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Aims and Scope

Aims

The Indonesian Journal of Cancer Control aims to contribute towards better knowledge as a result of scientific studies that can be accessed by academic circles and researchers.

Scope

The Indonesian Journal of Cancer Control is a scientific quadrimester journal, managed by the Indonesian Society of Oncology. This journal is designed as a place of dissemination of information and scientific knowledge. It publishes original articles, case reports or case series, and review articles. These comprise of biomedical science, clinical medicine, public health science, and medical science education in the cancer field.

The Indonesian Journal of Cancer Control (InaJCC) is a quadrimester electronic journal, publishing papers in a wide spectrum of cancer control. The journal was launched in 2021 as the official publication of the Indonesian Society of Oncology and its first volume was published in 2021.

The InaJCC with its distinguished, diverse, and Indonesian & International-wide team of editors, reviewers, and readers, ensure the highest standards of research communication within the cancer control community across Indonesia as well as globally. The InaJCC accepts manuscripts on the whole spectrum of cancer control.

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Editorial

Advancing Cancer Knowledge: Insights from Lung Cancer to Rare Malignancies

Cosphiadi Irawan

We are pleased to present Volume 3, Issue 2 of *The Indonesian Journal of Cancer Control (InaJCC),* highlighting significant advancements in cancer research and management. This issue highlights a diverse array of studies and case discussions, emphasizing the importance of tailored approaches in oncology and the continuous need for innovation in cancer control strategies.

Lung cancer is the leading cause of cancer-related mortality. The case report on lung adenocarcinoma with skin metastases sheds light on the rarity and clinical challenges posed by such presentations. With skin metastases affecting only 3.4% of lung cancer patients, this report underscores the diagnostic complexity and poor prognosis often associated with these cases, emphasizing the critical need for precise clinical assessment to differentiate malignant from benign lesions.[1]

Adding depth to our understanding of lung cancer, a cross-sectional study examines the expression of thyroid transcription factor-1 (TTF-1), P40, and cytokeratin 5/6 (CK 5/6,) elucidating their distinct roles in differentiating adenocarcinoma from squamous cell carcinoma.[2] The findings reveal their potential utility in diagnosis while noting the limitations of simultaneous application, highlighting the ongoing quest for reliable biomarkers. Complementing this, a comprehensive review explores the epidemiology, prevention, and treatment modalities for lung cancer, advocating for personalized medicine as a cornerstone for improving survival outcomes.

Turning to therapeutic innovation, a review on Panduratin A, a natural compound derived from fingerroot plants, demonstrates its promising anticancer properties in non-small cell lung cancer.[3] With mechanisms such as apoptosis induction and PI3K/Akt pathway inhibition, this compound offers hope for overcoming drug resistance and toxicity challenges in conventional therapies.

Moreover, this issue also addresses rare malignancies through a compelling case series on Marjolin's ulcer. Chronic wounds transforming into aggressive malignancies after decades underscore the importance of cautious long-term care.[4] The case series highlights advancements in diagnostic techniques like dermoscopy and innovative surgical approaches, including Mohs micrographic surgery.

Together, these articles exemplify the journal's commitment to advancing cancer control through rigorous research and thoughtful discourse. We extend our gratitude to the authors, reviewers, and readers for their dedication to advancing cancer research and care. We sincerely hope that this issue will bring a new insight especially into lung cancer for the oncology community.

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InaJCC The Indonesian Journal of Cancer Control

Original Article

Expression of thyroid transcription factor-1, P40, and cytokeratin 5/6 in non-small cell lung carcinoma at Persahabatan Hospital in 2021

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Abstract

Background: Non-small cell Lung carcinoma (NSCLC) comprises 80% of lung cancer and mainly consists of adenocarcinoma and squamous cell carcinoma. Immunohistochemistry plays an important role in the accurate diagnosis of different types of lung cancer.
Aim: To determine the expression of thyroid transcription factor-1 (TTF-1), P40, and cytokeratin 5/6 (CK 5/6) in lung cancer and to determine the differences in the expression of TTF-1, P40, and CK 5/6 in adenocarcinoma and squamous cell carcinoma.
Method: This study is a cross-sectional study with 47 samples, 35 adenocarcinoma and 12 squamous cell carcinoma for immunohistochemistry examination. Immunohistochemistry examination on TTF-1 expression using monoclonal mouse antibody 8G7G3/1, P40 expression using polyclonal rabbit antibody, and CK 5/6 expression using CK5/6.007 monoclonal mouse antibody.
Results: Expression of TTF-1 was found in 25 cases of adenocarcinoma (71.4%) and in four cases of squamous cell carcinoma (33.3%). P40 was expressed in eight cases of squamous cell carcinoma (66.7%) and in six cases of adenocarcinoma (17.1%). Cytokeratin 5/6 was expressed in eight cases of squamous cell carcinoma (66.7%) and in four cases of adenocarcinoma (11.4%). Thyroid transcription factor-1 had a positive correlation with adenocarcinoma, whereas P40 and CK 5/6 negatively correlated with adenocarcinoma, but were more associated with squamous cell carcinoma.
Conclusions: There were significant differences in TTF-1, P40, and CK 5/6 expressions between adenocarcinoma and squamous cell carcinoma, but the three expressions could not be used simultaneously. Thyroid transcription factor-1 expression was more accurate than P40 and CK 5/6 for differentiating adenocarcinoma with squamous cell carcinoma.

***Keywords**: adenocarcinoma, CK 5/6, squamous cell carcinoma, P40, TTF-1*

Abstrak

Latar Belakang: Kanker paru karsinoma bukan sel kecil (KPKBSK) mencakup 80% kanker paru dan terutama terbagi menjadi adenokarsinoma dan karsinoma sel skuamosa. Imunohistokimia berperan penting untuk diagnosis yang akurat pada tipe kanker paru yang berbeda.
Tujuan: Mengetahui prevalensi ekspresi dari TTF-1, P40, dan CK 5/6 pada jaringan kanker paru dan mengetahui perbedaan ekspresi TTF-1, P40, dan CK 5/6 pada adenokarsinoma dan karsinoma sel skuamosa.
Metode: Penelitian ini merupakan penelitian potong-lintang dengan jumlah sampel 47, yaitu 35 sampel adenokarsinoma, dan 12 sampel karsinoma sel skuamosa untuk dilakukan pemeriksaan imunohistokimia. Pemeriksaan Imunohistokimia pada ekspresi TTF-1 menggunakan antibodi tikus monoklonal 867 63/1, pada ekspresi P40 menggunakan antibodi kelinci poliklonal dan pada ekspresi CK 5/6 menggunakan antibodi tikus monoklonal CK/6.007
Hasil: Ekspresi TTF-1 ditemukan pada 25 kasus adenokarsinoma (71,4%) dan pada empat kasus karsinoma sel skuamosa (33,3%). Ekspresi P40 ditemukan pada delapan kasus karsinoma sel skuamosa (66,7%) dan pada enam kasus adenokarsinoma (17,1%). Ekspresi CK 5/6 ditemukan pada delapan kasus karsinoma sel skuamosa (66,7%) dan pada empat kasus adenokarsinoma (11,4%). Ekspresi TTF1 mempunyai korelasi yang positif dengan adenokarsinoma sedangkan ekspresi P40 dan CK 5/6 memiliki korelasi negatif dengan adenokarsinoma, dengan kata lain lebih berhubungan dengan karsinoma sel skuamosa.
Kesimpulan: Terdapat perbedaan bermakna dalam ekspresi TTF-1, P40, dan CK 5/6 pada adenokarsinoma dan karsinoma sel skuamosa, namun ketiga ekspresi tersebut tidak dapat digunakan secara bersamaan. Ekspresi TTF-1 lebih akurat dibandingkan P40 dan CK 5/6 dalam membedakan adenokarsinoma dengan karsinoma sel skuamosa.

***Kata kunci:** adenokarsinoma, CK 5/6, karsinoma sel skuamosa, P40, TTF-1.*

Introduction

Lung cancer is one of the most common causes of death in the world.[1] There are 2 main types of lung cancer with 80 % non-small cell lung cancer (NSCLC) and 20% small cell lung carcinoma (SCLC). Non-small cell lung carcinoma (NSCLC) mainly consists of adenocarcinoma and squamous cell carcinoma. Adenocarcinoma is the most common NSCLC type in the world. [2,3] Persahabatan Hospital from 2004-2006 showed NSCLC adenocarcinoma was the most common lung cancer with 56.3%.[3] Epidemiological studies from WHO reported NSCLC adenocarcinoma was 40% from all of NSCLC cases.[4] Lung adenocarcinoma incidence increase in Asia and United States mainly in female, young age and non-smokers.[4]

Immunohistochemistry (IHC) plays a significant role in diagnosing different lung tumor accurately.[5] Immuno-histochemistry staining from mucin can identify a subtype of non-small cell carcinoma lung cancer and help to predict final subtype from non-small cell carcinoma lung cancer that cannot be specifically identified. [5,6] Immunohistochemistry staining of TTF-1 was found negative in almost all squamous cell carcinoma cases and 70-85% of adenocarcinoma. Antibody towards CK 5/6 and P40 has been used to identify squamous cell phenotype[7].

Methods

This study is a cross-sectional study. The subject of this study is 51 paraffin blocks of non-small cell carcinoma lung cancer that fulfil immunohistochemistry standards. Of 51 sample, 37 adenocarcinoma and 14 squamous cell carcinoma sample underwent immunohistochemistry examination. A total of 35 adenocarcinomas and 12 squamous cell carcinomas went for further examination due to the heating process in immunohistochemistry process. All research samples were taken from 1st September 2021 to 31st December 2021. This research occurred at the Pulmonology Department and Respiratory Division of Faculty Medicine of the University of Indonesia RSUP Persahabatan National Lung Center.

Immunohistochemistry

Paraffin block were cut into 3 mm thickness, and went to deparaffination with Xylol, antigen retrieval deblocking chamber (heated with deblocking chamber 95^0C degree for 30 minutes, slide chilled and washed in Phosphate Buffered Saline (PBS) and went to deblocking with tissue primer, blocking with background blocker, given primary primer antibody (TTF1, P40 and CK/56 seen on table 1) for 60 minutes, with 1:1000 dilution, washed in PBS and given secondary antibody for 10 minutes for further binding, then carried Host Radish Peroxidase (HRP). This enzyme catalyzed hydrogen peroxide into water and oxygen for 10 minutes, then performed diaminobenzidine tetrahydrochloride (DAB) chromogen 1 ml on 1 drop for 5 minutes, identifying positivity. Suppose the result was positive indicated with brown staining. Afterwards, the slide was washed, given gradual alcohol dehydration for 5 minutes and Xylol. Lastly, the sample underwent mounting and closed with a glass lid.

Statistical Analysis

The numerical and categorical results are presented in table and pie diagram. The analysis consists of univariate and bivariate. The univariate analysis includes proportion distribution from categorical variables and frequency distribution for numerical variables. The univariate analysis includes proportion distribution for categorical variable and frequency distribution for numerical variable. Bivariate analysis of chi square was used to analyze the relation between two categorical variables.

Table 1. Antibody Panel Used in this esearch

Antibodies	Mono/Polyclonal	Source	Clone	Dilution
TTF-1	M	Biocare Medical, USA	8G7G3/1	1: 100
p40	P	Biocare Medical, USA		1: 100
Cytokeratin 5/6	M	Biocare Medical, USA	CK5/6.007	1: 100

Results

A total of 47 subject were successfully retrieved in this research. **Table 2** showed comparison between female and male were similar. The majority of subjects were active and passive smokers (72.3%). Subject with familial history of cancer were higher compared with a history of cancer (23.4 vs 12.8%), although majority of subject did not have a previous history or familial history of cancer. A higher proportion of subjects had stage IV cancer (83%) and had PA diagnosis of adenocarcinoma (74.5%). The median age of subject was 59.1 years old. The positivity rate of TTF-1 was higher compared to negative (61.7%). The positivity of p40 and CK5/6 were lower than the negative (29.8 and 25.5% respectively).

Table 2. Subject Characteristics

Characteristics	N	%
Gender		
Male	26	55.3
Female	21	44.7
Age		
Median		61
Mean		59.1
SD		11.7
Smoking		
Yes	34	72.3
No	13	27.7
Family history of cancer		
Yes	11	23.4
No	36	76.6

Table 3. Subject's Clinical Characteristics

Characteristics	n	%
Cancer Cell Type		
Adenocarcinoma	35	74.5
Squamous Cell Carcinoma	12	25.5
Staging		
I-II	0	0
IIIA/B/C	8	17.0
IVA/B	39	83.0
Previous History of Cancer		
Yes	6	12.8
No	41	87.2

Table 4. Result of TTF-1,p40, and CK5/6 expression on NSCLC

PA		N	%
TTF 1	Positive	29	61.7
	Negative	18	38.3
P40	Positive	14	29.8
	Negative	33	70.2
CK 5/6	Positive	12	25.5
	Negative	35	74.5

Gender, smoking habit, history and familial history of cancer, staging, and PA diagnosis are categorical variables. These variables were examined to determine whether they related to TTF-1, p40, and CK5/6 expression using Chi- Square test. Several variables that did not fulfill the Chi-Square requirement were analyzed using Fisher's exact test.

