The Role of Docetaxel in Non-Castrate Resistant Metastatic Prostate Cancer: An Evidence-based Case Report

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ABSTRAK

Tujuan: *untuk mengetahui peran docetaxel pada pasien kanker prostat metastasis non-castrate resistant.* ***Metode:*** *penelusuran literature dilakukan untuk mencari studi mengenai perbandingan antara kombinasi docetaxel dan terapi deprivasi androgen (ADT) dengan ADT pada pasien kanker prostat metastasis non-castrated resistant. Penelusuran dilakukan dengan menggunakan PubMed, Cohrane Library, Proquest, EBSCO, and Scopus. Penilaian kualitas literature dilakukan dengan menggunakan Bond University Rapid Critical Appraisal of a Systematic Review.* ***Hasil:*** *kami menemukan 494 studi dari penelurusan literature, namun hanya 2 studi yang sesuai dengan kriteria seleksi. Berdasarkan analisis validitas, kami memilih satu studi untuk dapat dibahas secara lebih lanjut. Studi ini menunjukkan bahwa kombinasi docetaxel dan ADT lebih baik dari ADT dalam angka kesintasan secara umum (HR 0,64; 95% CI 0,55, 0.75; p<0,0001; NNT=3), angka kesintasan bebas progresi biokimia (HR 0,63; 95% CI 0,57, 0,69; p<0,0001; NNT=2), dan angka bebas progresi klinis (HR 0,73; 95% CI 0,64, 0,84; p<0,0001; NNT=2). Keuntungan dari kombinasi docetaxel dan ADT terutama terlihat pada kanker prostat dengan volume tinggi (HR 0,67; 95% CI 0,54, 0,83; p=0,0003; NNT=3).* ***Kesimpulan:*** *penambahan docetaxel pada ADT memiliki efek yang menguntungkan dalam angka kesintasan secara umum dan angka bebas progresi pada kanker prostat metastasis non-castrated resistant.*

Kata kunci: *Docetaxel, terapi deprivasi androgen, evidence-based case report, kanker prostat metastasis, angka kesintasan.*

ABSTRACT

Aim: *to learn the role of docetaxel in non-castrate resistant prostate cancer patient.* ***Methods:*** *literature search was conducted to find relevant study comparing the combination of docetaxel and androgen deprivation therapy (ADT) to ADT alone in non-castrate resistant prostate cancer using PubMed, Cohrane Library, Proquest, EBSCO, and Scopus database. Quality assessment of studies was done using Bond University Rapid Critical Appraisal of a Systematic Review.* ***Results:*** *we found 494 studies from literature search, but only two studies were included in final selection. Based on validity assessment, we chose one study to be discussed further. This study showed that combination of docetaxel and ADT is better than ADT alone in regards of overall survival (HR 0.64; 95% CI 0.55, 0.75; p<0.0001; NNT=3), biochemical progression free survival (HR 0.63; 95% CI 0.57, 0.69; p<0.0001; NNT=2) and clinical progression free survival (HR 0.73; 95% CI 0.64, 0.84; p<0.0001; NNT=2). Benefit of docetaxel and ADT combination was especially seen in high volume disease (HR 0.67; 95%*

CI 0.54, 0.83; p=0.0003; NNT=3). ***Conclusion:*** *addition of docetaxel into ADT has beneficial effects in terms of overall survival and progression free survival in patients with non-castrate resistant metastatic prostate cancer.*

Keywords: *Docetaxel, androgen deprivation therapy, evidence-based case report, metastatic prostate cancer, overall survival.*

INTRODUCTION

Prostate cancer (PCa) is the fourth most common cancer with more than three hundred thousand death worldwide.[1] Compared to North America and Europe, Asia has much lower incidence and mortality rates, but its incidence keeps increasing.[2,3] In Indonesia, PCa has become the third most common cancer in men after lung and colorectal cancer.[4]

In developing country, like Indonesia, metastatic prostate cancer is still a problem. Data from Indonesia Society of Urologic Oncology (ISUO) showed that stage 4 prostate cancer was the most common form of prostate cancer found (50.5%).[5] Median survival of metastatic prostate cancer is 42 months. Until today, standard protocol for metastatic prostate cancer is androgen deprivation therapy (ADT), either surgical or hormonal.[6] However, this treatment will lead into castrate-resistant prostate cancer, which has poorer prognosis.

