THE ROLE OF DOCETAXEL AS FIRST-LINE CHEMOTHERAPY ON PSA LEVEL AND QOL IN CRPC PATIENTS

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ABSTRACT

Objective: *Prostate cancer is the second most common cancer in men and the fifth leading cause of death worldwide. 10-20% of cases can progress to a more aggressive stage called castration-resistant prostate cancer (CRPC) with a higher death rate. Clinical guidelines recommend docetaxel as first-line chemotherapy and evaluated using the PSA test. This study aims to investigate the effect of docetaxel chemotherapy on PSA levels in CRPC.* ***Material & Methods:*** *A retrospective study was conducted from January 2016 until August 2022 according to the medical records database Saiful Anwar Hospital. There were 16 patients who met the inclusion criteria, including male patients with a diagnosis of CRPC who received castration therapy and found an increase in PSA 3 times of nadir or found 2 or more bone metastatic lesions or soft tissue lesions > 2 cm, received 6 series of docetaxel chemotherapy, and have a PSA data was performed before and after chemotherapy. Statistical analysis was performed using a differential T-test.* ***Results:*** *The results, obtained were significantly different ($p<0.05$) on the average PSA (log) pre-post chemotherapy, visual analog scale (VAS), and quality of life, and not significantly different on BMI pre-post chemotherapy.* ***Conclusion:*** *6 cycles of docetaxel chemotherapy resulted in a decrease in PSA levels of CRPC significantly. It showed an excellent response to docetaxel chemotherapy in managing CRPC patients. Limitations of this study were specifically the retrospective cohort study model and the ability to reduce PSA levels in assessing the prognosis of CRPC.*

Keywords: *Castration-resistant prostate cancer, chemotherapy, docetaxel, prostate-specific antigen.*

ABSTRAK

Tujuan: *Kanker prostat adalah kanker paling umum kedua pada pria dan penyebab kematian kelima di dunia. 10-20% kasus dapat berlanjut ke tahap yang lebih agresif yang disebut kanker prostat yang resisten terhadap pengebirian (CRPC) dengan tingkat kematian yang lebih tinggi. Pedoman klinis merekomendasikan docetaxel sebagai kemoterapi lini pertama dan dievaluasi menggunakan tes PSA. Penelitian ini bertujuan untuk mengetahui pengaruh kemoterapi docetaxel terhadap kadar PSA pada pasien CRPC.* ***Bahan & Cara:*** *Studi retrospektif dilakukan dari Januari 2016 hingga Agustus 2022 berdasarkan database rekam medis RSUD Saiful Anwar. 16 pasien memenuhi kriteria inklusi, termasuk pasien laki-laki dengan diagnosis CRPC yang mendapatkan terapi kastrasi dan ditemukan peningkatan PSA 3 kali nadir atau ditemukan 2 atau lebih lesi metastasis tulang atau lesi jaringan lunak > 2 cm, mendapatkan 6 seri kemoterapi docetaxel, dan memiliki data PSA yang dilakukan sebelum dan sesudah kemoterapi. Analisis statistik dilakukan menggunakan uji-T diferensial.* ***Hasil:*** *Hasil analisis didapatkan perbedaan yang bermakna ($p<0.05$) pada rata-rata PSA (log) pre-post kemoterapi, visual analog scale (VAS), dan kualitas hidup, serta didapatkan perbedaan yang tidak bermakna pada IMT pre-post kemoterapi.* ***Simpulan:*** *6 siklus kemoterapi docetaxel menghasilkan penurunan kadar PSA CRPC secara signifikan. Ini menunjukkan respons yang sangat baik terhadap kemoterapi docetaxel dalam mengelola pasien CRPC. Keterbatasan penelitian ini meliputi model penelitian kohort retrospektif dan kemampuan penurunan kadar PSA dalam menilai prognosis CRPC.*

Kata kunci: *Castration-resistant prostate cancer, kemoterapi, docetaxel, prostate-specific antigen.*