Bivariate

Table 5. Relation between age and TTF1, P40 and CK/56 expression

		TTF1				P (Chi-square)	P40				P (Chi-square)	CK 5/6				P (Chi-square)
		positive		negative			positive		negative			positive		negative		
		n	%	n	%		n	%	n	%		n	%	n	%	
Gender	Female	13	61.9	8	38.1	0.9	5	23.8	16	76.2	0.4	4	19	17	81	0.5*
	Malei	16	61.5	10	38.5		9	34.6	17	65.4		8	30.8	18	69.2	
Age	Mean	59.8		57.8		0.6	61.9		57.8		0.3	62.6		57.8		0.2
	SD	12.1		11.1			9.9		12.3			10.5		11.9		
Smoking	Yes	21	61.8	13	38.2	0.9	12	35.3	22	64.7	0.3*	10	29.4	24	70.6	0.5*
	No	8	61.5	5	38.5		2	15.4	11	84.6		2	15.4	11	84.6	
History of cancer	Yes	3	50	3	50	0.7*	2	33.3	4	66.7	1*	1	16.7	5	83.3	1*
	No	26	63.4	15	36.6		12	29.3	29	70.7		11	26.8	30	73.2	
Family history of cancer	Yes	7	63.6	4	36.4	1*	3	27.3	8	72.7	1*	3	27.3	8	72.7	1*
	No	22	61.1	14	38.9		11	30.6	25	69.4		9	25	27	75	
Stage	III	3	37.5	5	62.5	0.23*	3	37.5	5	62.5	0.7*	3	37.5	5	62.5	0.4*
	IV	26	66.7	13	33.3		11	28.2	28	71.8		9	23.1	30	76.9	
Histopatology	KSS	4		8	66.7	0.04*	8	66.7	4	33.3	0.03*	8	66.7	4	33.3	0.001*
	Adeno Ca	25		10	28.6		6	17.1	29	82.9		4	11.4	31	88.6	

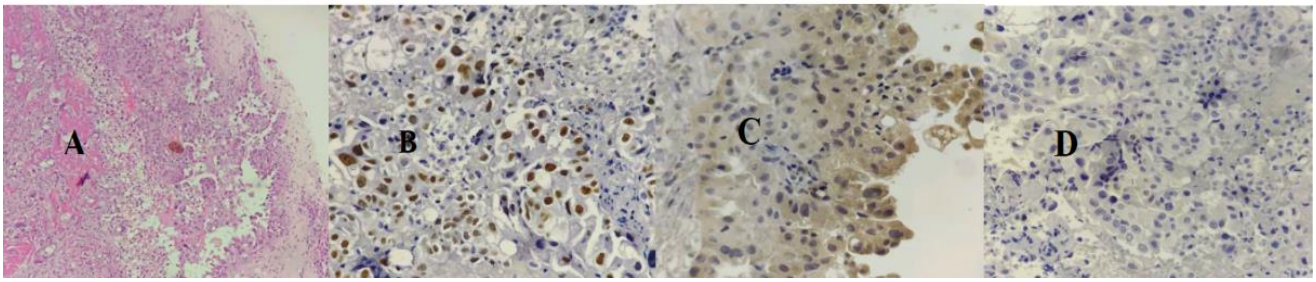

Figure 1. A. Adenocarcinoma, B. Positive staining of TTF1 expression showed as yellow or brown particle expressed in nucleus, C. Negative staining of P40 expression, D. Negative staining of CK/56 expression

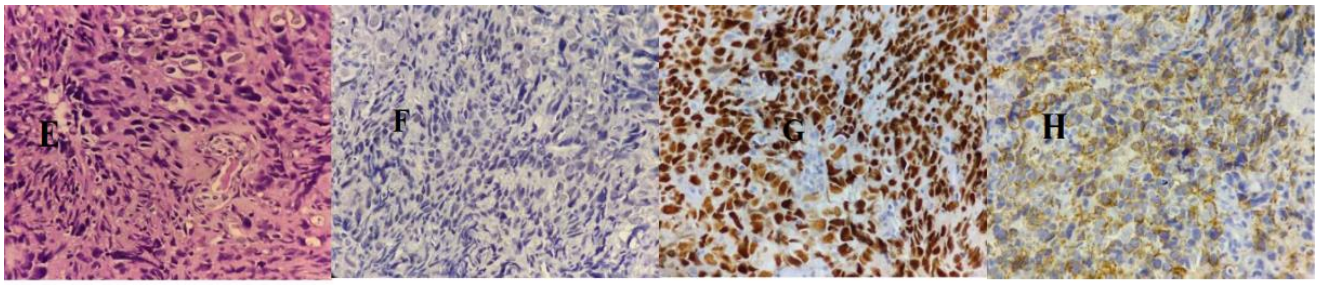

Figure 2. E. Squamosa cell carcinoma, F. Negative staining of TTF1 expression, G. Positive staining of P40 expression showed as yellow or brown particle expressed in nucleus, H. Positive staining of CK5/6 expression showed as yellow or brown particle expressed in membrane cell and cytoplasm.

Table 5 showed significant relationship between PA diagnosis and TTF-1, p40 and CK5/6 expression. The adenocarcinoma group showed a higher positive proportion of TTF-1 compared to squamous cell carcinoma (inversely related with adenocarcinoma, the negative proportion of TTF1 in SCC was higher than the positive result). **Table 6** showed similar result negative proportion of p40 and CK5/6 were higher on adenocarcinoma than in squamous cell carcinoma.

Age distribution as a numerical variable was analyzed based on mean-median, standard deviation, skewness, and kurtosis. Normal distribution was fulfilled. Hence, a T-test was used to analyzed age and TTF-1, p40, and CK5/6 expression. There was no statistically significant difference in age median between the three groups (Table 5).

Table 6. Result of TTF-1, P40 and CK5/6 expression between adenocarcinoma and squamous cell carcinoma.

Cancer Cell Type	TTF-1				P40				CK5/6			
	Positive		Negative		Positive		Negative		Positive		Negative	
	N	%	N	%	N	%	N	%	N	%	N	%
Adenocarcinoma	25	71,4	10	28,6	6	17,1	29	82,9	4	11,4	31	88,6
Squamous Cell Carcinoma	4	33,3	8	66,7	8	66,7	4	33,3	8	66,7	4	33,3

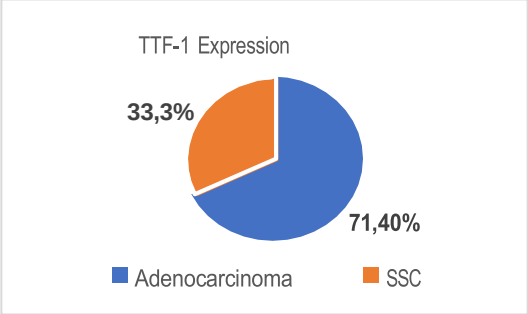

Figure 3. Positive expression of TTF-1 on adenocarcinoma and squamous cell carcinoma

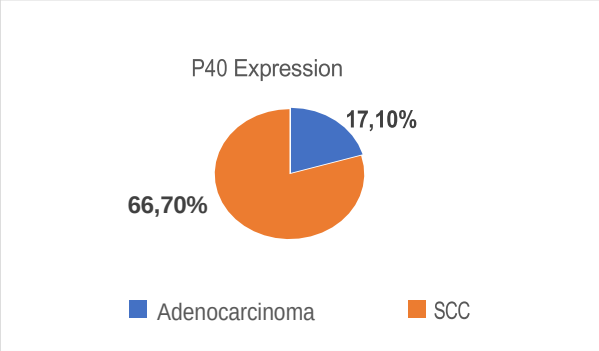

Figure 4. Positive expression of P40 on adenocarcinoma and squamous cell carcinoma

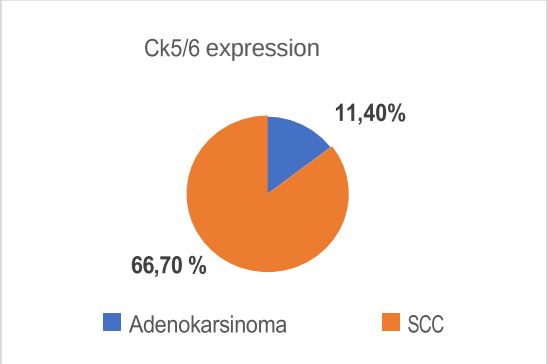

Figure 5. Positive expression of CK5/6 on adenocarcinoma and squamous cell carcinoma

Table 7 showed multiple regression analysis on 3 gene expression. The regression coefficient (beta) was not consistently indicated from P (z) higher than the expected significant result (0.05), Hence three modalities cannot be used simultaneously. This statement was strongly supported by simple regression analysis on table 8 to table 10.

All coefficient marks on each modality were significantly different from 0 (P (z) < 0.05). Only TTF-1 showed a positive correlation (positive coefficient mark) with pathology anatomy result od adenocarcinoma. P40 and CK5/6 expression negatively correlated with Adeno Ca, which had more association with SCC. Table 11 showed TTF1 had the highest accuracy (ROC area 70%, 95% CI 50;80%) compared to P40 and CK 5/6.

Table 7. Multiple Regression Analysis

PA Diagnosis	Coefficient	P (Z)	P Chi	Pseudo RSq
TTF1	0.6	0.5	0.00	0.3
P40	14.6	0.9		
CK 5/6	-16.9	0.9		
Constanta	1.5	0.1		

Table 8. TTF 1 Regression Analysis

PA Diagnosis	Coefficient	P (Z)	P Chi	Pseudo RSq
TTF1	1.6	0.02	0.02	0.1
Constanta	0.2	0.6		

Table 9. P 40 Regression Analysis

PA Diagnosis	Coefficient	P (Z)	P Chi	Pseudo RSq
P40	-2.3	0.003	0.00	0.2
Constanta	1.9			

Table 10. PA Regression Analysis

PA Diagnosis	Coefficient	P (Z)	P Chi	Pseudo RSq
CK 5/6	-2.7	0.0	0.0	0.2 37
Constanta	2	0.0		ch

Table 11. Accuracy

PA Diagnosis	ROC area	95% CI	
TTF1	0.7	0.5	0.8
P40	0.2	0.1	0.4
CK 5/6	0.2	0.1	0.4

Discussion

TTF-1 is a tissue-specific homeodomain with a transcription factor mainly found on alveolar pneumocyte type II. TTF-1 can also be found on thyroid tissue since embryogenesis in human lungs and brain. TTF-1 have primarily functions on epithelial morphogenesis and stimulates pneumocyte surfactant protein regulating transcription gene secretion on Klara's cell.[8-10] TTF-1 is a 38 kDa nuclear protein member of

the NKx2 family of homeodomain transcription factors. Human TTF-1 is a single polypeptide of 371 amino acids. With gene located on chromosome 14q13.[11-13]

TTF-1 specific to lung carcinoma and carcinoma origin from the thyroid.[14] Nowadays, TTF-1 is mainly used as marker for adenocarcinoma. Recent studies have found that TTF-1 has high sensitivity and specificity for adenocarcinoma.[12] In lung non-small cell carcinoma, TTF-1 was found in 76% adenocarcinoma but rarely on squamous cell carcinoma.[8] Moldvay et al[7] reported in primary bronchial adenocarcinomas found immunopositivity in 46/50 cases among them 30 cases showed strong nuclear immunostaining and four primary adenocarcinoma cases observed immunopositivity was localized to the cytoplasm. Stenhouse et al[8] reported of the pulmonary adenocarcinomas, 75% were strong positive for TTF-1.

Lau et al[10] demonstrated TTF-1 positivity in the majority of tumours (75-80% in reported series). Unlike adenocarcinomas, squamous carcinomas in consistently express TTF-1, with reported positivity ranging from 0 to 37,5% of cases studied.

TTF-1 appears to be a reasonably sensitive and highly specific marker for pulmonary adenocarcinomas, with potential for diagnostic use in distinguishing primary pulmonary adenocarcinomas from metastatistic extrapulmonary adenocarcinomas metastatic to the lung, or establishing a lung origin for metastatic adenocarcinomas of unknown primary site.

Kawai et al[15] found TTF-1 expression in 53 out of 82 adenocarcinoma case (65%) with moderate and weak differentiation. Expression P40 was 2% and CK5/6 0% in adenocarcinoma. TTF-1 was observed in only 9% of squamous cell carcinomas, while P40 was 85% and CK5/6 81%. Yaman et al[14] reported TTF-1 was 84,8% in adenocarcinoma but being negative in SCC. TTF- 1 it was for AC with 84,4% sensitivity and 100% specifity.

Yatabe et al[16] reported that expression of TTF-1 in adenocarcinoma was 72% and had statistically significant prevalence of female and nonsmoker. In this research, we reported 25 positive results of TTF-1 expression on adenocarcinoma (71.4%) and 4 positive results on squamous cell carcinoma (33.3%). And same with studied TTF-1 in adenocarcinoma was positive 70-85% and SCC was 0-37,5%.

P40 is one of the most specific markers for basal cells and squamous cells. It has a significant function compared to p63 in diagnosing squamous cell carcinoma.[17] P40 antibody that has been identified as Np63 has been widely available. Nowadays, it has known to differentiate squamous cell carcinoma and adenocarcinoma.[17] P40 is a fraction isoform from N-terminal p63, dominantly expresses on squamous cell carcinoma, and has great specificity in diagnosing squamous cell carcinoma.[18,19] Bishop et al[18] showed that p40 has a sensitivity and specificity of 100% for squamous cell carcinoma. Thus p40 is highly recommended in cases of poorly differentiated carcinomas.[17]

While Tacha et al[19] reported that p40 sensitivity was 85% and specificity was 98% on squamosa cell carcinoma. Affandi et al[17] found that p40 was expressed in 27 of squamous cell carcinoma cases (77.1%) and all adenocarcinoma cases showed negative expression of P40. Reactivities P40 on carcinoma cell squamosa were diffuse and strong. p40 isan excellent marker for distinguishing lung squamous cell carcinoma from adenocarcinoma with specificity 100% sensitivity 77,1%. Wang et al[20] TTF-1 was positive in adenocarcinoma 84,2% and SCC 7,2% with specificity 93,44% and sensitivity 79,82%. While P40 was positive in KSS 100% and adenocarcinoma 8,7% with specificity 98,8% and sensitivity 24,9%. CK5/6 was positive in KSS 94% and adenocarcinoma 6,67% with specificity 96,5% and sensitivity 77,05% P40 more specificity CK5/6 in SCC.

This study found p40 positive expression in 66.7% SSC and 17.1% on adenocarcinoma. P40 is a nucleus marker that is easier to evaluate. CK5/6 is essential keratin with moderate size and molecular weight of 58 kDa.[21] CK5/6 is cytokeratin with high molecular weight and found on epithelial breast muscle and basal epithelial on lung bronchiole and spinous cell in skin which however is rarely expressed in glandular ephitelium.[20,22]

CK5/6 showed as a stain on cytoplasm, useful in diagnosis of SCC especially in the poorly differentiative cell type.[5] Sensitivity on squamous cell carcinoma reported 73-100%.[6] Xu et al[22] reported CK5/6 was positive in biopsies from 91 of 99 SCC, and 5 of 111 adenocarcinoma. TTF-1 was present in 105 of 111 adenocarcinoma and none of SCC than TTF- 1 specificity 100% , sensitivity 94,59%.

CK5/6 has relatively high specificity of 91.92% in carcinoma cell squamous. Although CK5/6 positivity

has been reported in a small percentage (2-8%) of primary pulmonary adenocarcinoma. Kriegsmann et al.[24] found two markers (CK5/6, P40) are similar to identifying squamous cell carcinoma. On lung cancer, sensitivity to identify squamous cell carcinoma from CK5/6, p40, and is 93.94%, and specificity CK5/6 is 98% and p40 is 97%. P40 showed the highest sensitivity and specificity combination for squamous differentiation compared CK5/6. These findings align with a previous study that reported range 80-99% for CK5/6, 85-100% for P40.

Argon et al[6] reported CK5/6 of the 72 SCC cases 56 had 3+ strong, 4 had 2+ and 10 had 1+ and no staining was seen in any of adenocarcinoma. CK5/6 had specificity 100% and sensitivity 97,8%. TTF-1 was see 100% in all adenocarcinoma cases but not seen in any of SCC. Nishino[25] TTF-1 demonstrated specificity 99% for adenocarcinoma and sensitivity 94% for TTF-1.

P40 demonstrated superior specificity to CK5/6 (94% vs 59%, respectively) for SCC and sensitivity P40 and CK5/6 100%. Marson et al[26] reported TTF-1 was 3% in SCC and 98% in adenocarcinoma. While CK5/6 was not found in adenocarcinoma and was detectable in 100% of primary lung SCC.