Docetaxel is a well-known treatment for castrate-resistant prostate cancer.[6] However, its efficacy in non-castrate resistant metastatic prostate cancer still in question.

CLINICAL QUESTION

Male, 63 years old, was referred from another hospital due to high prostate specific antigen (PSA) level and was planned to do prostate biopsy. In general, patient did not have any serious complaint, had very well general appearance with 100 Karnofsky score, and normal physical examination. However, we found hard prostate palpation on digital rectal examination. From lab analysis, he had normal range lab parameter, except for total PSA level, whichreached 600.8 ng/ml. Patient underwent prostate biopsy and bone scan examinations. Prostate biopsy result showed that patient had prostate adenocarcinoma with Gleason score 4+5=9, whereas his bone scan indicates dissemination of prostate cancer into more than 5 bone lesions which involved parietal, scapula, costae, vertebrae, sacrum, and femur bone. Therefore, the patient was diagnosed with prostate adenocarcinoma T2c N0 M1b with Gleason score 4+5 = 9.

Patient was planned to receive androgen deprivation therapy with combination of goserelin acetate 10.8 mg every 3 months and bicalutamide 50 mg daily, which are our standard protocol in treating patient with metastatic prostate cancer. However, we have read one article which stated that the addition of docetaxel into standard treatment have beneficial outcome in metastatic prostate cancer patient. Therefore, the aim of this study is to learn theeffect of docetaxel addition into standard treatment in non-castrate resistant metastatic prostate cancer patient.

We proposed this following question to be answered in this study: could addition of docetaxel into androgen deprivation therapy provides beneficial effect regarding overall survival and progression free survival for non-castrate resistant metastatic prostate cancer patient?

METHODS

To answer our clinical question, we conducted systematic literature searching using PubMed, Cohrane Library, Proquest, EBSCO, and Scopus database on October 16th, 2016 (**Table 1**). Collected studies retrieved from literature searching, was then screened for duplication using EndNote X6. We only included interventional studies or meta-analysis of interventional studies and the studies must be written in English. Four reviewers independently reviewed all title and abstracts. Studies which fulfilled the criteria underwent full text screening. Interventional studies already included in meta-analysis will be excluded from our included studies. A priori, we decided to choose the best

Table 1. Literature searching

Search Engine	Search Terms
Pubmed	(((((metastatic prostate cancer) AND (chemotherapy OR docetaxel)) AND androgen deprivation therapy) AND overall survival)) NOT "castration resistant prostate cancer"
Cochrane Library	'metastatic prostate cancer in Title, Abstract, Keywords and docetaxel OR chemotherapy in Title, Abstract, Keywords and androgen deprivation therapy in Title, Abstract, Keywords and survival in Title, Abstract, Keywords'
Proquest	All (metastatic prostate cancer) AND all((chemotherapy OR docetaxel)) AND all(androgen deprivation therapy) AND all(survival) NOT all("castration resistant prostate cancer")
Scopus	(TITLE-ABS-KEY (metastatic prostate cancer) AND TITLE-ABS-KEY (chemotherapy OR docetaxel) AND TITLE-ABS-KEY (androgen deprivation therapy) AND TITLE-ABS-KEY (survival) AND NOT TITLE-ABS-KEY ("castration resistant prostate cancer"))
EBSCO	Metastatic prostate cancer AND (chemotherapy OR docetaxel) AND androgen deprivation therapy AND survival NOT "castration resistant prostate cancer"

study to discussed based on validity assessment and publication year if we found more than one systematic review and meta-analysis studies.

