CORRELATION BETWEEN ALDEHYDE DEHYDROGENASE 1A1 LEVEL AND BONE METASTASIS IN PROSTATE CANCER

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ABSTRACT

Objective: To determine the association between Aldehyde Dehydrogenase 1A1 (ALDH1) expression and metastasis in prostate cancer. **Material & methods:** This study was a prospective study in 45 patients diagnosed with prostate cancer in Sardjito General hospital. Patient characteristics and patient clinical data were recorded. Paraffin blocks of 45 patient surgery results were performed with immunohistochemical staining with monoclonal antibody of anti ALDH1A1 (EP1933Y, Biocare, dilution 1: 200). ALDH1 expression differences between prostate cancer without metastases and prostate cancer with metastasis was compared and analyzed with Chi-square. **Results:** This study involved 45 prostate cancer patients with median of age of 74 years. A high Gleason scores was found in 25 (55.6%) patients with prostate cancer and 24 (53.3%) patients had metastasis to the bone. The high expression of ALDH1 was found in 30 (66.7%) patients. The incidence of bone metastasis in patients with prostate cancer was associated with high levels of ALDH1 (p < 0.001, OR, 95% CI 17.88 (3.28-97.83) and was not associated with Gleason score (p = 0.316). **Conclusion:** Prostate cancer cells with high ALDH1A1 level increased the risk of the incidence of bone metastasis. ALDH1A1 level in prostate cancer cells can be considered as a predictor factor of the bone metastasis in prostate cancer.

Keywords: Aldehyde Dehydrogenase 1A1, prostate cancer, bone metastasis.

ABSTRAK

Tujuan: Untuk mengetahui adanya hubungan ekspresi Aldehyde Dehydrogenase 1A1 (ALDH1) dengan metastasis pada kanker prostat. **Bahan & cara:** Studi ini dilakukan secara prospektif, dengan subjek 45 pasien yang terdiagnosis kanker prostat di Rumah Sakit Umum Pusat Dr. Sardjito. Karateristik pasien dan data klinis pasien dicatat. Parafin blok dari 45 hasil operasi pasien, dilakukan pengecatan imunohistokimia dengan antibodi monoklonal anti ALDH1A1 (EP1933Y, Biocare, pengenceran 1:200). Perbedaan ekspresi ALDH1 antara kanker prostat tanpa metastasis dan kanker prostat dengan metastasis akan dibandingkan dan akan dianalisis dengan Chi-square. **Hasil:** Sebanyak 45 pasien kanker prostat sebagai subjek pada penelitian ini, median usia 74 tahun. Gleason skor tinggi ditemukan pada 25 (55.6%) pasien kanker prostat dan 24 (53.3%) pasien mengalami metastasis ke tulang. Ekspresi ALDH1 yang tinggi ditemukan pada 30 (66.7%) pasien. Kejadian metastasis tulang pada pasien dengan kanker prostat berhubungan dengan tingginya kadar ALDH1 (p < 0.001, OR, IK 95% 17.88 (3.28 – 97.83) dan tidak berhubungan dengan skor gleason (p = 0.316). **Simpulan:** Sel kanker prostat dengan level ALDH1A1 tinggi meningkatkan risiko kejadian metastasis tulang. Level ALDH1A1 pada sel kanker prostat dapat dipertimbangkan sebagai faktor prediktor metastasis tulang pada kanker prostat.

Kata kunci: Aldehyde Dehidrogenase 1A1, kanker prostat, metastasis tulang.

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INTRODUCTION

Prostate cancer is the second most-common cancer in men in the world, and ranks fifth leading cause of death from cancer in men.[1] The treatment of prostate cancer depends on the stage of the disease, resulting in various clinical outputs.[2] Although prostate cancer at an early stage can be eradicated with radical prostatectomy or radiotherapy, no curative treatment is available for cancer that has metastasized. The incidence of metastasis, especially metastasis of prostate cancer to bone is up to 90% of the total population of patients with end-stage, which will lead to high rates of morbidity and

mortality of prostate cancer.[3] Therefore, prognostic marker is very necessary to identify a possible prostate cancer that will be aggressive and will be high potential for early metastasis.