With specificity and sensitivity 100% This report found a positivity rate 66.7% on SCC and 11.4% for adenocarcinoma. And we found P40 and CK5/6 was positive 66,7% in KSS. But P40 more positivity compared CK5/6 in adenocarcinoma (17,1% PS 11,4%). Expression of CK5/6 in some pulmonary adenocarcinomas is not surprising because CK5/6 is present in normal basal cells of the respiratory epithelium.[27]

There was a significant difference between the expression of TF-1, P40, and CK 5/6 in differentiating adenocarcinoma and squamous cell carcinoma. However, these three expressions cannot be used simultaneously. Because the coefficient values were significantly different. TTF-1 expression has the highest accuracy compared to p40 and CK5/6.

Conclusion

The positive expression of TTF-1 is 71.4% in adenocarcinoma and 33,3% in SCC. The positive expression of p40 and CK5/6 are 66.7% in squamous cell carcinoma, but p40 expression positivity was 17,1% in adenocarcinoma and CK5/6 expression 11,4% in adenocarcinoma. There was a significant difference between the expression of TTF-1, P40, and CK 5/6 in differentiating adenocarcinoma and squamous cell carcinoma. However, these three expressions cannot be used simultaneously. TTF-1 expression has the highest accuracy compared to p40 and CK5/6.

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Original Article

Efficacy of gefitinib versus erlotinib as first-line treatment in EGFR mutant advanced lung adenocarcinoma at RSP. Dr. H. A. Rotinsulu

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Abstract

Background: Gefitinib and erlotinib are superior to chemotherapy in adenocarcinoma with epidermal growth factor receptor (EGFR) mutation patients. Both drugs can be accessed as first-line therapies. However, the determination of the choice of gefitinib or erlotinib is not yet clear.
Aim: To compare the progression-free survival (PFS), overall survival (OS) and time on treatment (TOT) of adenocarcinoma with epidermal growth factor receptor (EGFR) mutation patients who receiving first-line gefitinib versus erlotinib.
Methods: This is a retrospective study used medical record of patients who were treated with first-line gefitinib 250 mg once daily versus erlotinib 150 mg once daily at Dr. H.A. Rotinsulu Lung Hospital from 1st January 2019 to 31th December 2021.
Results: There are 103 patients (74,1%) who received gefitinib and 36 patients (25,9%) who received erlotinib as first-line treatment. Median PFS in gefitinib and erlotinib group was 26 months and 17 months (P=0,184), respectively. Median overall survival time of the gefitinib group was the 46,78 months but in erlotinib group cannot be analysed. Median time-of-treatment was 12 months in gefitinib group and 11 months in erlotinib group (P=0,172). The incidence rate ratio in the TKI group did not show a causal relationship with death due to IRR values of 0,74 and 95% CI IRR of 0,21;3,24. Based on univariate analysis, gender affects PFS (HR1,7;CI95%;1,0-3,4;P=0,049) and TOT (HR1,6;CI95%;1,1-2,6;P=0,020). The data also showed that age affects TOT (HR1,5;CI95%;1,0-2,4;P=0,037).
Conclusion: There was no difference in efficacy between gefitinib and erlotinib in the treatment of pulmonary adenocarcinoma patients with EGFR gene mutations at Dr. H.A. Rotinsulu Lung Hospital.

***Keyword**: EGFR mutations, erlotinib, gefitinib, non-small cell lung cancer.*

Abstrak

Latar belakang: Gefitinib and erlotinib lebih superior dibandingkan kemoterapi pada pasien adenokarsinoma dengan mutasi EGFR. Kedua obat tersebut dapat diberikan sebagai terapi lini pertama, namun dasar penentuan pilihan antara gefitinib atau erlotinib masih belum jelas.
Tujuan: Penelitian ini bertujuan untuk membandingkan *progression-free survival* (PFS), *overall survival* (OS) and *time on treatment* (TOT) antara pasien adenokarsinoma dengan mutasi EGFR yang memperoleh terapi lini-pertama gefitinib dengan yang memperoleh terapi lini pertama erlotinib.
Metode: Penelitian ini merupakan studi retrospektif berdasarkan data rekam medis pasien yang memperoleh gefitinib lini pertama 250 mg sekali sehari dan erlotinib lini pertama 150 mg sekali sehari di Rumah Sakit Paru Dr. H.A. Rotinsulu dari 1 Januari 2019 hingga 31 Desember 2021.
Hasil: Terdapat 103 pasien (74,1%) yang mendapatkan gefitinib dan 36 pasien (25,9%) yang mendapatkan erlotinib sebagai terapi lini pertama. Median PFS pada kelompok gefitinib adalah 26 bulan, sedangkan pada kelompok erlotinib adalah 17 bulan (P=0,184). Median OS pada kelompok gefitinib yaitu 46,78 bulan, namun yang di kelompok erlotinib tidak dapat dianalisis. Median TOT yaitu 12 bulan di kelompok gefitinib, dan 11 bulan di kelompok erlotinib (P=0,172). Rasio rerata insidens pada kelompok TKI tidak menunjukkan hubungan sebab akibat dengan kematian berdasarkan nilai IRR 0,74 dan 95% CI IRR 0,21;3,24. Berdasarkan analisis univariat, jenis kelamin memengaruhi PFS (HR1,7;CI95%;1,0-3,4;P=0,049) dan TOT (HR1,6;CI95%;1,1-2,6;P=0,020). Data juga menunjukkan bahwa usia memengaruhi TOT (HR1,5;CI95%;1,0-2,4;P=0,037).
Kesimpulan: Tidak terdapat perbedaan efikasi yang bermakna antara gefitinib dan erlotinib dalam tata laksana pasien adenokarsinoma paru dengan mutase EGFR di Rumah Sakit Paru Dr. H.A. Rotinsulu.

***Kata kunci**: erlotinib, gefitinib, mutasi EGFR, non-small cell lung cancer.*

Introduction

Cancer is the leading cause of death in the world.[1] Data from WHO in 2020 showed that there were 19.29 million new cases and 9.95 million deaths from cancer. The five most diagnosed cancer areas in 2020 in all sexes were breast (11.7%), pulmonary (11.4%), colorectal (10%), prostate (7.3%), stomach (5.6%).[1]

Among malignant diseases, primary lung cancer is the leading cause of death in the world. Every year there are more than 2.2 million cases of lung cancer in the world that cause the death of more than 1.7 million people. In 2020, the disease is estimated to be deadly around 1.1 million in Asia. Data from Asia landmark 2020, lung cancer caused the deaths of 109,250 people.[1]

Lung cancer is the most common type of cancer in men in Indonesia, and the fifth most common type of cancer in women. Lung cancer is also the leading cause of cancer death in men and second in women.[1] Bukittinggi's consensus in 2005 stipulated that EGFR-TKI could be given as a first-line treatment if patients for various reasons could not or refused chemotherapy.[1] From various research results consensus 19 could no longer be used because the EFGR mutation examination technique had been carried out in Indonesia. And efficacy is influenced from the location of the mutation that occurs.[3.4]

Studies in East Asian populations on erlotinib or gefitinib administration gave good results in cases with positive EGFR gene mutations in exon 19 and 21.[5,6] However, there was no significant difference in the efficacy of erlotinib with gefitinib in patients with EGFR gene mutations.[6] Given the importance of efficacy data on drugs that work as inhibitors on epidermal growth factor inhibitor receptors (EGFR-TKI) in this case the difference in the efficacy of gefitinib with erlotinib in the treatment of pulmonary adenocarcinoma patients with EGFR gene mutations at dr. H. A. Rotinsulu Lung Hospital.

With the access of TKI for lung cancer with EGFR mutation as a first-line therapy for generation 1 and 2 migrant workers. However, the determination of the choice of the 1st generation TKI, gefitinib or erlotinib, is not yet clear. Whether there are differences in the efficacy of gefitinib with erlotinib in the treatment of pulmonary Adenocarcinoma patients with EGFR gene mutations at DR. H. A Rotinsulu Lung Hospital and influencing factors such as patient characteristics and types of mutations.

Material and Methods

The design of this study is descriptive analytic. Secondary data are taken from medical records with retrospective cohort designs. The research site at the poly oncology of Dr. H.A. Rotinsulu Lung Hospital and the research time is from October 1, 2021 to March 31, 2022. The study samples were taken through existing medical record data from all pulmonary Adenocarcinoma patients with EGFR gene mutation of Dr. H. A. Rotinsulu Lung Hospital who received gefitinib or erlotinib treatment as a first line from January 1st, 2019 to December 31th, 2021. Inclusion Criteria: Patients with KPKBSK diagnosis based on cytopathological and histopathological examinations; mutational EGFR test results (+) on exón 19, 21; using TKI > 2 months; have never received other therapies (surgery, radiotherapy, chemotherapy). Exclusion Criteria: Double Primary Cancer Patients.

Results

Research has been conducted at the Dr. H.A. Rotinsulu Lung Hospital on 258 patients with pulmonary adenocarcinoma patients with EGFR gene mutations who received gefitinib or erlotinib treatment as the first line from January 1st, 2019 to December 31th, 2021, and 139 met the inclusion and exclusion criteria. Sample Collection was carried out in a retrospective cohort. Secondary data was taken from medical records.

The characteristics of the study subjects are broadly summarized in table 1. Includes age, gender, smoking status, stage, EGFR mutations and their types, and Performance Status. The characteristic distribution has proportions that do not differ significantly in the groups of erlotinib and gefitinib, except for smoking characteristics. The proportion of those who used gefitinib was greater in the non-smoking group than in the group that smoked. A total of 139 subjects took part in this study.

Table 1. Characteristics of adenocarcinoma patients who received gefitinib and erlotinib therapy.

Characteristic	*Tyrosine Kinase Inhibitor*		*p-Value*
	Gefitinib (n=103)	*Erlotinib (n=36)*	
Age			
Median (Range)	59 (34-80)	61(39-81)	0.362
≥60 years	51 (49.6)	21 (58.3)	
<60 years	52 (50.4)	15 (41.6)	
Sex			0.219
Male	45 (43.6)	20 (55.5)	
Female	58 (56.4)	16 (44.5)	
Smoking (N=110)			0.03
Yes	17 (16.5)	14 (38.9)	
No	60 (83.5)	19 (61.1)	
Staging			0.361
Stage IIIA and IIIB	16 (15.5)	8 (22.2)	
Stage IVA and IVB	87 (84.5)	28 (77.8)	
Mutation Type of EGFR			0.93
Single	78 (75.7)	27 (0.75)	
Multiple	25 (24.3)	9 (0.25)	
EGFR Mutation			0.042
Exon 19, del	55 (53. 3)	12 (33.3)	
Exon 21; L858R	22 (21.3)	15 (44.7)	
Lain-lain	26 (25.2)	9 (25.0)	
Performance Status			0.997
<2	83 (80.5)	29 (80.5)	
≥2	20 (19.5)	7 (19.5)	

For EGFR mutation type, there are two largest types of mutations found in the subject group, including Exon 19 del and Exon L858R. The types of mutations found in this study are presented in **Image 1**.

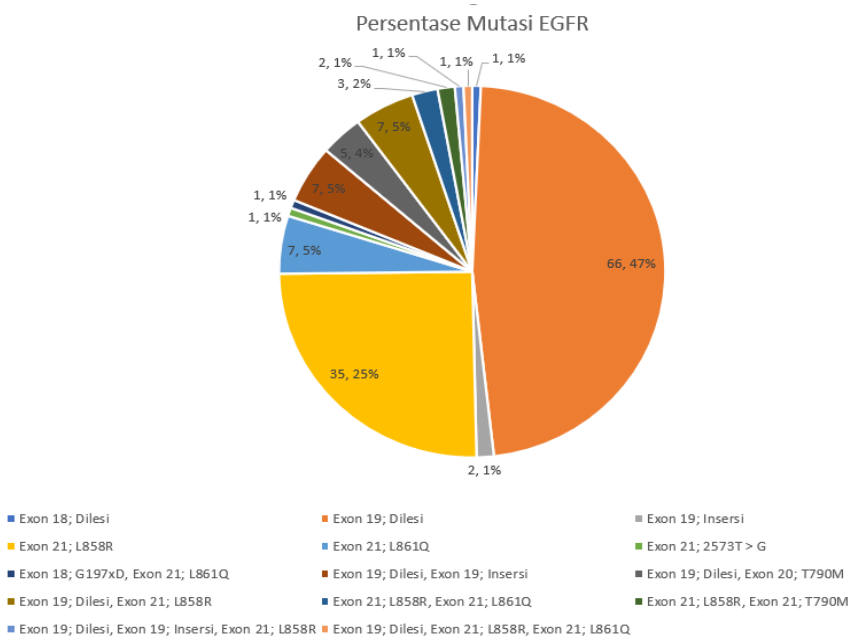

Image 1. Diagram for Type EGFR Mutation

Progression Free Survival

The median PFS group gefitinib 26 months, the erlotinib group 17 months with log rang test p> 0.5.

The PFS for both groups at 1 year, 2 years, and 3 years respectively were (80% vs 87%), (53% vs 0%), dan (19% vs 0%), p=0,184.

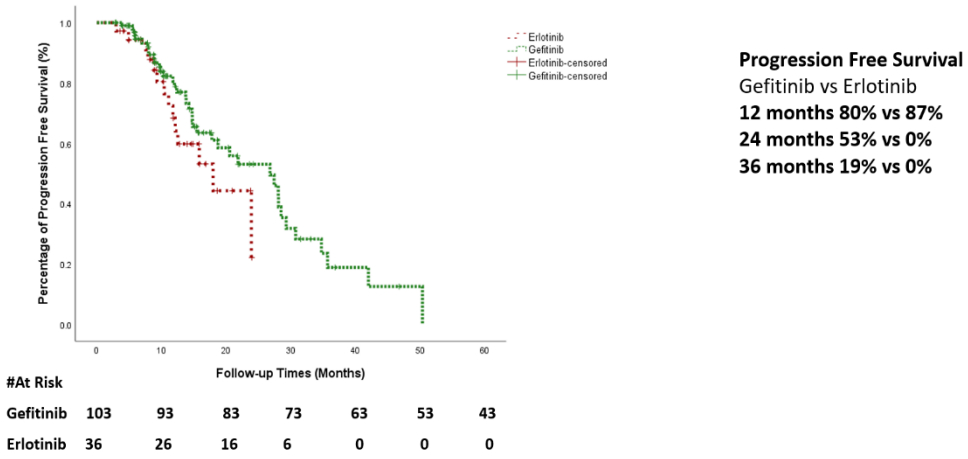

Image 2. Graph of Kaplan-Meier PFS for Gefitinib and Erlotinib

Table 2. Effect Hazard Ratio (HR) of Each Characteristic on PFS

Variable	HR	P (z)	95% CI	
Age	1.6	0.076	0.9	2,8
Sex	1,7	**0.049**	1,0	3.0
Mutase	1,4	0.287	0.7	2,5
TNM	1,5	0,169	0.8	3,0
PS	0,8	0.687	0.4	1,7
TKI	1.5	0.188	0.8	2.9

All characteristic variables with significant values of P (z) > 0.05, except for the sex variable HR 1.7 CI95% 1.0-3.0 p=0.049, which confirmed multivariate analysis of HR 1.9 CI95% 1.0-3.4, p=0.033.

