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Original Article

The Differences in Urokinase Plasminogen Activator System in Lung Cancer Patients Before and After Chemotherapy

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Abstract

Background: *Lung cancer is still the leading cause of death for malignancies worldwide. Urokinase plasminogen activator (uPA), its soluble receptor (suPAR), and its inhibitor (PAI-1) play an important role in tumor invasion and metastasis. This study aimed to evaluate the differences in the urokinase plasminogen activator system (uPA, suPAR, and PAI-1) in lung cancer patients before and after chemotherapy.*

Methods: *This research was an observational analytical study with a cross-sectional design. The subjects were 30, consisting of 17 lung cancer patients before chemotherapy and 13 lung cancer patients after chemotherapy for 4 or 6 cycles. The levels of serum uPA, suPAR, and PAI-1 were measured by enzyme-linked immunosorbent assay (ELISA).*

Results: *In lung cancer patients before chemotherapy, there were no significant (P>0.05) differences in levels of serum uPA, suPAR, and PAI-1 between patients with stage III and IV. The highest serum uPA and suPAR levels were found in adenocarcinoma cell types and the highest serum PAI-1 level in adenoepidermoid cell types. After chemotherapy, serum suPAR and PAI-1 were significantly (P<0.05) decreased in lung cancer patients. However, there were no significant (P>0.05) differences in the levels of serum uPA, suPAR, and PAI-1 between patients with chemotherapy responses for stable and progressive diseases.*

Conclusion: *This study revealed that suPAR and PAI-1 levels were decreased in lung cancer patients who had received chemotherapy. This can occur due to decreased tumor cells activity.* ***(J Respirol Indones 2021; 41(4): 228–35)***

Keywords: *Lung cancer; Chemotherapy; uPA; suPAR; PAI-1*

Analisis Perbedaan Sistem Aktivator Plasminogen Urokinase pada Penderita Kanker Paru Sebelum dan Sesudah Kemoterapi

Abstrak

Latar Belakang: *Kanker paru masih menjadi penyebab utama kematian akibat keganasan di seluruh dunia. Aktivator plasminogen urokinase (uPA), reseptor terlarutnya (suPAR), dan inhibitornya (PAI-1) memainkan peran penting dalam invasi dan metastasis tumor. Penelitian ini bertujuan untuk mengevaluasi perbedaan sistem aktivator plasminogen urokinase (uPA, suPAR, dan PAI-1) pada pasien kanker paru sebelum dan sesudah menjalani kemoterapi.*

Metode: *Penelitian ini merupakan penelitian analitik observasional dengan rancangan cross-sectional. Subjek penelitian berjumlah 30 orang, terdiri dari 17 pasien kanker paru sebelum menjalani kemoterapi dan 13 pasien kanker paru setelah menjalani kemoterapi selama 4 atau 6 siklus. Kadar uPA serum, suPAR, dan PAI-1 diukur dengan enzyme-linked immunosorbent assay (ELISA).*

Hasil: *Pada pasien kanker paru sebelum menjalani kemoterapi, tidak terdapat perbedaan bermakna (P>0,05) kadar serum uPA, suPAR, dan PAI-1 antara pasien stadium III dan IV. Kadar uPA dan suPAR serum tertinggi ditemukan pada jenis sel adenokarsinoma dan kadar PAI-1 serum tertinggi pada jenis sel adenoepidermoid. Setelah mendapat kemoterapi, kadar suPAR dan PAI-1 serum menurun secara bermakna (P<0,05) pada pasien kanker paru. Namun, tidak ada perbedaan yang bermakna (P>0,05) pada tingkat serum uPA, suPAR, dan PAI-1 antara pasien dengan respons kemoterapi stabil dan progresif.*

Kesimpulan: *Hasil penelitian menunjukkan penurunan kadar suPAR dan PAI-1 pada pasien kanker paru yang menjalani kemoterapi. Hal ini dapat terjadi karena aktivitas sel tumor yang menurun.* ***(J Respirol Indones 2021; 41(4): 228–35)***

Kata kunci: *Kanker paru; Kemoterapi; uPA; suPAR; PAI-1*

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INTRODUCTION

According to the World Health Organization (WHO) data, lung cancer is the most frequent cancer worldwide. In 2020, there were an estimated 2.21 million new cases. The majority of cases occur in less developed countries. Lung cancer is also the leading cause of cancer mortality (1.8 million deaths).[1,2] Several biomarkers for lung cancer have been discovered in recent years, the most well-known of which are K-Ras, epithelial growth factor receptors, p53, p16, and Bcl-2. However, the outcomes are frequently contradictory.[3] In addition, there are no biomarkers that can evaluate the progress of lung cancer therapy so far. Therefore, further research is required to assess the progress of therapy and the prognosis of the disease.