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INTRODUCTION

Prostate cancer is the second most common cancer suffered by men worldwide. The incidence was estimated at 900.000 cases with 258.000 deaths in 2008. This occurs due to population aging and increasing the PSA test in prostate cancer screening. In asymptomatic patients with elevated PSA, prostate tissue biopsy is recommended to perform for early detection.[1,3] Almost all prostate cancers lead

to progression despite clinical improvement with initial treatment. This shows the resistance of prostate cancer to anti-androgen hormonal therapy.[3-4]

According to The European Association of Urology, The CRPC criteria are serum testosterone castrate < 50 ng/dL or 1.7 nmol/L and either: a. Biochemical progression: Three consecutive rises of PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on a bone scan or a soft tissue lesion by RECIST (Response Evaluation Criteria in Solid Tumors).[5] 10 – 20% of prostate cancer develop CRPC within 5 years.[6] This Progression increases patient morbidity and mortality, with median survival ranging from 9 to 30 months. This is accompanied by a decrease in patients' quality of life with complaints of pain, nausea, vomiting, shortness of breath, and decreased appetite.[7]

Docetaxel is a chemotherapy that has been shown to increase the survival of CRPC patients in 2 previous phase III clinical trials, namely the TAX327 and SWOG 9916 clinical trials.[3-4] Docetaxel can be given alone or in combination with prednisone or estramustine.[4,8] The recommended dosage are 75 mg/m^2 every 3 weeks or 30 mg/m^2 per week for 5-6 weeks.[3] Docetaxel be given within 6 to 10 cycles to achieve an optimal response without increasing the risk of toxicity.[9]

Evaluation of chemotherapy response can use various clinical and laboratory parameters such as Gleason score, presence of visceral metastases, pain complaints, prostate-specific antigen (PSA) nadir levels, hemoglobin levels, albumin, lactate dehydrogenase (LDH), Alkaline phosphatase (ALP), number of chemotherapy cycles. , neutrophil to lymphocyte ratio (NLR), and duration for castration resistance to occur.[2,9,10] PSA levels are related to tumor grade and patient clinical outcomes, mostly used in evaluating chemotherapy response and prognosis of CRPC patients.[10] and PSA kinetics is a significant predictor in assessing response to therapy, disease progression and survival of prostate cancer patients.[10]

PSA evaluation is recommended to be performed after the patient has undergone at least 4 chemotherapy regimens. Failure to achieve improvement in PSA levels is an indication for discontinuation and replacement of CRPC therapy regimens.[11] Therefore in this study, we observed how docetaxel chemotherapy affects changes in PSA levels in CRPC patients.

MATERIAL & METHODS

This research is a retrospective cohort study based on medical records of CRPC patients. The inclusion criteria are male patients with a diagnosis of CRPC who received castration therapy and found an increase in PSA 3 times of nadir or found 2 or more bone metastatic lesions or soft tissue lesions > 2 cm, received 6 series of docetaxel chemotherapy, and have a PSA data was performed before and after chemotherapy. Meanwhile, the exclusion criteria for research subjects were CRPC patients who had not completed the docetaxel 6 series of chemotherapy.

In addition, the patient's pain assessment was analyzed using the Visual Analog Scale (VAS), and quality of life used the Functional Assessment of Cancer Therapy General (FACT-G) version 4 questionnaire. The data has been collected and then analyzed by descriptive data and analytical correlation using a paired T-test. Paired T-test is carried out compare PSA value before and after chemotherapy.

RESULTS

There were 16 subjects who fit the inclusion-exclusion criteria. All subjects in the study went through 6 cycles of chemotherapy according to hospital service standards. The median age of CRPC patients was 67 years in the 59-79 year range. The subjects studied had various stages of cancer, 4 subjects were at stage T2cNxM1b. The median pre-chemotherapy PSA was 80.12 ng/ml and 19.70 ng/ml post-chemotherapy. In addition, the median BMI before chemotherapy (20.92 kg/m^2) has more slightly than the median BMI after chemotherapy (21.20 kg/m^2).