Overall Survival

The overall median survival time (MST) in patients receiving TKI without distinction from gefitinib or erlotinib was 46.78 months with an average incidence of 0.007. View in **Table 3.**

Table 3. Median Survival Time Over-all

	Incidence rate	subject	MST
Total	0.007	139	46.78

The median survival time of the gefitinib group is the same as the overall MST which is 46.78 months. MST in the erlotinib TKI group cannot be analyzed. Incidence rate ratio (IRR) in TKI group 0.74 dan 95% CI IRR 0.21; 3.24.

Table 4. Median Survival Time TKI

Dead	Incidence rate	Subject	MST	IRR	95% CI IRR	
erlotinib	0.009	36	.46.78	0.74	0.21	3.24
gefitinib	0.007	103				

The results of the overall survival analysis in both groups, gefitinib and erlotinib groups at 1 year, 2 years, and 3 years respectively were (96% vs 95%), (91% vs 0%), and (91% vs 05) with significant values p=0.356, shown in **Image 3**

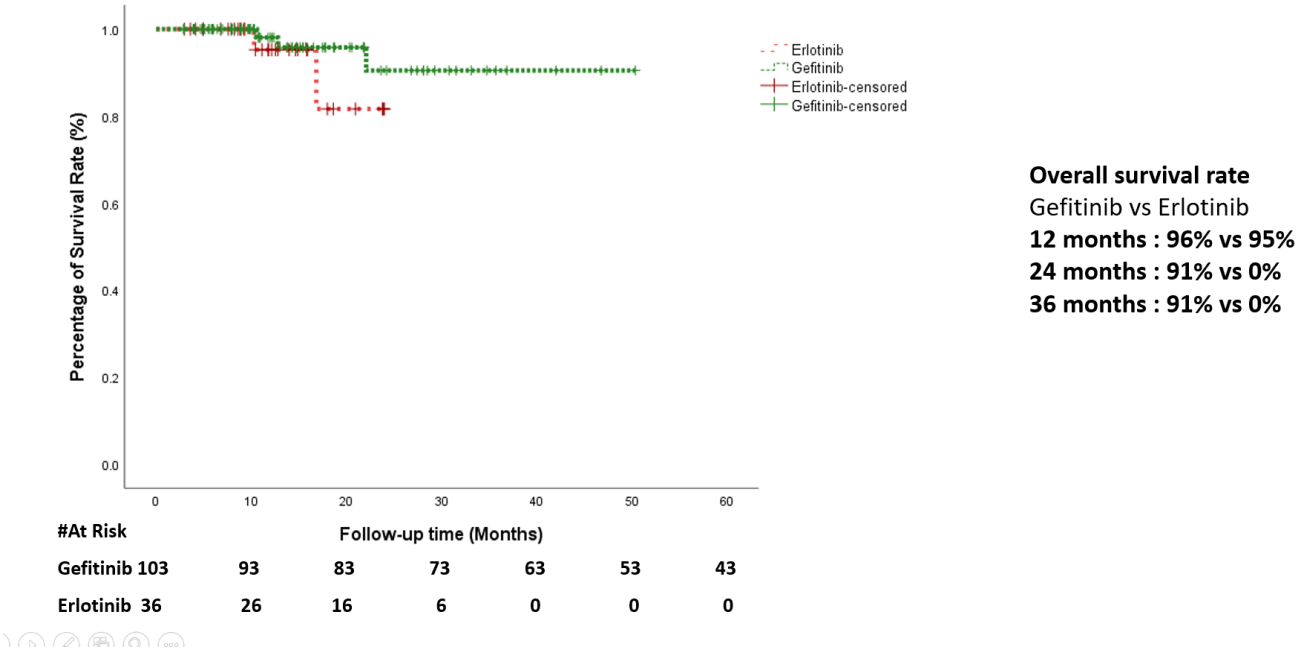

Image 3. Graph of Kaplan-Meier OS for Gefitinib and Erlotinib groups

Hazard Ratio (HR) of each characteristic to the OS with bivariate analysis is shown in table 4.5-3. All characteristic variables with significant values of P (z) > 0.05 and confirmed with a value of 95% CI.

Table 5. Effect Hazard Ratio (HR) Effect of Each Characteristic on OS

Dead	HR	P (z)	95% CI	
Age	0.54	0.27	0.19	1.59
Sex	2.5	0.11	0.81	7.74
Smoking	1.39	0.66	0.35	5.14
Mutation	0.97	0.95	0.32	2.94
TNM	2.29	0.08	0.89	5.91
PS	1.02	0.95	0.52	2.02
TKI	0.66	0.5	0.19	2.2

Time of Treatment

Median TOT of the gefitinib group of 12 months, the 11-month erlotinib group with a log rank test of p> 0.5 The results of the TOT analysis in the two groups of groups at 1 year, 2 years, and 3 years respectively were (98% vs 87%), (53% vs 0%), and (19% vs 0%) p=0.172

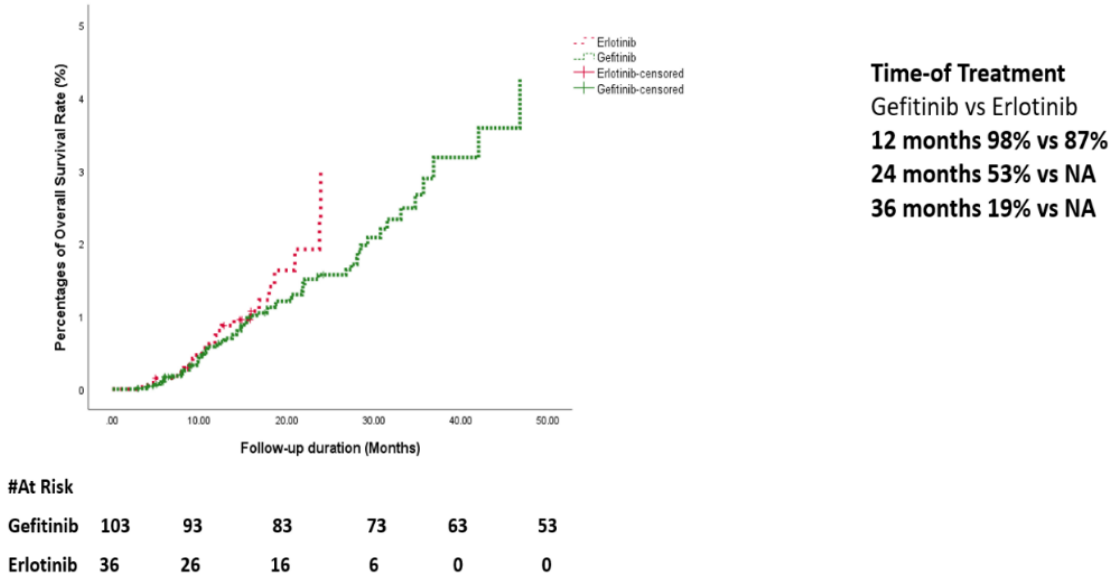

Image 4. Kaplan-Meier chart for TOT for Gefitinib and Erlotinib Groups

Table 6. Effect Hazard Ratio (HR) of Each Characteristic on TOT

Variable	HR	P (z)	95% CI	
Age	1.5	0.037	1.0	2,4
Sex	1,6	0.020	1,0	2,6
Mutation	1,4	0.149	0.8	2,3
TNM	1,3	0,241	0.8	2,3
PS	0,9	0.920	0.5	1,6
TKI	1.4	0.184	0.8	2.2

All characteristic variables have significant values of P(z) > 0.05 and are confirmed with a value of 95% CI, except age and gender. Age < 60 years against >60 years with confirmation of bivariate test (HR 1.7; 95%CI 1.1-2.7; P 0.013), while men against women with confirmation of bivariate tests were significantly meaningful (HR 1.8; 95%CI 1.1-2.8; P 0.012).

Discussion

The median duration of monitoring in the gefitinib and erlotinib groups was 10.5 and 11.4 months. In this study, the PFS median results of the Gefitinib group were 26 months PFS median and in erlotinib 17 months. The PFS for both groups at 1 year, 2 years, and 3 years respectively were (80% vs 87%), (53% vs 0%), and (19% vs 0%). Although gefitinib is higher compared to erlotinib in PFS but its meaning is not statistically meaningful (p=0.184).

Laitupa A at Poli One at RSUD DR. Soetomo Surabaya compared the efficacy of gefitinib with erlotinib, obtaining PFS and OS results in the two groups did not differ significantly.[28] Research of Sutandyo N et al, comparing the efficacy of gefitinib with erlotinib and afatinib obtained PFS results in subjects who received gefitinib and erlotinib were 9 and 13 months, respectively, Log-rank analysis showed that the two groups did not differ significantly p=0.28.[29]

In contrast to the research of Yang JJ et al who got the median results of PFS gefitinib and erlotinib were 10.4 and 13 months.[22] Krawczyj P's research obtained the median PFS in gefitinib and erlotinib was 9 months and 10 months.[34] Studies of Urata Y et al, obtained median PFS at gefitinib 6.5 months and erlotinib 7.5 months and 10 months (HR, 1.125; 95% CI, 0.940- 1.347; HR 1,068; 95% CI, 0.893-1.277).[31] A meta-analysis study conducted by Yang Z et al showed no significant differences in PFS between the gefitinib and erlotinib groups (HR, 1.00; 95% CI, 0.95 to 1.04, p 5 0.89).[21]

Univariate and multivariate analyses for PFS were performed with Cox-proportional hazard regression. When p<0.05, the data is said to be significant statistics. The output of the magnitude of the influence of variables on patient survival is expressed in the form of a hazard ratio (HR) using a 95% confidence interval to assess precision. Variables are made in nominal form, including age, gender, SF, stage, EGFR mutation, and the type of TKI used. PFS univariate analysis showed no significant differences in all six variables, PFS univariate analysis showed that sex affected the PFS of both groups (p=0.049, HR 1.7 CI95% 1.0-3.0). A multivariate analysis confirmed that gender (p=0.033, HR 1.9 CI95% 1.0-3.4) as well as age (p=0.034, HR 1.8 CI95% 1.0-3.3).

The median survival time of the gefitinib group is the same as the overall MST of 46.78 months. MST in the erlotinib TKI group could not be analyzed. The OS at 1 year, 2 years, and 3 years in the gefitinib and erlotinib groups were (96% vs 95%), respectively, (91% vs 0%), and (91% vs 05)." Although there were differences between the two groups in OS, no meaningful differences were obtained between the gefitinib and erlotinib groups with the results of the cox regression analysis obtained a p value of 0.356.

The research conducted by Asami K et al obtained the average OS results of the gefitinib group ranging from 17.5-35.5 months and in the erlotinib group ranging from 19.3-22.7 months.[15] A meta-analysis study conducted by Yang Z et al showed no meaningful differences in the OS between the gefitinib and erlotinib groups (HR, 0.99; 95% CI, 0.93 to 1.06, p 5 0.82; heterogeneity I2 5 42%, p=0.450).[21] Studies of Urata Y et al, obtained median OS in gefitinib 6.5 months and erlotinib 22.8 months and 24.5 months (HR, 1,038; 95% CI, 0.833 - 1.294).[32]

Univariate and multivariate analysis for the OS was performed with *Cox-proportional hazard regression*. When p<0.05, the data is said to be significant statistics. The output of the magnitude of the influence of variables on patient survival is expressed in the form of a *hazard ratio* (HR) using a 95% confidence interval to assess precision. Variables are made in nominal form, including age, gender, SF, stage, EGFR mutation, and the type of TKI used. Univariate analysis of OS did not show any significant differences in the six variables, however, in multivariate analysis age became an important predictor in the OS (p=0.036, HR 15.4 CI95% 1.2-201.2).

Median TOT group gefitinib 12 months, erlotinib group 11 months with log rank test p>0.05. The TOT at 1 year, 2 years, and 3 years in the gefitinib and erlotinib groups respectively were (98% vs 87%), (53% vs 0%), and (19% vs 0%). Although there were differences between the two groups in TOT, no meaningful differences were obtained between the gefitinib and erlotinib groups with the results of the cox regression analysis obtained a p value of 0.172. Research of Urata Y et al, obtained median TOT at gefitinib 5.6 months and erlotinib 5.3 months (HR, 1.032; 95% CI, 0.866 to 1.231).[32]

This study has some unavoidable limitations that can affect the results of the study. Some of these limitations include: this study was carried out with an observational design of a retrospective cohort method taken through secondary data from the medical records of lung cancer patients so that these

data are highly dependent on the medical records. Some patient medical records could not be found or the required patient data were incomplete, for example, recording side effects of therapy targets and records of patient clinical development making it difficult to see or assess the patient's subjective and semisubjective response.

Conclusion

Based on the results of the study, there was no difference in efficacy between gefitinib and erlotinib in the treatment of pulmonary Adenocarcinoma patients with EGFR gene mutations at Dr. H.A. Rotinsulu Lung Hospital.

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Case Report

Marjolin's ulcer: A case series

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Abstract

Background: Marjolin's ulcer (MU) is a rare but aggressive malignant transformation of long-standing scars or chronic wounds.

Case Illustration: we present three cases of MU that arise from post-traumatic scar. Two of the cases were found on the lower extremity and one on the scalp. Two lesions of lower extremities were preceded by burn injury from various causes. One lesion on the scalp was caused by non-burn trauma. Diagnosis was confirmed after tissue biopsy which revealed well-differentiated squamous cell carcinomas. Two patients underwent surgical intervention (wide excision and Mohs micrographic surgery) followed by split-thickness skin graft (STSG). In one patient, a wide excision was planned to be performed but the patient died before the surgery.

Discussion: the most frequent type of MU is squamous cell carcinoma (SCC). Extremity is the most common sites of predilection followed by the head and neck region. Marjolin's ulcer with histopathological feature of SCC is more aggressive and carries a poor prognosis with a high rate of recurrence.

Conclusion: early recognition of malignant conversion followed by comprehensive staging and early treatment, are of the utmost importance. Surgery remains the optimal treatment for MU, frequent and intense follow-up after surgery is required.

Keywords*: marjolin's ulcer, scar, squamous cell carcinoma, ulcer*

Abstrak

Latar Belakang: Ulkus Marjolin (UM) merupakan keganasan yang jarang namun bersifat agresif yang berasal dari jaringan parut atau luka kronik.