The recent research revealed that a more tumorigenic fraction of prostate cancer cells existed in prostate tissue resulted from surgery, could grow faster, had the ability for self-regenerating, and was capable of being more metastatic and invasive.[3-6] Some researchers believed that cancer cells were able to resemble stem cells, so that it was called stem cell-like cancer of the prostate or the Cancer Stem Cell (CSC).

So far, marker which can identify CSC in prostate cancer continued to be developed. Lately a new candidate for CSC in the prostate was proposed. Aldehyde dehydrogenase 1A1 (ALDH1) had a role in the early differentiation of stem cells through its function to oxidize retinol into retinoic acid. In some previous studies, ALDH1 was proposed to be the perfect candidate for the CSC identification in prostate cancer.[7-10] Prostate cancer cells with high ALDH1 content had been shown to have the clonal ability and high tumorigenic both in vitro and in vivo.[5]

The association between ALDH1 and metastasis capability had been demonstrated in several cancers, such as colon, breast, lung, and acute myeloid leukemia.[11-13] The high expression of ALDH1 in prostate was proven to increase the migration of cancer cells in vitro and to improve metastasis capability in vivo.[3]

In this study, we examined differences in ALDH1 expression between prostate cancer without metastasis and prostate cancer with metastasis. This marker was expected to use as a prognostic marker for the possibility of metastasis in prostate cancer, and also might be used as a therapeutic target to prevent metastasis of these cancers.

OBJECTIVE

To determine the association between Aldehyde Dehydrogenase 1A1 (ALDH1) expression and metastasis in prostate cancer.

MATERIAL & METHODS

The design of this study was a prospective study. The subjects of this study were 45 male patients diagnosed with prostate adenocarcinoma at Dr. Sardjito Hospital. The information recorded would include: Medical Record number, age, clinical diagnosis, metastasis, and the anatomic pathology result. Paraffin blocks of prostate tissue from each patient would be stained with immunohistochemistry. Antibody used was a monoclonal antibody of anti ALDH1A1. Male patients diagnosed with prostate adenocarcinoma were included. Male patients recognized to have other malignancies and Paraffin blocks with a focus on small tumors (< 5 per field of view) were excluded. HE preparation was examined to confirm the diagnosis of prostate cancer. Paraffin tissue blocks were processed by immunohistochemical staining (IHC) using a monoclonal antibody anti ALDH1A1 (EP1933Y, Biocare, dilution 1: 200). ALDH1 expression would be checked by two criteria: 1. Intensity (ALDH1 intensity would be assessed at the 5 fields of view with the following scale: no visible staining: 0, cryptic staining: 1, medium staining: 2, and strong staining: 3). 2. Percentage (The percentage of cells with positive staining was assessed with a value of 0, < 10, 10-25, 25-50, 50-75%, and > 75% (value of 0, 1, 2, 3, 4, 5)). The final score was obtained by multiplying the two scores above. Then, ALDH1 expression was grouped into two levels; low ALDH1 (specimen has a score < 2), and high ALDH1 (specimen with a score ≥ 2).[5] To analyze ALDH1 expression the researcher used SPSS 15.0 software. The correlation between ALDH1 expression and prostate cancer with metastatic prostate cancer and without metastases was examined using Chi-square test ($p < 0.05$).

RESULTS

This study involved 45 patients with median of age of 74 years and mean of age of 70.9 years. A high Gleason score (8-10) was found in 25 (55.6%)

Table 1. Characteristics of the research variable.

Variable	
Age, median (x ± SD)	74 (70.96 ± 8.70)
Gleason score, median (x ± SD)	8 (7.36 ± 2.06)
Low (≤ 7), n (%)	20 (44.4)
High (8-10), n (%)	25 (55.6)
ALDH1, n (%)	
Low	15 (33.3)
High	30 (66.7)
Bone Metastasis, n (%)	
Yes	24 (53.3)
No	21 (46.7)