Critical Appraisal

Included studies were critically appraised by four reviewers independently using critical appraisal sheet by Center for Evidence-Based Medicine[7] for interventional study and Bond University Rapid Critical Appraisal of a Systematic Review[8] for systematic review and meta-analysis study. The results of the studies' critical appraisal were discussed among authors to choose final selected studies.

RESULTS

Results of literature searching and study selection could be seen in **Figure 1**.

We found 494 studies from literature searching. After we conducted title-abstract and full text screening, six studies were included. However, four studies, which are Gravis et al.[9,10] Sweeney et al.[11] and James et al.[12] were already discussed in meta-analysis included in this study. Therefore, we had two studies to be further analyzed.

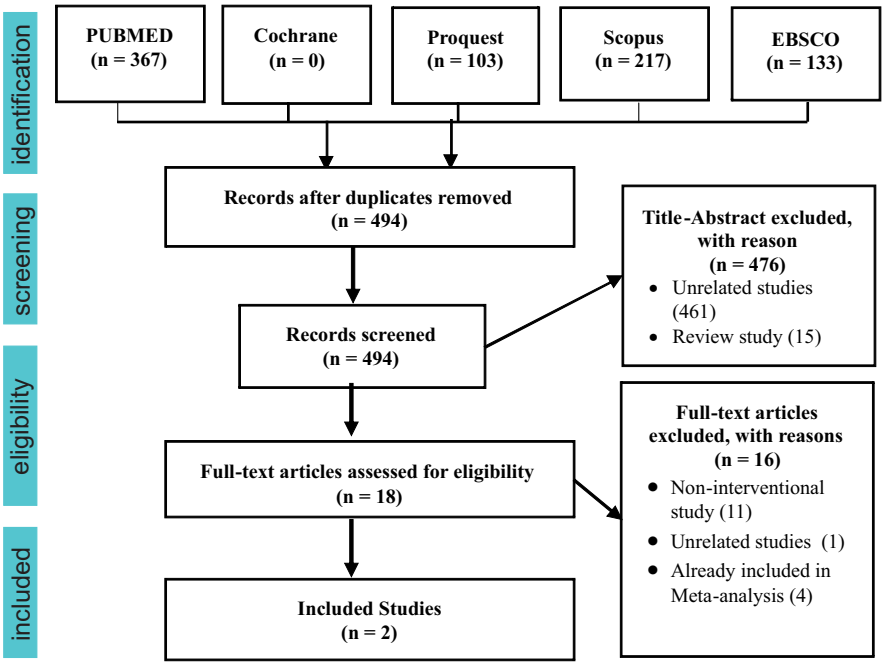

Figure 1. Flow chart of search strategy

Table 2. Subject's baseline characteristic in Docetaxel + ADT group

Characteristics	Gravis et al[1,2]	Sweeney et al[3]	James et al[4]
Number of subjects (n)	192	397	362
Median age (years)	63 (IQR 57-68)	64 (range 36-88)	65 (IQR 61-71)
Median performance status	Karnofsky score 100 (IQR 90-100)	ECOG 0-2	WHO performance score
Median PSA (ng/ml)	26.7 (IQR 5.0-106.2)	50.9 (range 0.2-8540.1)	0-2
Gleason Score			70 (IQR 27-181)
- ≤6	10%	6%	
- 7	35%	27%	≤ 7 = 20%
- ≥8	55%	67%	74%
Unknown	-	-	9%
Median follow up (months)	83.9	29	42

Two studies included in the final selection had similar clinical question with ours. We found that both studies had similar included study. However, Botrel et al.[13] also compared docetaxel and ADT to ADT alone in regard of its safety. Subject's baseline characteristic of included study and results of validity assessment are shown in **Table 2** and **Table 3**, respectively.

After discussion among authors, we decided to choose Botrel et al.[13] to be discussed further based on its validity assessment.