Ilustrasi Kasus: dilaporkan tiga kasus UM yang berasal dari jaringan parut pascatrauma pada masa anak-anak. Ulkus terdapat pada regio ekstremitas bawah dan kulit kepala. Dua kasus berupa lesi pada ekstremitas bawah muncul pada jaringan parut terkait luka bakar, sedangkan satu kasus berupa lesi pada skalp disebabkan oleh trauma lain. Pemeriksaan histopatologi untuk ketiga kasus tersebut menunjukan hasil karsinoma sel skuamosa berdiferensiasi baik. Tindakan bedah (eksisi luas dan bedah Mohs) diikuti penutupan defek dengan split-thickness skin graft (STSG) sudah dilakukan pada dua pasien. Satu pasien dengan lesi di skalp direncanakan untuk tindakan eksisi luas.

Diskusi: karsinoma sel skuamosa (KSS) merupakan jenis keganasan pada UM yang paling banyak ditemukan. Ulkus Marjolin paling banyak ditemukan pada regio ekstremitas, diikuti kepala dan leher. Ulkus Marjolin dengan gambaran histologi KSS lebih agresif dan memiliki prognosis yang buruk dengan risiko kekambuhan tinggi.

Kesimpulan: deteksi dini adanya perubahan ke arah keganasan, menentukan stadium kanker secara komprehensif, dan tata laksana sedini mungkin, merupakan hal yang penting. Tata lakasana utama UM adalah tindakan bedah dan diperlukan pengamatan berkala secara ketat pascabedah.

Kata kunci: *jaringan parut, karsinoma sel skuamosa, ulkus, ulkus Marjolin*

Background

Marjolin's ulcer (MU) is a rare cutaneous malignancy originating from scar tissue formed by any cause or chronic injury.[1,2] Jean-Nicolas Marjolin, a French surgeon, first discovered chronic ulcers in scar tissue caused by burns in 1828. Most MU occur in scar tissue caused by burns with an incidence of 0.77 –2%, especially in second to third-degree burns with secondary wound healing.[2,3] In addition to burns, chronic inflammatory conditions could also be a predisposition to MU, such as osteomyelitis, hidradenitis suppurativa, venous ulcers, diabetic ulcers, and anal fistulas.[2]

Marjolin's ulcer most commonly occur in the fifth decade of life with a male to female ratio of 2:1.[2] The latent period from the onset of trauma to progression into become a malignancy is generally slow, at 30-35 years.[4] The lower extremities are the most common site of MU (53.3%). The scalp region has the highest risk of bone invasion.[5,6]

Marjolin's ulcer is often misdiagnosed as an infection or chronic ulcer and leads to delayed treatment. When compared to sun exposure-related skin malignancies, scarring-related carcinomas have a risk of regional metastasis, poorer prognosis, and higher mortality.[3,5] Surgery is the main modality in the management of MU.[7,8]

We report 3 cases of a MU arising in areas of healing burn and non-burn scars. Physicians should have a high index of suspicion in chronic wounds that are recalcitrant to therapy and should remember to biopsy all suspected lesions. Early recognition and definitive treatment are the mainstays ensuring the best prognosis.

Case Illustration

Case 1

A 49-year-old male presented with 45-year history of scar wound on the head which developed an enlarging ulcer within 6 months. The wound was malodourous, bleed easily, and painful. In the parieto-occipital region, there was a hypertrophic scar, 10 x 8 cm in size, irregular, partly shiny surface, skin-coloured, accompanied by a 7 x 5 x 0.5 cm ulcer and alopecia (Figure 1A). The finding of dermoscopy were consistent with SCC (Figure 1B). There were no palpable enlarged lymph nodes. Histopathological examination revealed acanthosis, ulcer, infiltrative epithelial malignant tumor mass between the connective tissue stroma, and horn pearl which corresponds to well-differentiated squamous cell carcinoma (Figure 2). Chest X-ray examination and abdominal ultrasound found no signs of metastases in the heart, lungs, or intra-abdominal organs. Brain multi-slice computed tomography (MSCT) scan with contrast showed a heterogeneous suspected malignant lesion in the cutis-subcutis of the left parieto-occipital region to the left posterior neck which destroys the parieto-occipital bone and attaches to the duramater, with multiple bilateral cervical lymphadenopathies with the largest size of 1 cm. The patient was diagnosed with SCC T4NxMx as well as secondary bacterial infection. Wide excision was planned to be performed by Oncologic surgeon and Neurologic surgeon, but the patient died before the surgery.

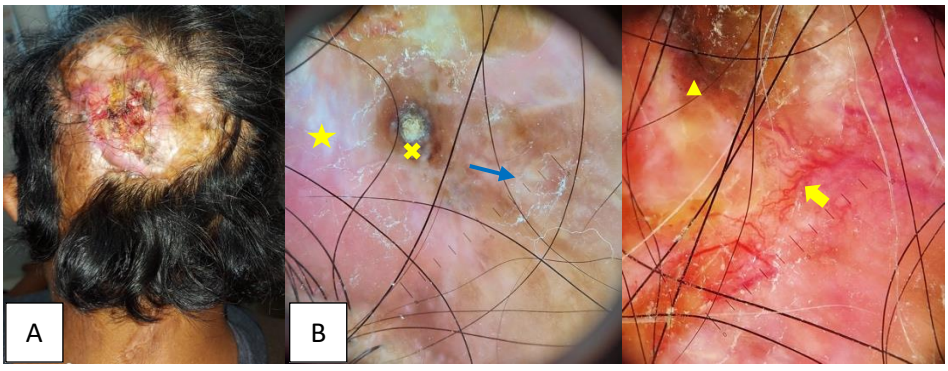

Figure 1. (A) Clinical manifestations of Marjolin's ulcer in the parieto-occipital region. (B) Dermoscopic features of white structureless areas (star), follicular hyperkeratosis (cross), scale-crust (blue arrow), polymorphous vessels

(yellow arrow), ulceration (triangle), and mixed background

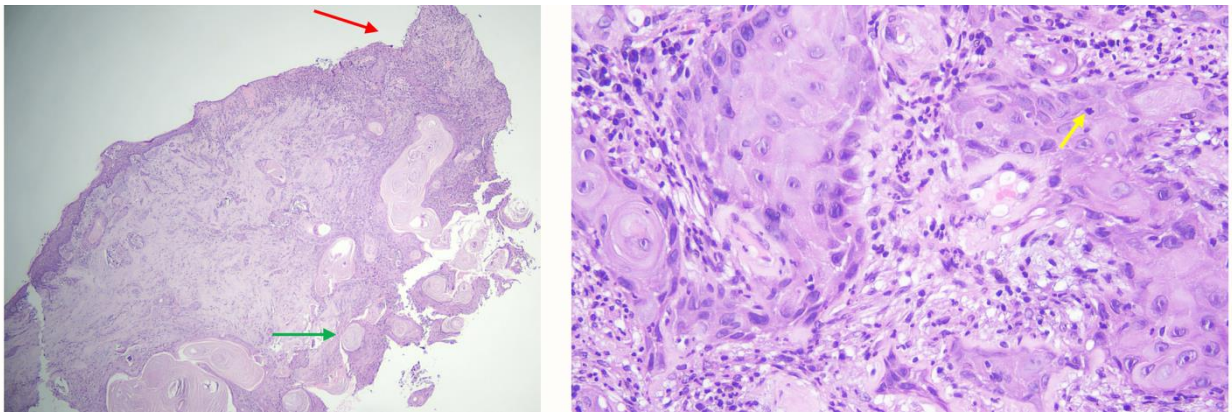

Figure 2. Well differentiated squamous cell carcninoma: ulceration (red arrow), acanthotic epidermis, keratin pearls (green arrow), pleomorphism and mitotic figures (yellow arrow).

Case 2

A 48-year-old male with long lasting, painful, chronic ulceration on burn scar on the left upper leg. The wound started as a small lesion and progressively enlarged within 2 years. The lesion had grown into 22 x 14 x 0.5 cm exophytic, raised edges, well-circumscribed, and malodorous ulcerated lesion (Figure 3A). Dermoscopy of the lesion showed polymorphous vessels, white circles, rosettes, white structureless areas, scale-crust, and mixed background (Figure 3B). Painless, mobile lymph nodes enlargement with 1.5 – 2 cm in size were palpated on the left inguinal. Skin biopsy results showed atypical mitosis, horn pearl, and dense inflammatory cells of lymphohistiocytes, eosinophils, and plasma cells in the dermis which corresponds to well-differentiated squamous cell carcinoma. MRI examination of the lower extremities indicated a malignant mass in the cutis to medial subcutis to the posterior side of left femoral region without muscle, bone, or neurovascular involvement, with left inguinal and external parailiac lymphadenopathy. Diagnosis of SCC T3NxMx with secondary bacterial infection was established. The patient underwent wide excision and dissection of inguinal lymph nodes performed by surgical oncologist. A defect was reconstructed with split-thickness skin graft (STSG) by plastic surgeon. The incision edges were tumor-free, no lymphovascular invasion was found. The entire lymph nodes were also tumor-free. There was no recurrence reported.

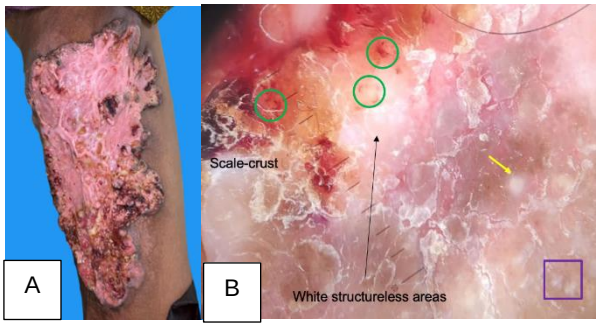

Figure 3. (A) Clinical manifestations of Marjolin's ulcer on the left upper leg region. (B) Dermoscopic features of polymorphous vessels (green circles), white circles (yellow arrow), rosettes (purple square), white structureless areas, scale-crust, and mixed background.

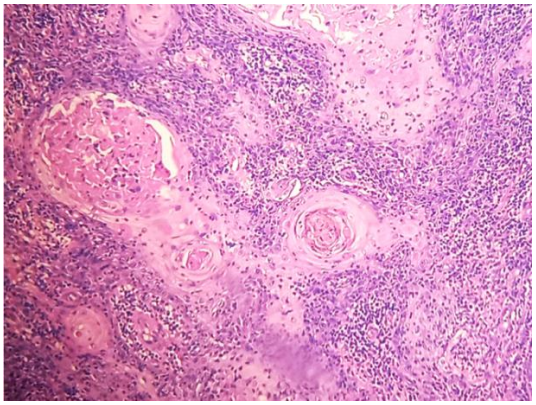

Figure 4. Well differentiated squamous cell carcinoma**:** atypical mitosis, horn pearl, and dense inflammatory cells of lymphohistiocytes, eosinophils, and plasma cells in the dermis.

Case 3

A 40-year-old female patient presented with a mass on the right lower leg which arises from long-standing burn scar. An irregular, ulcerated mass lesion with an approximate length of 8 x 5 x 1 cm was observed (Figure 5A). The dermoscopic examination revealed the presence of dotted vessels, hairpin vessels, hemorrhage, white structureless area, and mixed background (Figure 5B). There was no palpable enlargement of the lymph nodes. Histopathologic examination showed the features of acanthosis, ulceration, horn pearl, and dense inflammatory cells of lymphocytes, neutrophils, and keratinocytes proliferation with atypical nuclei, consistent with well-differentiated squamous cell carcinoma in the dermis. Immunohistochemical examination showed positive results for AE1/AE3 and CK5 staining. Staining with Ki67 was also positive in 30% of the tumor cells. No intra-abdominal or lymph nodes organ metastasis was found from abdominal and inguinal ultrasound examination. Right lower leg MRI showed a mass with characteristics of malignancy in the cutis of the posterolateral region of the right cruris, infiltration to the subcuticular fat, and no muscle involvement. Patient was diagnosed with SCC T3N0M0 as well as secondary bacterial infection. Mohs micrographic surgery and STSG surgery was conducted. Seven months following the surgery, we observed a recurrent lesion manifested as a single ulcer measuring 5.2 x 4 x 0.5 cm at the identical anatomical site. The patient underwent a second Mohs micrographic surgical procedure. A subsequent STSG was conducted by a plastic surgeon.

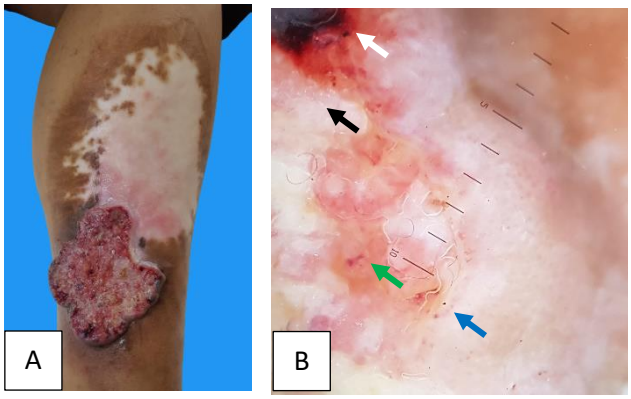

Figure 5. (A) Clinical manifestations of Marjolin's ulcer on the right lower leg. (B) Dermoscopic features: dotted vessels (blue arrow), hairpin vessels (green arrow), hemorrhage (white arrow), white structurless area (black arrow), and mixed background

Table 1. Differences in Characteristics of Marjolin's Ulcer Cases

	Case 1	**Case 2**	**Case 3**
Gender	Male	Male	Female
Age	49-year-old	48-year-old	40-year-old
Etiology of scarring	Wound infection	Burn injury	Burn injury
Location	Scalp	Upper leg	Lower leg
Age of trauma	4 years	6 years	10 years
Latent period	45 years	42 years	30 years
Onset of the disease	6 months	2 years	6 months
Secondary infection isolates	*Acinetobacter spp*.	*Pseudomonas aeruginosa*	*Escherichia coli*
Diagnosis*	SCC T4NxMx	SCC T3NxMx	SCC T3N0M0

SCC: squamous cell carcinoma. *According to National Comprehensive Cancer Network (NCCN) guideline in 2022.[9]

Discussion

Marjolin's ulcer is a cutaneous malignancy that occurs in scar tissue or chronic wounds with the most clinical manifestations in the form of chronic ulcers. The average age of onset of MU is 52.1 years.[10] Based on its latent period, MU is classified into acute and chronic. Acute ulcer is defined as malignant changes that occur within one year after the initial injury. Malignancies that occur for more than one year are called chronic ulcers.[11] All three patients in this case report were ≥40 years old and had a history of post-traumatic scarring that occurred at the young age with a latent period of MU of more than 30 years. Patients in case number 2 and 3 had a history of burns in the lower extremities. The most common etiology of MU is scar tissue caused by burns (82.5%), however, MU can also occur in chronic wounds and non-burn-related scars.[12] A cohort study by Xiang F, et al. in 2018 conducted on 140 patients with Marjolin's ulcers, showed that the most common location of MU lesions was the lower extremities (42.1%) followed by the head, face, and neck (34.5%).[6] The prevalence of bone invasion in patients with MU in the head, face, and neck regions is higher than MU lesions in other parts of the body.[6] In case 1, from the examination results of the brain MSCT scan with contrast, malignant lesions appear to destroy the occipital-parietal bone.