The urokinase plasminogen activator (uPA) system consists of uPA serine protease, its receptors (uPAR or suPAR), and its inhibitor (PAI-1). These components have an important role in tumorigenesis, extracellular matrix degradation, angiogenesis, proliferation, migration, and adhesion of tumor cells. They are prognostic factors in various types of cancer. For example, high levels of uPA have a prognostic role in cancers of the breast, colon, esophagus, ovaries, and stomach. High levels of suPAR are associated with a poor prognosis in breast and colon cancers. In addition, PAI-1 levels correlate with survival in cancers of the kidneys, ovaries, and breast.[4–6]

The uPA and PAI-1 play an important role in tumor invasion and metastasis. They are new tumor biological factors validated based on a very high level of evidence (level I) related to their clinical use in breast cancer. The European Organization for Research and Treatment of Cancer (EORTC) has validated this prognostic data derived from an analysis of more than 8,000 breast cancer patients. In breast cancer, uPA and PAI-1 are predictors for distant metastases. Using a combination of these two components, uPA/PAI-1 (both low and high), is superior to using one. The uPA/PAI-1 can optimally differentiate between high-risk and low-risk patients. Recent observations indicate that high-risk patients who are determined with uPA/PAI-1 will benefit from adjuvant chemotherapy compared to those who only get standard chemotherapy.[5–7]

In lung cancer, increased levels of uPA or suPAR are positively correlated with gender, stage of the tumor, positive nodal status, metastasis, and recurrence of the disease. A study stated that uPA mRNA and uPA protein are predictive factors for disease-free and life expectancy.[8] However, the uPA system has not been widely studied in lung cancer. This study aimed to evaluate the differences in the uPA system in lung cancer patients before and after chemotherapy.

METHODS

This research was an observational analytical study with a cross-sectional design. Subjects were outpatient and inpatient pulmonary clinics patients at Dr. Saiful Anwar Hospital in Malang, Indonesia, in 2013. The consecutive sampling method was applied to meet 30 subjects. The subjects were divided into two groups, a group of lung cancer patients who had not received (before receiving) chemotherapy (n=17) and a group of lung cancer patients who had received (after receiving) chemotherapy for 4 or 6 cycles (n=13).

According to the Helsinki declaration, all protocols were performed and approved by the Institutional Ethics Committee of Faculty of Medicine, Universitas Brawijaya (No. 547/EC/KEPK/12/2013). Written informed consent was obtained from all the subjects for being included in this study.

Inclusion criteria were lung cancer patients aged 40-70 years, male or female, diagnosed with stage III-IV non-small cell lung cancer (NSCLC) who had not received chemotherapy and had received chemotherapy for 4 or 6 cycles, and patients with small cell lung cancer (SCLC) diagnosed in the limited or extensive stage of the disease. Exclusion criteria, on the other hand, were lung cancer patients who did not have malignant histological findings or lung cancer patients who had other comorbidities such as infection, diabetes mellitus, or cardiovascular disease.

Venous blood samples were taken to measure levels of serum uPA, suPAR, and PAI-1. These levels were measured by enzyme-linked immunosorbent assay (ELISA) using the human uPA ELISA kit and human PAI-1 ELISA kit (Assaypro, St. Charles, MO, USA), as well as the human suPAR ELISA kit (Wuhan Elabscience Co., Ltd., Wuhan, China). All samples were measured in duplicate. The data is shown as median (minimum-maximum). Differences between groups were analyzed using the Mann-Whitney test with SPSS Statistics version 22 (IBM Corp.). Only probability values of $P<0.05$ were considered statistically significant.

RESULTS

In this study, up to the prescribed time limit, we only obtained 17 lung cancer patients before and 13 lung cancer patients after chemotherapy. Table 1 shows the characteristics of subjects.

Based on subject characteristics, it was found that the number of males was more than females in groups before and after chemotherapy (82.00% and 53.85%, respectively). The largest age group was 51–60 years old in both before and after chemotherapy groups (47.05% and 53.85%, respectively). Most of the patients were active smokers in groups before and after chemotherapy (76.47% and 46.15%, respectively).

The most common complaint was shortness of breath in groups before and after chemotherapy (64.70% and 61.54%, respectively). Additional complaints often found in groups before and after chemotherapy were coughing (100% and 69.23%, respectively) and weight loss (35.29% and 30.77%, respectively).