The average value of PSA (log) before undergoing chemotherapy was 1.78 ± 0.70 units. The average PSA value (log) after chemotherapy was 1.21 ± 0.97 units. There was a decrease in the post-chemotherapy PSA value (log) of 0.565 units with a significant value (p = 0.035) (Table 2).

The average PSA (log) during pre-chemotherapy was higher than the PSA (log) during post-chemotherapy. The difference in PSA (log) between pre and post-shows is significant difference. The correlation test showed a correlation coefficient value of 0.354 with p = 0.178, so it can be

concluded there was no significant relationship between PSA (log) in pre and post. The lowest and highest PSA values before chemotherapy were 2.52 and 1360 respectively. The lowest PSA values after chemotherapy were 0.74.

The mean visual analog scale (VAS) before and after therapy was significantly different. The average value of VAS before and after chemotherapy was statistically significantly different. The VAS value before chemotherapy was 5.23 ± 0.34 and after chemotherapy, it was 3.22 ± 0.34 units. (p = 0.04) (Table 3).

The average value of body mass index (BMI) before and after chemotherapy was not statistically significantly different. The mean value of BMI before chemotherapy was 20.92 ± 1.70 kg/m^2 and after chemotherapy, it was 21.20 ± 1.40 kg/m^2 (p=0.075). (Table 4).

The degree of quality of life (QoL) shows different results which are statistically significantly different. The QoL degree value before chemotherapy was 55.78 ± 1.70 and after chemotherapy, the QoL degree value was 76.56 ± 6.78 (p = 0.03) (Table 5).

Table 1. Baseline characteristic of the study.

		Docetaxel	
		(n: 16)	%
Age Median (range)		67 (59-79)	
T Stage	1	1	6.25
	2	10	62.5
	3	3	18.75
	4	2	12.5
Nodal Status	0	3	18.75
	Positive	12	75
	Unreported	1	6.25
Metastatic	M0	3	18.75
	M1	13	81.25
PSA pre-chemotherapy Median (range) ng/ml		80.12 (3-1360)	
PSA post-chemotherapy Median (range) ng/ml		19.70 (1-1836)	
BMI pre-chemotherapy Median (SD)		20.92 (1.70)	
BMI post-chemotherapy Median (SD)		21.20 (1.40)	

SD: Standart Deviation, PSA: Prostate Specific Antigen, BMI: Body Mass Index

Table 2. PSA comparison (log) between pre and post-chemotherapy.

Variable	Pre	Post	Average difference	p[a]	p[b]
PSA (log)	1.78 ± 0.70	1.21 ± 0.97	0.565	0.035	

[a] By paired t-test [b] By correlation test

Table 3. Visual analog scale (VAS) values between pre and post chemoterapy.

Variable	Pre	Post	p
VAS [a]	5.23 ± 0.34	3.22 ± 0.34	0.04

[a] By paired t-test

Table 4. The average value of body mass index (BMI) between pre and post-chemoterapy.

Variable	Pre	Post	p
Body Mass Index (BMI)[a]	20.92 ± 1.70	21.20 ± 1.40	0.075

[a] By paired t-test

Table 5. The average value of quality of life (QoL) between pre and post-chemoterapy.

Variable	Pre	Post	Nilai p
Quality of Life (QoL)[a]	55.78 ± 1.70	76.56 ± 6.78	0.03

[a] By paired t-test

DISCUSSION

Prostate cancer is a high morbidity and mortality disease.[12] The PSA in clinical services helps improve early detection and survival among prostate cancer patients, but most of them have developed in advanced or metastatic stages when diagnosed.[10] Castration-resistant prostate cancer (CRPC) is an advanced stage of prostate cancer characterized by disease progression, sustained increase in PSA levels, or the emergence of new metastases.[1] Treatment to reduce androgen levels is the main modality for prostate cancer, but it has a low response treatment, especially in CRPC.[12]