The pathogenesis of MU is still not fully understood. Scar tissue is suspected to lose immune cells that play a role in skin physiology. Thus, malignant cells can evade the immune response and become more aggressive. Cicatrisation of burn wounds can cause obliteration of lymphatic vessels leading to an impaired physiological immune system and increased risk of neoplastic growth.[13] Recent theories suggest an association between MU and genetic factors associated with human leukocyte antigen (HLA) DR4 and mutations of p53 and/or FAS genes.[11] Ultraviolet radiation (UV) also plays a role in the pathogenesis of MU because it can reduce the number of Langerhans cells that interfere with the function of the immune system and cause mutations of the p53 genes.[13] The patient in case 1 had a history of chronic sun exposure due to the patient's occupation as a motorcycle driver for more than 5 years. Whereas in the other two patients, it may be due to post-burn cicatrisation which causes lymphatic disorders and immune system disorders.

Squamous cell carcinoma is the most common histologic variant of MU (81.32%), followed by malignant melanoma (7.69%), basal cell carcinoma (4.40%), and osteosarcoma (2.20%).[14] Dermoscopic examination can help to distinguish the type of malignancy from MU and rule out the possibility of a chronic infection diagnosis. In all three patients, dermoscopic features in the form of ulceration, polymorphous vessels, scale-crust, white structureless area, and mixed background which corresponds to squamous cell carcinoma were found.[15] Histopathological examination is the gold standard to diagnose MU. Although the histopathological features in all three cases were well-differentiated SCC, but based on the National Comprehensive Cancer Network (NCCN) guidelines for SCC, all three patients were categorized as high-risk category based on location (head) and size (more than 4 cm).[9]

At the time of the initial visit, all three patients had secondary bacterial infections and had received definitive antibiotic therapy according to the results of culture and resistance tests. The management of patients in case 2 and 3 was wide excision and Mohs micrographic surgery followed by STSG. The patient in case 1 was planned for extensive excision by a Neurosurgeon and Oncologist surgeon because on examination there was a suspicion of invasion to the skull bone. This is in accordance with the NCCN guidelines for the management of high-risk SCC, namely Mohs micrographic surgery and wide excision with an incision limit of 2–4 cm followed by reconstruction with skin graft or local flaps. Radiotherapy is recommended for patients for whom surgery is not feasible or for cases of recurrence.[7,9] One patient (case 3) had local recurrence. Marjolin's ulcer has a recurrence risk of 20–50% and a metastatic risk of 27.5–40%. Tumor size greater than 10 cm increases the risk of distant metastasis and the risk of recurrence is higher in moderately poorly differentiated SCC or lymph node involvement.[7,10]

Conclusion

Marjolin's ulcer, a cutaneous malignancy that occurs in scar tissue, is most commonly caused by burns, and generally has a slow latent period. The most common histologic variant is SCC, while the most vulnerable area of invasion is the skull bone. Biopsy of any suspicious lesion should not be delayed to rule out malignancy. Dermoscopic examination can help to distinguish the type of malignancy of MU and surgery is the main therapy of MU. Close follow-up for the years ahead is necessary to ensure the patient's well-being.

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None

Author Contribution

All authors contribute equally to this project in the study preparation, data collection, case analysis and the writing of the manuscript

Conflict of interest

The authors report no conflicts of interest.

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Case Report

Unusual site of skin metastasis from lung adenocarcinoma: A case report

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Abstract

Background: Skin metastasis incidence is approximately 3,4% of lung cancer with highest incidence in man. It arises mostly in man from primary cancer of the lung (24%), colon (19%), melanoma (13%) and oral cavity (12%). In woman, it arises from breast (69%), colon (9%), melanoma (5%), ovaries (4%) and lung (4%) primary cancer. It may occur at the same time or before the primary cancer detected.
Case Illustration: Forty-sixth years old male referred with lesion found in chest x-ray during the medical check-up procedure. Nodules arose at parietal and abdomen region since three months prior. Chest CT scan revealed a solid 6,4 cm mass in long axis at the medial of left lung lobe. Head CT scan revealed subsolid nodule at cutaneous-subcutaneous of the left occipital attached to the periosteum without bone destruction and solid nodule at cortex-subcortex of right frontoparietal accompanied by perifocal edema. Bronchoscopy procedure found edematous mucosa of left B1 to B3 orificium. Histopathology and cytology examination confirmed adenocarcinoma with *wild-type* EGFR mutation.
Discussion: Preference site of lung cancer skin metastasis is at supra-diaphragm region. Nodules are usually firm, painless and appear as oval or round form. Ulceration may be seen. In our case, the lesion were ulcerate with granulation tissue at the edge and black scars form containing necrotic tissue. Adenocarcinoma is the most common type of lung cancer with skin metastases.
Conclusion: It is essential to consider any skin pathological form in patient with lung adenocarcinoma as skin metastases.

***Keywords*:** adenocarcinoma, lung cancer, skin metastasis

Abstrak

Latar belakang: Metastasis kanker paru ke kulit berkisar 3,4% dengan insidens tertinggi pada laki-laki yang umumnya berasal dari keganasan primer paru (24%), kolon (19%), melanoma (13%) dan rongga mulut (12%). Pada perempuan umumnya berasal dari keganasan primer payudara (69%), kolon (9%), melanoma (5%), ovarium (4%) dan paru (4%). Hal ini dapat terjadi pada saat yang sama atau sebelum kanker primer terdeteksi.
Ilustrasi kasus: Seorang laki-laki berusia 46 tahun datang dengan nodul pada foto toraks saat pemeriksaan kesehatan yang diawali kemunculan benjolan pada regio parietal dan abdomen tiga bulan sebelumnya. CT Scan toraks menemukan massa solid dengan ukuran terpanjang 6,4 cm pada lobus medius paru kiri. CT Scan kepala menemukan nodul subsolid pada lapisan kutis-subkutis di regio occipital yang melekat pada periosteum tanpa destruksi tulang dan nodul solid pada lapisan korteks-subkorteks di regio frontoparietal dengan edema perifokal. Pada bronkoskopi didapatkan mukosa edematosa di orifisium lobus atas kiri dengan stenosis kompresi pada sebagian orifisium B1 hingga B3 kiri. Pemeriksaan histopatologi dan sitologi menegakkan adenokarsinoma dengan mutasi EGFR *wild-type*.
Diskusi: Lokasi utama metastasis kulit pada kanker paru adalah regio supradiafragma dengan nodul yang keras, tanpa nyeri dan berbentuk oval atau bulat yang dapat disertai ulkus. Pada kasus ini, ditemukan lesi ulkus dengan jaringan granulasi pada tepi dan skar hitam yang mengandung jaringan nekrotik. Metastasis kulit pada kanker paru paling banyak ditemukan pada adenokarsinoma.
Kesimpulan: Lesi di kulit yang ditemukan pada pasien dengan adenokarsinoma paru harus diwaspadai sebagai metastasis.

Kata kunci: adenokarsinoma, kanker paru, metastasis kulit

Background

Skin metastases incidence is 3,4% of lung cancer with highest incidence in men that arise mostly from primary cancer of the lung (24%), colon (19%), melanoma (13%) and oral cavity (12%). In women, it arise from breast (69%), colon (9%), melanoma (5%), ovaries (4%) and lung (4%). In general, cutaneous metastasis from primary visceral malignancy is vary between 1-12%. It may occur at the same time or before the primary cancer detected. All histological types of lung cancer may develop metastases in the skin. Lung cancer is the fastest in developing skin metastases after initial diagnosis and a sign of poor prognosis, that combined with other extracutaneous metastases may decreases the survival time to approximately three months compared to ten months in skin metastases only. Preference site of lung cancer skin metastases is at supra-diaphragma region. Nodules are usually firm, painless and appear as oval or round form, adherent or mobile. Ulceration may be seen. Other form are plaque-like lesions, erysipelas-like papules, zosteriform lesions and scars. [1-5]

Case Illustration

A forty six-year-old male with history of smoking was referred to our hospital with lesion found in chest x-ray during the medical check-up before nodules biopsy procedure at the parietal and abdominal regions. Two months earlier, the nodules arised as tender and pain nodules that increasing in size. Blood streak and shortness of breath were sometimes occured accompanied by loss of body weight in three months. Pain also felt in right hand since year 2020 after ORIF procedure for right radius fracture caused by accident. Later on, several times seizures followed. Physical examination found mass at left parietal, left hypochondrium and suprapubic regions. Thoracic CT Scan procedure revealed solid 6,4 cm mass in long axis measured at the medial of the left lobe. The head CT Scan also revealed subsolid nodule at cutan-subcutaneous of the left occipital attached to the periosteum without any bone destruction ad solid nodule at cortex-subcortex of right frontoparietal accompanied by perifocal oedema that suggest a metastatic processes.

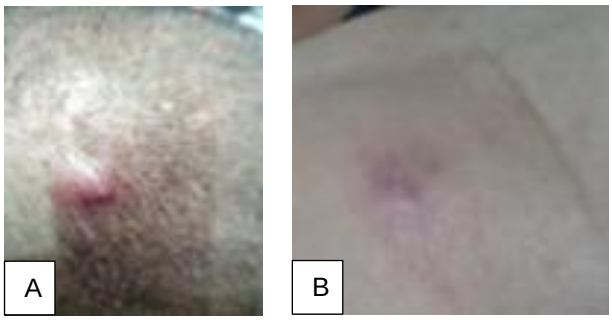

Figure 1. (A). Nodul in parietal region, (B). Nodul in abdominal region

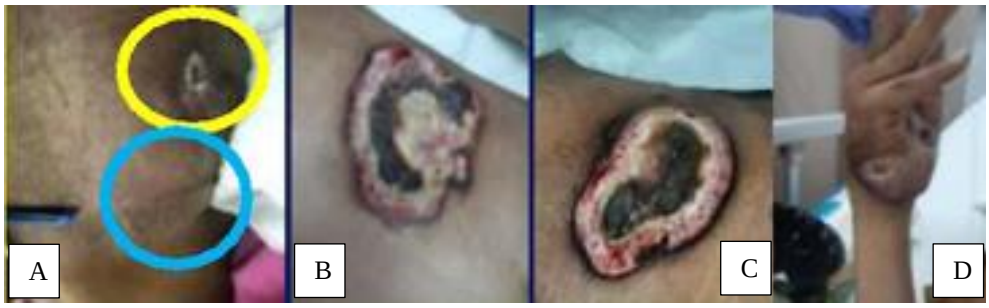

Figure 2. (A). Nodul in parieto-occipital region**, (B).** Ulcerative mass in abdominal region, **(C).** Ulcerative mass in suprapubic region, **(D).** Masses in right hand.

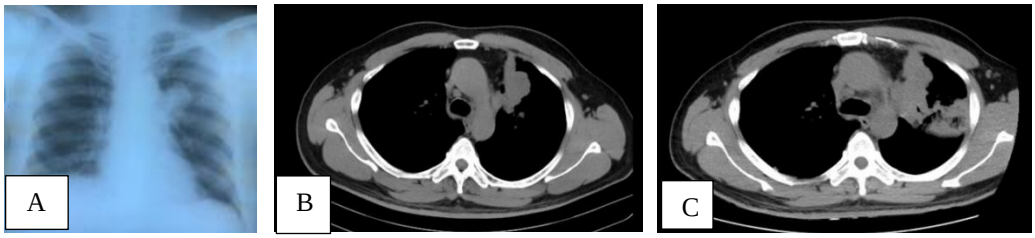

Figure 3. (A). Chest X-Ray prior to nodules biopsy, **(B).** Chest CT Scan following (A) **(C).** Chest CT Scan prior to diagnostic bronchoscopy procedure

Diagnostic bronchoscopy procedure found edematous mucosa at left upper lobe orificium with compression stenosis covering part of left B1, B2 and B3 orificium. Anatomical pathology result from histopathology examination from bronchial biopsy sample as well as cytology examination confirmed adenocarcinoma with wild type. The Epidermal Growth Factor Receptor (EGFR) mutation. Nodules biopsy from the chest wall, hand and inguinal confirmed metastases of adenocarcinoma. Bone scan concluded suspicion on osteoblastic metastatic lesion at right distal radius. In conclusion, the final diagnosis was left lung adenocarcinoma T4N2M1c (multiple subcutaneous nodules, brain, bones) stage IVB PS 2 wild type EGFR mutation, progressive disease. Patient underwent 5 cycles of external radiation continued with 10 cycles of whole brain radiotherapy and 6 cycles of chemotherapy with cisplatin and pemetrexate. Bondronat regiment also performed. As the disease progressed, new nodules found at occipital, femur and gluteus region.

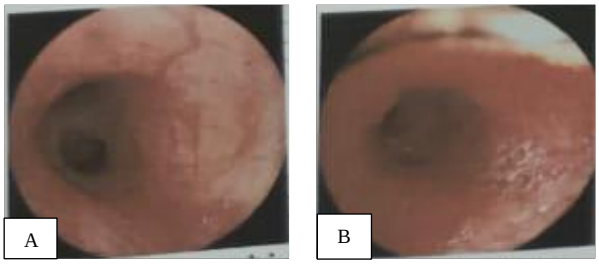

Figure 4. (A). Edematous hypervascularization and bumpy mucosa at left upper lobe orificcium, **(B).** Compression stenosis with edematous mucosa covering part of left B1+B2 and B3

Discussion

Lung cancer can metastasize to all organs with only 3,4% incidence at the skin. It is uncommon with poor prognostic indicator, one of which is due to poor response to chemotherapy. It becomes poorer with extracutaneous metastases and may be detected at the same time or before the primary cancer detected in 20-60% of cases that mostly occur in regions close to the primary site. The most common is adenocarcinoma, followed by squamous cell carcinoma, small cell and large cell carcinomas. The common sites of metastases from lung cancer are the head, neck, chest and abdomen, while skin metastasis is found mostly at supra-diaphragma region in single or multiple presentations. Cancer to the upper lobes of the lung also has a higher tendency to skin metastasis. The formation are firm, painless and appear as oval or round nodules. Some may mimic specific dermatological conditions such as cutaneous cyst, dermofibroma, pyogenic granuloma, hemangioma, papular eruptions, herpes zoster eruptions, rapidly infiltrating plaques, alopecic patches, cellulitis, erysipelas, bullae and vascular tumors with telangiectasis. Ulceration may be seen.[1-10] In our case, the lesions ulcerated with granulation tissue at the edge and black scars formed containing necrotic tissue. Patient also suffered with brain, bone, abdomen, wrist join and inguinal metastases. Seizure took place several times and pain was felt at metastatic site with easily bleed as well.