Botrel et al.[13] included 3 studies with a total of 2262 subjects. Median follow up ranges 29–83.9 months. All studies using docetaxel protocol as 75 mg/m^2 every 3 weeks with maximum of nine cycles in study conducted by Gravis et al.[10], maximum six cycles in Sweeney et al.[11], and six cycles with additional 10 mg of prednisolone in James et al[12]. This study showed that combination of docetaxel and ADT is better than ADT alone in regards of overall survival (HR 0.64; 95% CI 0.55, 0.75; p<0.0001; NNT=3), biochemical progression free survival (HR 0.63; 95% CI 0.57, 0.69; p<0.0001; NNT=2) and clinical progression free survival (HR 0.73; 95% CI 0.64, 0.84; p<0.0001; NNT=2). This study also conducted subgroup analysis which compared high volume disease (presentation of four or more bone metastatic lesion with at least one beyond the vertebral bodies and pelvis or visceral metastasis) and low volume disease in terms of overall survival. Benefit of docetaxel and ADT combination was seen in high volume disease (HR 0.67; 95% CI 0.54, 0.83; p=0.0003; NNT=3), but not in low volume disease (HR 0.87; 95% CI 0.61, 1.23; p=0.42). The results of all pooled analysis were homogeny, except for subgroup analysis which were low-moderate heterogeneity.

Table 3. Level of evidence and validity assessment

Author	LOE	Validity[a]				Validity score
		Q	F	A	S	
Tucci et al, 2015[14]	1a	+	+	-	+	3/4
Botrel et al, 2016[13]	1a	+	+	+	+	4/4

LOE, level of evidence; Q, focused PICO and use it to direct the search; F, find all the relevant evidence; A, studies appraisal by more than one reviewer; S, summary tables/plots and similarity between studies.
[a] Validity assessments were done using Bond University Rapid Critical Appraisal of a Systematic Review.

DISCUSSION

Androgen deprivation therapy is a metastatic prostate cancer standard treatment since Huggins and Hodges found that castration could lead into regression of metastatic prostate cancer in 1941.[15] However, the search for better treatment continues until today. In this study, based on meta-analysis conducted by Botrel et al.[13] we found that additional of docetaxel to androgen deprivation therapy in non-castrate resistant prostate cancer patient had positive impact in regards of overall survival and progression free disease. We also found that this beneficial effect is especially seen in metastatic prostate cancer with high volume disease.

Baseline characteristics of our patient were similar with baseline characteristic of study included in meta-analysis (**Table 3**) in terms of age, performance status and Gleason score. However, our patient had higher pre-treatment PSA compared to study included in meta-analysis. Unfortunately, there was no subgroup analysis which analyzed treatment outcome based on pre-treatment PSA.

Even though positive outcome was shown by additional of docetaxel, we had to consider possible adverse outcomes, which might appear. Botrel et al.[13] also compared potential adverse outcome between combination of docetaxel and ADT to ADT alone. This study showed that addition of docetaxel to ADT had higher risk in developing neutropenia (RR=108.78; 95% CI 15.25-775.80; p<0.0001, NNH=6), febrile neutropenia (RR 38.87; 95% CI 5.35-282.20; p=0.0003; NNH=17) and fatigue (RR=108.78; 95% CI 3.26-42.69; p=0.0002; NNH=20).

Furthermore, additional cost would be another problem for this combination therapy. In Indonesia, both docetaxel and ADT are covered by national health care security (BPJS Kesehatan). However, the combination of both treatments has not become a standard protocol yet in Indonesia health care system. Moreover, it also would become a potential problem from legal point of view in Indonesia.

Considering both pros and cons previously stated above, we still recommend the addition of docetaxel to our patient since it has beneficial effect, especially in patients with high volume disease which was seen in our patients. However, we had to provide clear explanations to our patient regarding the potential adverse effect and its cost.

CONCLUSION

From this study, we conclude that additional of docetaxel into ADT has beneficial effects in terms of overall survival and progression free survival in patients with non-castrate resistant prostate cancer.

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