Table 1. Characteristics of Patients

Characteristics of Patients		Before Receiving Chemotherapy (n=17)	After Receiving Chemotherapy (n=13)
Gender	Male	14 (82%)	7 (53.85%)
	Female	3 (18%)	6 (46.15%)
Age group	<20 years	0	0
	21–30 years	1 (5.88%)	1 (7.69%)
	31–40 years	2 (11.76%)	1 (7.69%)
	41–50 years	2 (11.76%)	2 (15.38%)
	51–60 years	8 (47.05%)	7 (53.85%)
	>60 years	4 (23.53%)	2 (15.38%)
Smoking	Yes	13 (76.47%)	6 (46.15%)
	No	3 (17.65%)	3 (23.08%)
	Passive	1 (5.88%)	4 (30.77%)
Laboratory examination	CEA levels (ng/mL)	12.48	6.52
	p=0.408*	(1.42–829.10)	(0.51–731.50)
Chest X-ray	Tumor	6 (35.29%)	5 (38.46%)
	Pleural effusion	4 (23.53%)	3 (23.07%)
	Tumor + effusion	3 (17.65%)	2 (15.38%)
	Tumor + atelectasis	2(11.76%)	1 (7.69%)
	Tumor + effusion + atelectasis	2 (11.76%)	2 (15.38%)
Histopathology	Small cell carcinoma	1 (5.88%)	2 (15.38%)
	Non-small cell carcinoma		
	- Adenocarcinoma	7 (41.17%)	4 (30.77%)
	- Epidermoid carcinoma	6 (35.29%)	2 (15.38%)
	Adeno-epidermoid carcinoma	3 (17.65%)	5 (38.46%)
Staging	Small cell carcinoma		
	- *Extended*	1 (5.88%)	2 (15.38%)
	Non-small cell carcinoma		
	- IIIA	2 (11.76%)	0
	- IIIB	2 (11.76%)	0
	- IV	12 (70.59%)	11 (84.62%)

Note: *$P>0.05$ indicates no significant difference between groups (Mann-Whitney test).

The carcinoembryonic antigen (CEA) measurement showed that the median level of CEA was 12.48 (1.42–829.10) ng/ml in the group before chemotherapy and 6.52 (0.51–731.50) ng/ml in the group after chemotherapy. Radiological images of chest X-rays found the mass in groups before and after chemotherapy (35.29% and 38.46%, respectively), while the rest were found to be effusion or atelectasis. The most common histopathological type in the group before chemotherapy was adenocarcinoma (41.17%), whereas in the group after chemotherapy were adenoepidermoid carcinoma (38.46%) and adenocarcinoma (30.77%).

Table 2. The Levels of uPA, suPAR, and PAI-1 Based on Groups

Parameter (ng/mL)	Groups (Before/After Receiving Chemo-therapy)	n	Median (Minimum-Maximum)	*P*
uPA	Before	17	1.23 (0.56–2.85)	0.183
	After	13	1.06 (0.47–1.72)	
suPAR	Before	17	3.65 (1.66–7.79)	0.035*
	After	13	2.89 (1.88–5.54)	
PAI-1	Before	17	33.31 (0.49–646.70)	0.010*
	After	13	1.69 (0.01–47.18)	

Note: *P<0.05 indicates a significant difference between groups (Mann-Whitney test).

The serum uPA, suPAR, and PAI-1 levels in patients before and after chemotherapy are presented in Table 2. The serum suPAR and PAI-1 levels were significantly (P<0.05) decreased in the group after chemotherapy compared to the group before chemotherapy. The serum uPA level was also decreased after chemotherapy compared to before, although not statistically significant (P>0.05).

The serum uPA, suPAR, and PAI-1 levels based on tumor staging in patients before chemotherapy are presented in Table 3. The serum uPA, suPAR, and PAI-1 levels were not significantly (P>0.05) different in patients with stage III or IV of the disease before chemotherapy.

Table 3. The Levels of uPA, suPAR, and PAI-1 Based on Tumor Staging in Patients Before chemotherapy

Parameter (ng/mL)	Tumor Staging	n	Median (Minimum-Maximum)	*P*
uPA	III	4	1.41 (0.93–1.88)	0.955
	IV	13	1.23 (0.56–2.85)	
suPAR	III	4	3.88 (1.66–5.74)	0.734
	IV	13	3.33 (2.61–7.79)	
PAI-1	III	4	63.95 (33.31–646.70)	0.089
	IV	13	7.99 (0.49–95.44)	

Note: P>0.05 indicates no significant difference between groups (Mann-Whitney test).