The results showed a significant decrease in PSA levels after chemotherapy compared to before chemotherapy with 62.5% of subjects having a PSA response rate (PSA RR) ≥ 50%. This shows that the CRPC patients in this study responded well to docetaxel chemotherapy.[13] These results are suitable with previous studies which showed that docetaxel chemotherapy, either alone or in combination with prednisone or estramustine, responded to a significant reduction in PSA levels.[1,10,14] The TAX327 clinical trial demonstrated a higher PSA response in CRPC patients receiving docetaxel (45% on docetaxel therapy per 3 weeks, and 48% on docetaxel therapy per week) compared to CRPC patients receiving mitoxantrone (32%).[4] The SWOG 9916 clinical trial showed that the administration of chemotherapy to docetaxel significantly reduced PSA levels accompanied by a 20% decrease in the risk of death and an increase in OS up to 18 weeks in CRPC.[8]

Research by Tannock et al. (2004) also showed an increase in PSA levels accompanied by quality of life improvement and survival of CRPC patients after receiving docetaxel chemotherapy per 3 weeks with prednisone compared to mitoxantrone.[15] Observation of decreased levels of PSA and PSA RR is useful in assessing the response to docetaxel chemotherapy in the early phase to assist in making decisions to continue or replace chemotherapy.[10] A significant decrease in PSA levels describes cancer cell death due to chemotherapy regimens found in CRPC patients.[2] CRPC patients who do not experience improvement in their PSA levels after at least 4 cycles of chemotherapy are recommended to stop docetaxel and replace alternative therapy regimens.[11]

Evaluation of the response to docetaxel chemotherapy for CRPC is recommended to be carried out after the patient has gone through 6 cycles of chemotherapy.[9] This is useful in preventing side effects due to docetaxel toxicity in prolonged therapy cycles.[10] All patients in this study received 6 cycles of docetaxel chemotherapy, according to the guidelines of the National Institute for Health and Clinical Excellence (NICE) which recommends docetaxel chemotherapy for no more than 10 cycles.[2]

This study shows that PSA levels after chemotherapy are not related to PSA levels before chemotherapy. This is following the research of Pei et al. (2019) which showed that there was an insignificant relationship between PSA levels before and after chemotherapy.[9] The theoretical basis of this discovery is the role of the transcriptional effect of chemotherapy in inhibiting PSA production which also causes a decrease in PSA levels, in addition to prostate cancer cell death.[2] However, a decrease in PSA and PSA RR levels ≥ 50% is a good predictor in assessing the response to docetaxel chemotherapy in CRPC because it has a significant relationship with the inhibition of CRPC development.[10]

This study has limitations, specifically the retrospective cohort study model and the ability to reduce PSA levels in assessing the prognosis of CRPC. Although reduced PSA and PSA RR levels can be useful in assessing the response to docetaxel chemotherapy, there is no significant relationship between reduced PSA levels and the OS of CRPC patients.[9] Then, the assessment of decreased PSA

levels after 6 cycles of chemotherapy is more recommended as an evaluation of chemotherapy response than an evaluation of the prognosis of CRPC.[12]

Meanwhile, PSA RR has a significant correlation with CRPC OS so it can be an easier, cheaper, and shorter alternative in assessing the long-term prognostics of CRPC patients.[10]

CONCLUSION

Docetaxel is the first-line chemotherapy for CRPC. PSA kinetics in the form of reduced levels of PSA and PSA RR determines the evaluation of the response to chemotherapy recommended after 6 cycles. Discontinuation and switching to CRPC therapy regimens is recommended if there is no change in PSA levels after at least 6 cycles of therapy. 6 cycles of docetaxel chemotherapy resulted in a decrease in PSA levels of CRPC significantly. So this shows an excellent response to docetaxel chemotherapy in managing CRPC patients. This study has limitations, specifically the retrospective cohort study model and the ability to reduce PSA levels in assessing the prognosis of CRPC. Going forward, we need multicenter and prospective studies with more extensive research scopes for better correlation analysis.

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