Pathogenesis of skin metastasis of lung cancer derived from lymphovascular invasion, that often limited to the dermis and subcutaneous layer with poor differentiation and upper lobe tumours increasing the risk of metastasis. Venous and arterial system may involve as the route of skin metastasis. Molecularly, skin metastasis is an organized, non-random and organ-selective process orchestrated by interaction among several heterogenous molecules which are largely unknown. The average time for lung cancer to metastasize to the skin is 5,7 months. [4,8-12]

The diagnosis is based on clinical information on respiratory and systemic complaints or a history of smoking, Physical examination finding is general as the skin metastasis may vary in form and location. The complementary examination is the chest X-ray followed by chest CT Scan that remains the best way to evaluate local extension. Diagnosis is confirmed by histopathological and immunohistochemistry (IHC) analysis, that often poorly differentiated.[5,11-14] In our case, diagnosis was confirmed by histopathological analysis from bronchial biopsy revealing malignancy with impression of adenocarcinoma. Biopsy from chest wall and right wrist and right inguinal also confirmed as metastases of adenocarcinoma. Cytology analysis were performed by bronchial washing and brushing that conclude a positivity of adenocarcinoma. The Epidermal Growth Factor Receptor (EGFR) mutation analysis was negative and patient then treated with chemotherapy. Bone survey was performed and stated no sign of metastases at the moment but as time goes by, there was suspicion on osteoblastic metastatic lesion at right distal radius found at bone scan.

Skin metastasis in lung cancer patients is associated with an aggressive tumor. Generally, only palliative chemotherapy is offered and radiotherapy to the cutaneous metastases is indicated associated with severe pain or bleeding for with survival times 3-6 months. Treatment for solitary cutaneous metastases

includes surgery, chemotherapy or radiotherapy. In case of multiple skin metastases, chemotherapy is the primary treatment. The respons is usually minimal due to poor blood supply to the skin. Resection of the skin lesion offers a better survival with three months of gain, but after all, the prognosis remains poor. Radiation therapy is indicated for pain and bleeding.[5,13-15] In our case, patient was treated with regiment of Cisplatin and Pemetrexate and 5 cycles of external electrone radiation continued with whole brain radiotherapy (WBRT) for the brain metastases, as radiotherapy is recommended for local palliation or prevention of symptoms such as pain and bleeding.[16] Response Evaluation Criteria in Solid Tumors (RECIST) after 4 cycles of chemotherapy was partial respons but came to progressive disease at the end of the cycle. Patient passed away 10 months after adenocarcinoma was confirmed and around 13 months after first nodul appearance at skin of abdomen and occipital region.

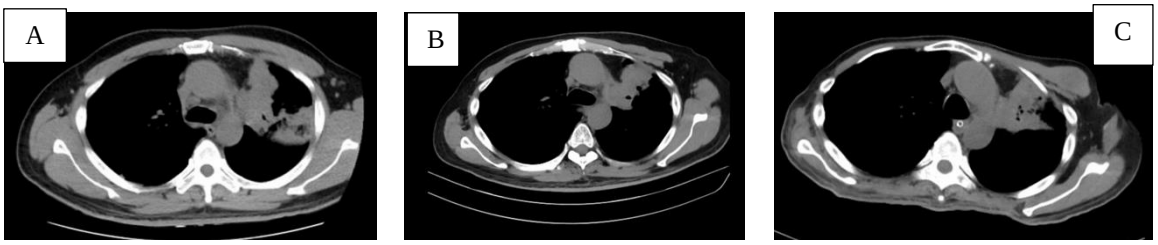

Figure 5. (A). Chest CT Scan prior to diagnostic bronchoscopy procedure, **(B).** Chest CT Scan after 4 cycles of chemotherapy – partial respons**, (C).** Chest CT Scan after 6 cycles of chemotherapy – progressive disease.

Conclusion

Skin metastases is an unusual form of lung adeno-carcinoma metastases. The lesion may be non-specific without any characteristic pattern and may be confused with other benign lesions. Therefore, it is essential to consider any skin pathological form in a patient with lung adenocarcinoma with suspicion to skin metastases as well as considering metastatic skin lesion in patient that leads to lung adeno-carcinoma diagnosis.

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Review Article

Anticancer potential of Panduratin A against non-small cell lung cancer

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Abstract

Lung cancer is one of the leading causes of cancer death worldwide and ranks first in the number of cancer cases that occur in men and fourth in women in Jakarta. Small cell lung cancer (SCLC) accounts for 15% of lung cancer cases, whereas non-small cell lung cancer (NSCLC) accounts for 85% of instances. Exposure to carcinogens, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) increases lung cancer risk. Repeated exposure to carcinogens can cause genetic mutations by forming DNA adducts. Genetic mutations commonly occur in EGFR, the p53 tumor suppressor gene, and failure in apoptosis. Conventional therapy has limitations such as severe side effects, drug resistance, and treatment costs. Therefore, a new strategy is needed to use natural plant compounds as chemopreventive agents or to slow cancer growth. Panduratin A is a natural chalcone-derived compound isolated from fingerroot or Temu Kunci (*Boesenbergia pandurata*). This compound exerted various antibacterial, anti-inflammatory, antioxidant, and anticancer activities. Panduratin A's anticancer mechanisms included cell cycle arrest, induction of apoptosis, and anti-angiogenesis in several cancer cell lines. Panduratin A was also selectively cytotoxic and inhibited the PI3K/Akt signaling pathway.

Keywords: *Angiogenesis, apoptosis, Boesenbergia pandurata, temu kunci, panduratin A*

Abstrak

Kanker paru merupakan salah satu penyebab utama kematian akibat kanker di seluruh dunia dan menempati urutan pertama dalam jumlah kasus kanker yang terjadi pada pria dan keempat pada wanita di Jakarta. Kanker paru sel kecil menyumbang 15% kasus kanker paru, sedangkan tipe non-sel kecil menyumbang 85% kasus. Paparan karsinogen, logam berat, dan hidrokarbon aromatik polisiklik meningkatkan risiko kanker paru. Paparan berulang terhadap karsinogen dapat menyebabkan mutasi genetik dengan membentuk hasil tambahan DNA. Mutasi genetik umumnya terjadi pada *epithelial growth factor receptor* (EGFR), gen tumor supresor p53, dan kegagalan apoptosis. Terapi konvensional memiliki keterbatasan seperti efek samping yang parah, resistensi obat, dan biaya pengobatan. Oleh karena itu, diperlukan strategi baru untuk memanfaatkan senyawa tumbuhan alami sebagai agen kemopreventif atau memperlambat pertumbuhan kanker. Panduratin A merupakan senyawa alami turunan kalkon yang diisolasi dari akar temu kunci (*Boesenbergia pandurata*). Senyawa ini memiliki berbagai aktivitas antibakteri, antiinflamasi, antioksidan, dan antikanker. Mekanisme antikanker Panduratin A meliputi penghentian siklus sel, induksi apoptosis, dan anti-angiogenesis pada beberapa lini sel kanker. Panduratin A juga bersifat sitotoksik selektif dan menghambat jalur pensinyalan PI3K/Akt.

Kata Kunci: Angiogenesis, apoptosis, *Boesenbergia pandurata*, temu kunci, panduratin A

Background

Lung cancer kills more people than any other type of cancer in the world, with only 15% of people being able to survive it.[1] The Population-Based Cancer Registry in Jakarta stated that lung cancer is the most common type of cancer in men and the fourth most common type in women.[2] Resistance during treatment, especially at an advanced stage, causes high mortality.[3] The leading cause of lung cancer was smoking, accounting for 80–90% of cases. Then, followed by other factors such as occupational exposure, family history, genetic susceptibility, and chronic obstructive pulmonary disease (COPD).[4]

According to the WHO, lung cancer is classified as non-small cell lung cancer (NSCLC) with 85% of cases and the remaining 15% of small cell lung cancer (SCLC). NSCLC is divided into squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Adenocarcinoma is the most common subtype, accounting for more than 40% of cases.[5] Exposure to carcinogens, heavy metals, and polycyclic aromatic hydrocarbons (PAHs) increases the risk of lung cancer.

Repeated exposure to carcinogens can cause genetic mutations by forming DNA adducts. Genetic mutations commonly occur in EGFR, the p53 tumor suppressor gene, and failure in apoptosis.[6-8] In several cases of NSCLC, it was found that Bcl-2 was overexpressed and up-regulated by Bax, causing the Bax per Bcl-2 ratio to be higher than 1. The heterodimerization of this complex, which controls the level of apoptosis, made it more resistant to apoptosis.[9]

Treatment of NSCLC is mostly stage specific. Patients with stage I-II could be treated with surgery, radiotherapy for non-surgical patients, and systemic therapy. Systemic therapy includes chemotherapy, immunotherapy, and targeted therapy.[10] The limitations of conventional therapy, such as drug side effects and treatment costs, lead to the urgency of developing a new therapeutic strategy. There were promising opportunities for utilizing natural plants as chemo-preventive agents in preventing or slowing disease progression. So, natural compounds from medicinal plants can be used to make new anticancer drugs that are safe and work well.[11,12]

Panduratin A is a hexenyl chalcone derivative isolated from Temu Kunci (*Boesenbergia pandurata*). Temu Kunci has been used for a long time as an ingredient in food and as a traditional treatment for aches and pains, coughs, rheumatism, fungal infections, and colic.[13] Panduratin A is reported to have antibacterial, anti-inflammatory, and antioxidant activities.[14,15] Recent studies have demonstrated the potential of panduratin A for anticancer activity in inhibiting cell proliferation in breast cancer cells, induction of apoptosis in colon cancer cells, cell cycle arrest in prostate cancer cells, and cytotoxic activity in melanoma cells.[16] This review aims to give a detailed understanding of the proposed anticancer mechanism of panduratin A for developing therapy against non-small cell lung cancer (NSCLC).

Panduratin A

Panduratin A is a chalcone-derived compound isolated from the rhizome of Temu Kunci (B. Pandurata).[17] A researcher has succeeded in isolating 12% of Panduratin A from Temu Kunci rhizome ethanol extract. This compound has the molecular formula of $C_{26}H_{30}O_4$ with a molecular weight of 406.5.[18] Panduratin A has been reported to have various activities, such as anti-inflammatory in periodontitis, hepatoprotection in a mouse model of liver cirrhosis, inhibitory activity against muscle atrophy, and its potential in treating atopic dermatitis.[19-21] Panduratin A also has anticancer effects on breast cancer, prostate cancer, colon cancer, skin cancer, and lung cancer cell lines. It does this by stopping the cell cycle and causing apoptosis.[12,16,22-24]

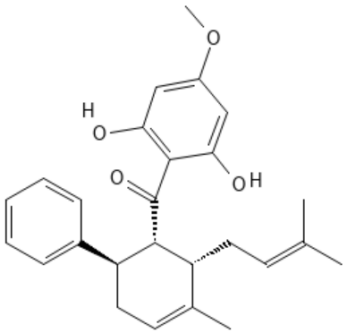

Figure 1. Chemical structure of Panduratin A[24]

Anticancer mechanism of Panduratin A

Cycle cell arrest

Two regulatory proteins regulate phase transitions in the cell cycle, namely positive and negative cell regulators. Positive cell regulators include cyclin and CDK (cyclin-dependent kinase), while negative cell regulators include p21 and

p27. Decreased cyclin levels (CDK becomes inactive) followed by increased expression of negative regulators (p21 and p27) can lead to cell cycle arrest. During the cell cycle, five CDKs are active. They are active in the G1 phase (cdk2, cdk4, and cdk6), the S phase (cdk2), the G2 and M phases (cdk1), and the S phase (cdk2).[25]

Cyclin B1 and cdc2 protein levels in prostate cancer cells were reduced by panduratin A, as shown by the study in PC3 and DUI145 cell lines. This suggested its involvement in cell cycle arrest in the G2/M phase. Meanwhile, in breast cancer cell lines, panduratin A decreased cyclin D1, which played a role in the G1 phase. Thus, it can be proposed that panduratin A can cause cell cycle arrest at G0/G1. The expression of cyclin D1, cyclin E1, cdk2, cdk4, and cdk6 in prostate cancer cells is reduced in a dose-dependent pattern following administration of panduratin A.[12,16,24]

Negative regulators such as p21 and p27 are bound to CDK or the CDK-cyclin complex to regulate and inhibit cell cycle activity. A study using breast cancer cells showed that panduratin A could induce the expression of p21 and p27. In another study using adenocarcinoma lung cancer (A549 cells), there was an increase in the expression of p53 and p21. The p53 tumor suppressor gene controls the expression of p21. Expression and activation of p27 and p21 mediated via CDK inhibition may contribute to growth arrest or cell cycle arrest. These results show that panduratin A can change the function of important regulatory proteins in the cell cycle.[12,16,24,26]

Apoptosis Induction

Panduratin A incubation in HT-29 cells caused an increase in DNA fragmentation, and morphological changes such as chromatin condensation and nuclear changes as a sign of apoptosis occurred. Caspases are the main mechanism of apoptosis and consist of initiators (caspases 2,8,9,10), which play a role in the initiation of the apoptotic pathway, and effectors (caspases 3,6,7), which play a role in the cleavage of cellular components. Panduratin A causes time-dependent proteolytic cleavage of PARP via procaspase-3 activation. During apoptosis, this activation leads to a buildup of 116 kDa fragments of PARP that are cut into 85 kDa pieces. 13 PC3 and DU145 also have their initiator caspase 9, 8, and procaspase 3,6 turned on by Panduratin A.[12,20,27]

Meanwhile, the extrinsic pathway might be triggered when a cell receives a death signal from another cell in the form of a ligand that binds to the death receptor to activate apoptosis through caspase 8. Panduratin A causes the expression of FADD (Fas-associated death domain) to increase and up-regulate the Fas receptor protein, as well as increased expression of TRAIL (TNF-related apoptosis-inducing ligand). There was a significant increase in Bax and a decrease in time-dose-dependent Bcl-2 expression, thereby changing the Bax: Bcl-2 ratio. In breast cancer cell lines (MCF-7), studies also found an increase in activity and expression of mitochondrial cytochrome C, caspase 7,8,9, and an elevation in the ratio of Bax: Bcl-2. Studies in the lung cancer adenocarcinoma (A549) cell line showed that Panduratin A-induced cell death due to apoptosis is mediated by caspase-3 activation and results in PARP cleavage. Therefore, panduratin A caused apoptosis through the extrinsic pathway and the mitochondria-dependent apoptosis pathway.[12,16,28]

Angiogenesis inhibition

Angiogenesis is the process of forming new blood vessels from existing ones to deliver oxygen and nutrients for the metabolism of tissues or cells in the wound-healing phase. Extracellular matrix reshuffle accelerates the basal membrane degradation followed by endothelial cell migration, proliferation, and the formation of new matrix components to form new blood vessels during angiogenesis. Vascular endothelial growth factor (VEGF) controls the growth and movement of endothelial cells, which are the building blocks of every blood vessel.[29] Panduratin A suppressed VEGF, cell proliferation, cell migration, invasion, and tube formation morphogenesis.[30]