In lung cancer patients before chemotherapy, the highest serum uPA and suPAR levels were found in adenocarcinoma cell types. The highest serum PAI-1 level was found in adenoepidermoid cell types, as listed in Table 4.

The serum uPA, suPAR, and PAI-1 levels based on chemotherapy response in patients after chemotherapy are presented in Table 5. The serum uPA, suPAR, and PAI-1 levels were not significantly (p>0.05) different in patients with stable or progressive diseases after chemotherapy.

Table 4. The Levels of uPA, suPAR, and PAI-1 Based on Histopathology Results in Patients Before chemotherapy

Parameter (ng/mL)	Histopathology	n	Median (Minimum-Maximum)
uPA	Small cell carcinoma	1	1.07 (1.07–1.07)
	Adenocarcinoma	7	1.68 (0.56–2.85)
	Epidermoid carcinoma	6	1.23 (0.93–1.88)
	Adenoepidermoid carcinoma	3	1.14 (0.60–1.60)
suPAR	Small cell carcinoma	1	2.79 (2.79–2.79)
	Adenocarcinoma	7	4.95 (2.70–7.79)
	Epidermoid carcinoma	6	3.49 (1.66–5.78)
	Adenoepidermoid carcinoma	3	3.13 (3.02–5.14)
PAI-1	Small cell carcinoma	1	49.73 (49.73–49.73)
	Adenocarcinoma	7	12.48 (2.59–646.70)
	Epidermoid carcinoma	6	20.04 (4.03–81.16)
	Adenoepidermoid carcinoma	3	67.45 (0.49–95.44)

Table 5. The Levels of uPA, suPAR, and PAI-1 Based on Chemotherapy Response

Parameter (ng/mL)	Chemotherapy Response	n	Median (Minimum-Maximum)	*P*
uPA	Stable Disease	8	1.14 (0.92–1.72)	0.770
	Progressive Disease	5	1.06 (0.47–1.61)	
suPAR	Stable Disease	8	2.88 (1.88–5.54)	0.884
	Progressive Disease	5	2.91 (2.43–3.41)	
PAI-1	Stable Disease	8	1.65 (0.20–47.18)	0.558
	Progressive Disease	5	28.31 (0.01–37.27)	

Note: P>0.05 indicates no significant difference between groups (Mann-Whitney test).

DISCUSSION

It was shown that the number of male patients was higher than that of females. This is consistent with the data from WHO (2014), which states that the incidences of lung cancer in Indonesia are 25,322 in males and 9,374 in females.[9] In Northeastern India, data from 2008 to 2012 indicates that the male: female ratio of lung cancer is 1.09:1.00.[10] In the United States, age-adjusted incidence rates of lung and bronchus cancers in 2014 are 59.36 and 47.25 per 100,000 in men and women, respectively.[11] Whereas global data in 2012 shows that the estimated number of lung cancer cases is 1,242 million in males and 583 thousand in females.[1] According to the previous study, the highest age-standardized rates of lung cancer among men are found in Central and Eastern Europe (53.5 per 100,000), Eastern Asia (50.4), Micronesia (47.5), and Southern Europe (46.4). The highest age-standardized rates among women are found in Northern America (33.8 per 100,000), Northern Europe (23.7), Micronesia (22.9), Australia/New Zealand (21.7), and Western Europe (20).[12]

The distribution of patients by age group showed that most were aged 51–60 years in groups before and after chemotherapy. However, in Northeastern India, lung cancer most commonly occurs over the age of 60 years, based on data from 2008 to 2012.[10] Moreover, in the United States, lung and bronchus cancers in 2014 most occur over the age of 65 years and increase with age.[11]

Based on smoking status, the result shows that most patients in groups before and after chemotherapy were active smokers. The cause-effect relationship between tobacco smoking and the incidence of lung cancer has been proven ecologically and clinically in many studies. From a global perspective, the trend of increasing tobacco consumption is followed by the trend of increasing lung cancer mortality rates, especially in developing countries.[13] In Indonesia, lung cancer is the leading cause of smoking-attributable mortality. Cancer due to smoking burdened the Indonesian economy by USD 1,309 million in 2013, consisting of USD 1,280 million for men and USD 29.5 million for women.[14]

In both groups, the chief complaint most commonly found was shortness of breath. Additional complaints in the group before chemotherapy were coughing, weight loss, and chest pain. In the group after chemotherapy, there were additional complaints of coughing, weight loss, and hemoptysis.

