22  | 70.9 | 23   | 60.5 |
| Decrease in the prostate-specific antigen level > 50 % | 13  | 41.9 | 11   | 28.9 |
| Decrease in the prostate-specific antigen level > 80 % | 6   | 19.3 | 3  | 7.9  |
| Stabilization of the prostate-specific antigen level   | 3   | 9.8  | 9  | 23.7 |

observed in 8 (25.8 %) patients in the 1st group and in 11 (28.9 %) patients in the 2nd group (more severe initially).

It should be noted, that in some patients, response in respect to the PSA level was observed only after the 2nd or even the 3rd therapy cycle. Therefore, an insignificant rise in the PSA level (less than 50 % compared to the previous result) and stabilization or improvement in clinical data should be considered a reason to continue the drug

**Table 3.** Dynamics of the performance status of patients receiving Octreotide-long therapy

| Karnofsky performance status, % | Octreotide-long prior to chemotherapy (n = 31) |                       | Octreotide-long after chemotherapy (n = 38) |                       |
|---------------------------------|--|-----------------------|---|-----------------------|
|                                 | before treatment, n (%)                        | after 3 months, n (%) | before treatment, n (%)                     | after 3 months, n (%) |
| 80–100. n = 18                  | 11 (36.5)                                      | 16 (51.6)             | 7 (18.4)                                    | 9 (23.7)              |
| 60–70. n = 31                   | 17 (54.8)                                      | 15 (48.4)             | 14 (36.8)                                   | 18 (47.4)             |
| 50–60. n = 20                   | 3 (9.7)  | 0                     | 17 (44.7)                                   | 11 (28.9)             |

**Table 4.** Characteristics of pain syndrome in the patient groups per the World Health Organization Scale

| Score | Octreotide-long prior to chemotherapy (n = 31) |                       | Octreotide-long after chemotherapy (n = 38) |                       |
|-------|--|-----------------------|---|-----------------------|
|       | before treatment, n (%)                        | after 3 months, n (%) | before treatment, n (%)                     | after 3 months, n (%) |
| 0     | 9 (29.0)                                       | 14 (45.2)             | 0   | 4 (10.5)              |
| 1     | 18 (58.0)                                      | 16 (51.6)             | 13 (34.2)                                   | 16 (42.1)             |
| 2     | 4 (12.9)                                       | 1 (3.2)               | 16 (42.1)                                   | 14 (36.8)             |
| 3     | 0  | 0                     | 9 (23.7)                                    | 4 (10.5)              |
| 4     | 0  | 0                     | 0   | 0                     |

therapy, because a later and long-term response in respect to the PSA level and performance status is possible.

An attempt to increase the dose of Octreotide-long from 30 mg to 40 mg in 2 patients due to an increase of the PSA level after long-term stabilization (more than 6 and 8 months, respectively) wasn't successful: progression continued while tolerance remained satisfactory.

Determination of the blood chromogranin A level in 8 patients with the goal to use it as a predictor of the response to Octreotide-long therapy for CRPC didn't yield any results: There was no correlation between its level and the rate of positive outcomes. It is possible that the number of observations was too low, or its level should be measured in the biopsied material.

Tolerance to Octreotide-long with dexamethasone was high, no significant side effects, hematological or clinical, were observed. There weren't any cases of treatment cancellation due to adverse effects.

### Conclusions

• Long-acting somatostatin analog Octreotide-long is an effective Russian drug allowing to achieve treatment

effect at dose 30 mg in combination with dexamethasone in 70.9 % of patients with CRPC.

• Therapy with long-acting somatostatin analogs is more effective and advisable in patients with CRPC prior to the 1st line chemotherapy with docetaxel. Overall response to treatment in respect to the PSA level (decrease + stabilization) was achieved in 70.9 % of patients in the prior-to-chemotherapy group and in 60.5 % of patients in the after-chemotherapy group.

• Duration of the response to therapy with Octreotide-long at dose 30 mg in combination with dexamethasone was also longer in prior-to-chemotherapy group. The number of treatment cycles in the 1st group varied from 2 to 25 (mean 6.8), in the 2nd – from 2 to 14 (mean 5.1).

• Octreotide-long is a safe and tolerable drug, therefore it can be used in older and weaker patients. No significant side effects or adverse events were observed during the course of combination therapy.

• Application of Octreotide-long at dose 30 mg once in 28 days in combination with dexamethasone is advisable in symptomatic and accompanying therapy of CRPC. This opens new possibilities of drug treatment of this prognostically unfavorable group of oncological patients.

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