Table 2. Bivariate analysis

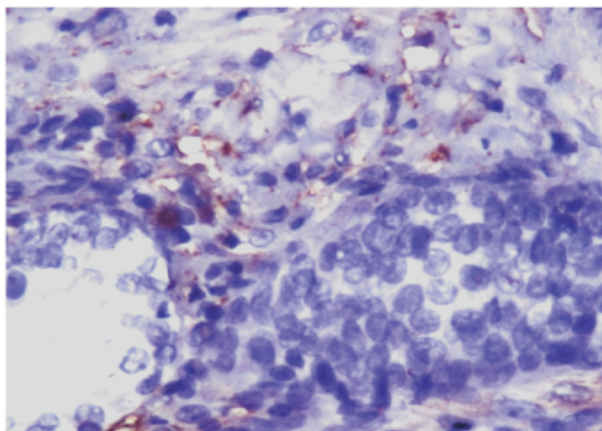| Variable	Bone Metastasis		OR, CI 95%	p
	Yes	No		
Gleason				
High (8-10)	15	10	1.83 (0.56-6.03)	0.316
Low (≤7)	9	11		
ALDH1				
High	22	8	17.88 (3.28-97.30)	< 0.001
Low	2	13		

Figure 1. A low expression of ALDH1A1 in prostate carcinoma.
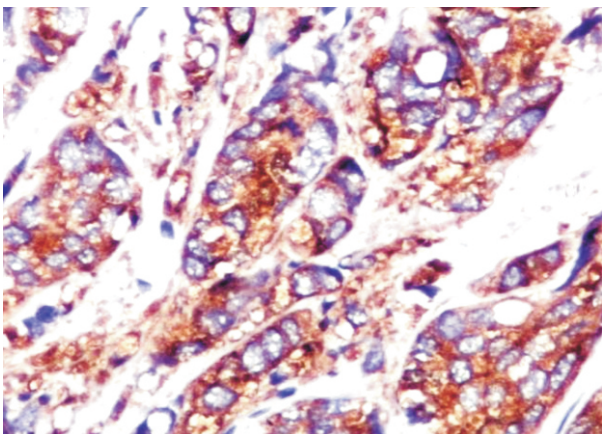

Figure 2. High Expression of ALDH1A1 in prostate carcinoma.

and low Gleason score (2-7 score), patients with prostate cancer and as many as 24 (53.3%) patients had metastasis to the bone. After examination, Immuno-histochemistry using monoclonal antibodies anti

ALDH1A1 (EP1933Y, Biocare, dilution 1: 200) was performed. High expression of ALDH1 was found in 30 (66.7%) patients.

The incidence of bone metastasis in patients with prostate cancer was associated with high and low Gleason score (p = 0.316). The level of ALDH1 was associated with bone metastasis in prostate cancer patients (p < 0.001, OR, 95% CI 17.88 (3.28-97.83).

DISCUSSION

Aldehyde dehydrogenase (ALDH) is an enzyme that functions in biosynsthesis retinoic acid, detoxification ability, the development of epithelial homeostasis, drug resistance, cell proliferation, differentiation, and response to oxidative stress. In humans, 19 ALDH enzyme isoforms had been found, one of which was Aldehyde Dehydrogenase 1A1 (ALDH1).[3,5] High content of ALDH1 was originally found in blood stem cell and normal nerve cells, which capable of high self-regenerating and multipotency. The content of high ALDH1 in most cancer cells was thought to make such cancer cells have ability as stem cells have the ability, so that some researchers referred to cancer cells as the Cancer Stem Cell (CSC). In studies with mice, the results of xenograft prostate cancer cells with high ALDH1 content demonstrated the ability to spread more rapidly at 100 times than the prostate cancer cells with low ALDH1 content.[5]

The high content of Aldehyde Dehydro-genase in cancer cells was associated with tumoro-genicity and metastasis ability. Cyclophosphamide chemotherapy resistance in breast cancer was associated with high levels of ALDH1.[14]

In this study, a high content of ALDH1 was not associated with Gleason score (p = 0.316). This

result was consistent with the previous study involving 30 samples.[3] In the other studies, however using larger sample of 71 samples,[15] and 99 samples,[5] a significant association between the content of ALDH1 and Gleason score was found.

The association between high level of ALDH1 in prostate cancer and the bone metastasis incidence in this study was significant (p < 0.001). This finding was consistent with studies in vitro and *in vivo* in mice,[3] and was in line with in vivo studies.[5] Prostate cancer patients with high levels of ALDH1 had a risk of bone metastasis by 17.88 times. In the *in vivo* study with mice, the spread of prostate cancer increased 100 times in mice with prostate cancer having high ALDH.[5]

CONCLUSION

Prostate cancer cells with high ALDH1A1 level increased the risk of the incidence of bone metastasis. ALDH1A1 level in prostate cancer cells can be considered as a predictor factor of the bone metastasis in prostate cancer.

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