Shortness of breath is a common complaint in patients with lung cancer. A study found shortness of breath in about 60% of patients. Shortness of breath is caused by airway obstruction, post-obstructive pneumonitis or atelectasis, pleural effusion, pericardial effusion, and as a complication of chemotherapy or radiotherapy such as pneumonitis. A previous study found 65–75% of lung cancer patients suffered from coughing, even more than 25% with a productive cough. Hemoptysis is found in 6–35% of patients, and as many as 3% of patients experience hemoptysis, which causes death. Chest pain is also common and varies from pain at the tumor's location or more severe pain due to the invasion of the chest wall or mediastinum. Other causes of chest pain are pulmonary embolism and post-obstructive pneumonia.[15]

The median level of CEA in the group before chemotherapy was higher than that of the group after chemotherapy. The CEA is used as a marker for pulmonary, colorectal, gastrointestinal, and breast carcinoma. A study revealed that abnormal serum CEA levels are strongly correlated with increased whole-body metastatic potential in advanced NSCLC.[16]

Radiological images of chest X-rays found the mass in groups before and after chemotherapy. There were also pleural effusion and atelectasis. This is consistent with the TNM system in lung cancer, which describes T: primary tumors including atelectasis, N: metastases to lymph nodes, and M: metastases to other organs, including the pleura.[17]

The most common histopathological type in the group before chemotherapy was adenocarcinoma, whereas in the group after chemotherapy were adenoepidermoid carcinoma and adenocarcinoma. This is in line with data from 2010 to 2014 in the

United States, in which the most common type of NSCLC is adenocarcinoma (46.6%), followed by squamous and transitional cell carcinoma (23.2%).[11] The most prevalent kind, epidermoid or squamous carcinoma, is gradually declining, whereas adenocarcinoma is increasing.[18]

In this study, most lung cancer patients were in stage IV. This shows that patients tend to visit doctors when there are respiratory and systemic complaints caused by tumor mass pressure or the process of lung malignancy itself. Symptoms of lung cancer initially tend to be less specific, and generally, coughing, which is the most common symptom, is only considered a normal cough. Data shows that about three-quarters of patients with lung cancer will present with symptoms, and most of them have advanced stages of the tumor at the time of diagnosis. Early-stage detection is rare and usually incidental.[19]

In this study, serum suPAR and PAI-1 levels of the group before chemotherapy were significantly higher than those after chemotherapy. This is consistent with the literature that suPAR is released by tumor cells, and the level of suPAR in the blood of cancer patients will increase. The suPAR plays an essential role in urokinase-mediated plasminogen activation, which will cause tumor invasion and metastasis.[20] Meanwhile, the lower level of suPAR in the group after chemotherapy can occur due to decreased tumor cells activity such as development, implantation, angiogenesis, inflammation, and metastasis. Moreover, several previous studies have shown that PAI-1 levels will increase significantly in malignancy compared to normal tissue and also be associated with patient prognosis.[21]

The highest serum uPA and suPAR levels were found in adenocarcinoma cell types and the highest serum PAI-1 level in adenoepidermoid cell types. However, the levels of uPA, suPAR, and PAI-1 based on staging did not show significant differences between stage III and IV patients. A study found that uPAR levels are significantly ($p < 0.01$) higher in NSCLC patients with stage I, II, and IIIa TNM compared to stage IIIb and IV TNM.[22] A study showed that PAI-1 levels in NSCLC are higher than SCLC. In this study, unfortunately, there were no subjects with stages I and II.[23] Therefore, the measurement of uPA, suPAR, and PAI-1 levels in this study has not been able to predict lung cancer progression.

Moreover, the insignificance of statistical analysis results in this study may occur because patients with stage III lung cancer who were diagnosed had undergone biochemical processes for damage that cannot be proven by medical support. Due to cost limitations, a complete examination was not performed on all patients to exclude distant metastases, such as a head CT scan, bone scan, etc. The difference in the number of subjects, namely four people for stage III compared to 13 people for stage IV, can also affect statistical analysis results.

Based on the chemotherapy response, this study found no significantly different results between serum uPA, suPAR, and PAI-1 levels in stable and progressive diseases. However, only chemotherapy responses of stable and progressive diseases were in the group, so they could not be compared with complete and partial responses. Therefore, the measurement of uPA, suPAR and PAI-1 levels in this study has not evaluated the chemotherapy response. Furthermore, there were no significant differences in the levels of uPA, suPAR, and PAI-1 in patients with stable and progressive diseases.

CONCLUSION

This study revealed that suPAR and PAI-1 levels were decreased in lung cancer patients who had received chemotherapy. This can occur because tumor cell activity decreases.

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