Matrix metalloproteinase-2 (MMP-2) is an enzyme that degrades extracellular matrix components and plays a role in cell migration under physiological and pathological conditions. MMP-2 is considered an angiomodulator because it can control the formation of new blood vessels for the growth and spread of cancer. Tumor cells cause MMP activity to rise out of control and interfere with the immune system by stopping tumor cells from being killed.[31] MMP-2 secretion and the formation of F-actin stress fibers can be suppressed by panduratin A to prevent migration in endothelial cells in HUVEC cell lines. The anti-angiogenic properties of panduratin A also inhibit neo-vessel formation in murine cells and angiogenesis in zebrafish embryos.[30]

The potential effect of Panduratin A on NSCLC in the PI3K/Akt pathway

Anticancer agents might achieve therapeutic goals and effectiveness if they are specifically toxic to tumor cells and less toxic to normal cells. Studies of Panduratin A on various cancer cell lines have been carried out to assess the antitumor effect through various mechanisms. The cytotoxic effect of panduratin A on healthy cells in the form of hepatic epithelial cells and human fibroblasts showed that healthy cells were more resistant.[30] Studies on healthy breast cell lines also showed no effect compared to breast cancer cell lines. Thus, it can be proposed that panduratin A is selectively cytotoxic.[16] As previously mentioned, Panduratin A caused apoptosis by turning on caspase-3 and stopping the cell cycle by making an adenocarcinoma lung cancer cell line express p21 and p53.[28]

PI3K, a protein heterodimer that consists of p85 and p110. Phosphorylated PI3K activated Akt and continued until downstream signaling occurred. The PI3K/Akt/mTOR pathway is one of the main pathways regulating cancer cell survival, metastasis, and autophagy. Utilization of inhibitors of PI3K, Akt, and mTOR has been developed and used to treat cancer. The following are examples of drugs that have been clinically approved, such as copanlisib (PI3K inhibitor) for follicular lymphoma, perifosine (Akt-inhibitor) for neuroblastoma, and temsirolimus (mTOR inhibitor) for some solid tumors. A study using a nutrient-poor model using the PANC-1 cell line showed that panduratin A inhibited the PI3K/Akt/mTOR signaling pathway.[23]

Based on all the above references, we proposed the anticancer mechanism of Panduratin A as depicted in Figure 2.

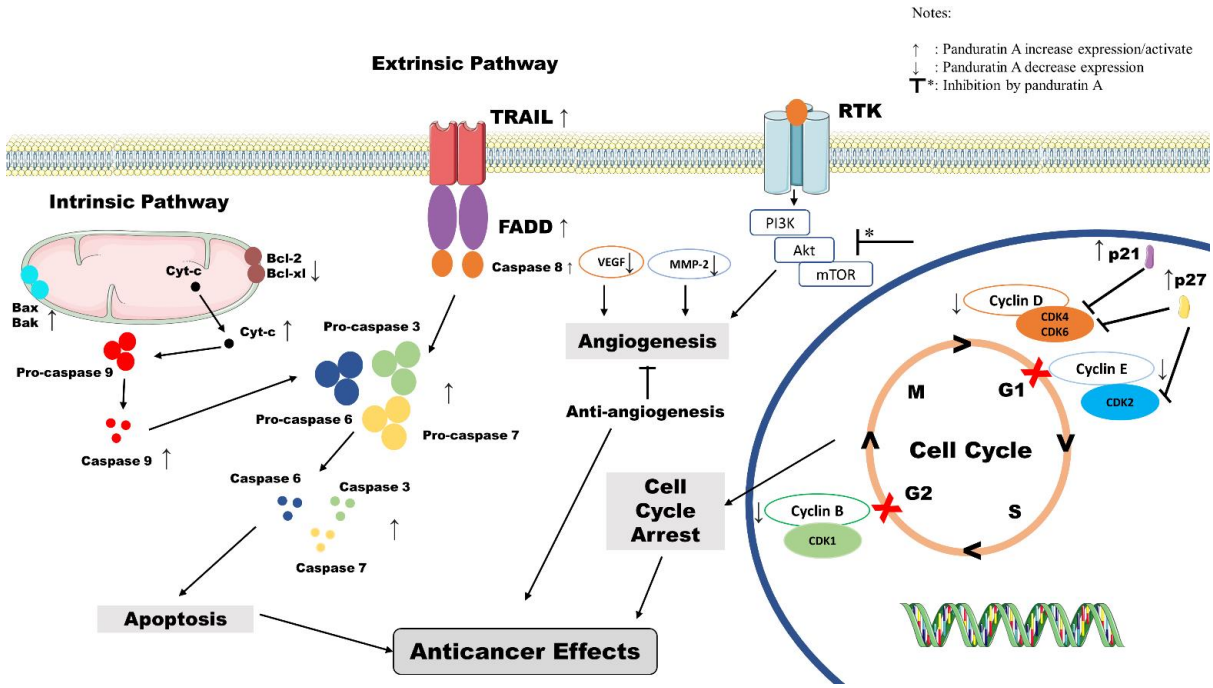

Figure 2. Proposed anticancer mechanism of Panduratin A
(Parts of the figure were drawn using pictures from Servier Medical Art and licensed under a Creative Commons Attribution 3.0 (https://creativecommons.org/licenses/by/3.0

Safety and dose study of panduratin A and temu kunci extract

In the *in vitro* cytotoxicity test against MCF-7 and T47D cell lines, administration of panduratin A gave IC50 values of 15 µM and 17.5 µM for 24 hours. In addition, non-tumorigenic MCF-10A cells were also examined, which showed that PA administration had no adverse effect and did not affect the proliferation of these cells.[16] In an acute toxicity study using female rats, panduratin A at a dose of 250 mg/kg did not show any toxicity. Biochemical parameters also showed that oral administration of panduratin A did not affect kidney and liver function.[27] Another study also conducted an acute toxicity test of the ethanol

extract of Temu Kunci rhizome using Wistar albino rats. The study's results showed that the LD50 value was greater than 4000 mg/kg BW, and there were no changes in behaviour, symptoms of toxicity, or lethal effects.[32]

A human dose study was carried out based on allometric scale data on mice, rats, and dogs. This study used panduratin A as a marker to assess systemic levels and estimate clearance based on allometric scaling. The estimated daily dose of the extract is 1500 mg for gingivitis, and clinical trials have been planned to determine efficacy. The factor of species differences had to be considered in predicting human doses. Several factors must be considered, such as differences in pharmacodynamic parameters (sensitivity and capacity of the receptor) and pharmacokinetics (protein binding, distribution, metabolism, and excretion). On the other hand, allometric scaling might be the best way to figure out doses based on what scientists know.[18]

The summary of experimental studies of panduratin A in cancer is given in Table 1.

Table 1. Summary of available studies with Panduratin A in cancer

Study (Author, year)	Design	Main outcome of Panduratin A
Yun MJ et al., 2006[12]	*In vitro* study of panduratin A in postate cancer cell (PC3 and DU145)	• IC50 of 13.5-14 μM in PC3 and DU145 cells • No effect in normal human prostate cells. • Inhibit procaspases 9, 8, 6 and 3 • Increase Bax/BCl2 • Upregulating TRAIL
Trakoontivakorn et al., 2001[13]	*Salmonella typhimurium* mutagenicity-based assay	• Antimutagenic effect of panduratin A at 12 μM
Yun MJ et al., 2003[15]	*In vitro* in RAW 264.7	• Inhibits NO and PGE at 0.175 μM • Inhibit LPS-induced NF-kB transcription
Liu Q et al, 2018[16]	*In vitro* study in MCF-7 and MCF-10A	• IC50 of 15 μM in MCF-7 cells • No effect on MCF-10A (normal breast cells) • G0/G1 arrest • Downregulation of CDK4 • Decreased in cyclin D1
Lai et al. 2015[22]	*In vitro* study in melanoma cells (A375)	• Panduratin A caused apoptosis by prolonged ER stress
Sun S et al., 2021[23]	*In vitro* study in PANC-1 human pancreatic cancer cells	• Cytotoxic to pancreatic cells at 1.6 μM • Inhibits PI3K/Akt/mTOR autophagy
Cheah SC et al., 2011[24]	*In vitro* study in A549 human non-small cell lung cancer	• IC50 at 10.8 μM • Inhibits NF-kB translocation from cytoplasm to nucleus
Lai SL et al. 2012[30]	*In vitro* study in HUVEC cells and *in vivo* study in zebrafish embryo	• IC50 of 6.9 μM on HUVEC cells • Angiogenesis effect in zebrafish embryo at 15 μM

Note:
CDK: cyclin dependent kinase; ER: endoplasmic reticulum; HUVEC: human umbilical vein endothelial cells; HSC: hepatic stellate cells; LPS: lipopolysaccharides; PDGF: platelet-derived growth factor; TGF-β1: Transforming growth factor beta 1; TRAIL: TNF-related apoptosis inducing ligand.

Multiple studies have examined the effects and molecular mechanisms of panduratin A on cancer cells, indicating that the substance has selective cytotoxic effects on cancer cells but not on healthy cells. However, no research has demonstrated panduratin A's efficacy in an animal model of non-small cell lung cancer. To validate the potential utility of panduratin A in the treatment of non-small cell lung cancer, further rigorous research in animal models that mirror human pathophysiology should be conducted. Prior to the start of clinical trials on humans, an extensive range of safety studies in animal models should be performed

Conclusion

According to the available literature, Panduratin A has several anticancer mechanisms, including cell cycle arrest, apoptosis induction, and angiogenesis inhibition. However, using Panduratin A to treat NSCLC requires further extensive study. On the other hand, the anticancer mechanism and selective cytotoxicity of Panduratin A are promising. There still a lot of research to be done on the dynamics, kinetics, and safety of NSCLC therapies

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Review Article

Comprehensive treatment of lung malignancy for meaningful survival

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Abstract

The American Cancer Society estimates, in 2023 there will be an estimated 238,340 new cases of lung cancer in which 117,550 cases in men and 120,790 cases in women. Non-Small-Cell Lung Cancer (NSCLC) is a prevalent type of lung cancer, accounting for approximately 80% of all reported lung malignancy cases and characterized by a poor 5-year survival rate. Lung cancer detected in early stages with prompt diagnosis and appropriate treatment will improve the patient's life expectancy. According to current data, patients admitted to the hospital with lung cancer in an advanced stage. Platinum-based chemotherapy is widely regarded as the gold standard of therapy for patients with advanced lung cancer across the world. Chemotherapy not only eliminates cancer cells, but also affects actively proliferating normal cells, such as hematopoietic cells in the bone marrow. Stem cells that secrete granulocytes, erythrocytes and platelets in the peripheral circulation will be harmed as well. Further research and new discoveries are required for treatment approaches that are projected to reduce the problem of adverse survivorship bias and improve the quality of life for lung cancer patients. Several targeted therapies, such as EGFR tyrosine kinase inhibitors and ALK inhibitors, have demonstrated significant clinical success in treating NSCLC patients with the corresponding gene mutations.

Keywords: *ALK inhibitors, EGFR tyrosine kinase inhibitors, NSCLC, targeted therapy*

Abstrak

Menurut *The American Cancer Society*, perkiraan kasus baru kanker paru pada tahun 2023 adalah sekitar 238.340 kasus, dengan 117.550 kasus pada pria dan 120.790 kasus pada wanita. *Non-Small-Cell Lung Cancer* (NSCLC) merupakan jenis kanker paru yang sering terjadi (sekitar 80%) dari keseluruhan kasus keganasan paru-paru dengan tingkat kelangsungan hidup 5-tahun yang buruk. Jika kanker paru ditemukan pada stadium awal dengan diagnosis yang cepat dan pengobatan yang tepat, harapan hidup pasien akan lebih tinggi. Data saat ini menunjukkan bahwa pasien kanker paru datang sudah dalam keadaan stadium lanjut. Kemoterapi berbasis platinum dianggap sebagai pengobatan standar dunia untuk pasien dengan kanker paru stadium lanjut. Kemoterapi tidak hanya membunuh sel kanker tetapi juga memengaruhi sel normal yang secara aktif membelah diri seperti sel hematopoietik dalam sumsum tulang. Sel induk yang memunculkan granulosit, eritrosit, dan keping darah di peredaran darah tepi juga akan rusak. dibutuhkan lebih banyak penelitian dan terobosan baru untuk rencana pengobatan yang diharapkan dapat meminimalkan masalah *survivor-ship bias* yang merugikan dan mencapai peningkatan kualitas hidup bagi pasien kanker paru. Beberapa terapi yang ditargetkan, termasuk EGFR tirosin kinase inhibitor dan ALK inhibitor, telah menunjukkan keberhasilan klinis yang signifikan dalam mengobati pasien NSCLC yang memiliki mutasi gen yang sesuai.

Kata kunci: *ALK inhibitor, EGFR tirosine kinase inhibitor, NSCLC, terapi target*

Background

Lung cancer is included as one of the leading causes of cancer-related mortality annually. According to data provided by The Global Cancer Observatory (Figure 1), lung cancer (11.4%) ranks second in the incidence of new cases, following breast cancer (11.7%), and is the leading cause of cancer-related mortality (18%) worldwide. In Asia (Figure 2), lung cancer ranks first both in the incidence of new cases (59.6%) and in the mortality rate (61.9%).[1]

The American Cancer Society estimates, in 2023 there will be an estimated 238,340 new cases of lung cancer in which 117,550 cases in men and 120,790 cases in women. While the estimated number of cancer-related fatalities is roughly 127,070, with 67,160 deaths in men and 59,910 deaths in women.[2]

Lung cancer is not a sudden occurrence; rather, it is the result of a protracted process. Symptoms of lung cancer may lack visibility during the initial stages. The enhancement of community awareness on risk factors, symptoms, and treatment options is crucial. If lung cancer detected in early stages with prompt diagnosis and appropriate treatment, the patient's life expectancy will improve.

The Prevention of Lung Cancer

Prevention offers the greatest opportunity for combating lung cancer. Nevertheless, it is important to note that not every case of lung cancer may be avoided. There are controllable risk factors (such as pollution, lifestyle, smoking) and uncontrollable risk factors (such as age, gender, family history of cancer).[3]

The most effective strategy to lower the risk of developing lung cancer is by quitting smoking and avoiding exposure to secondhand smoke. At this point, smoking is the primary risk factor of lung cancer. It is widely recognized that approximately 80% of fatalities resulting from lung cancer may be attributed to smoking. Individuals who smoke are significantly more susceptible to developing lung cancer than nonsmokers. The risk increases with the duration and number of packs of cigarettes per day spent. Nonsmokers, but are inhaling secondhand smoke in the surrounding environment, have a higher chance of acquiring lung cancer. Secondhand smoke is the third leading cause of lung cancer in the United States.[4-6]

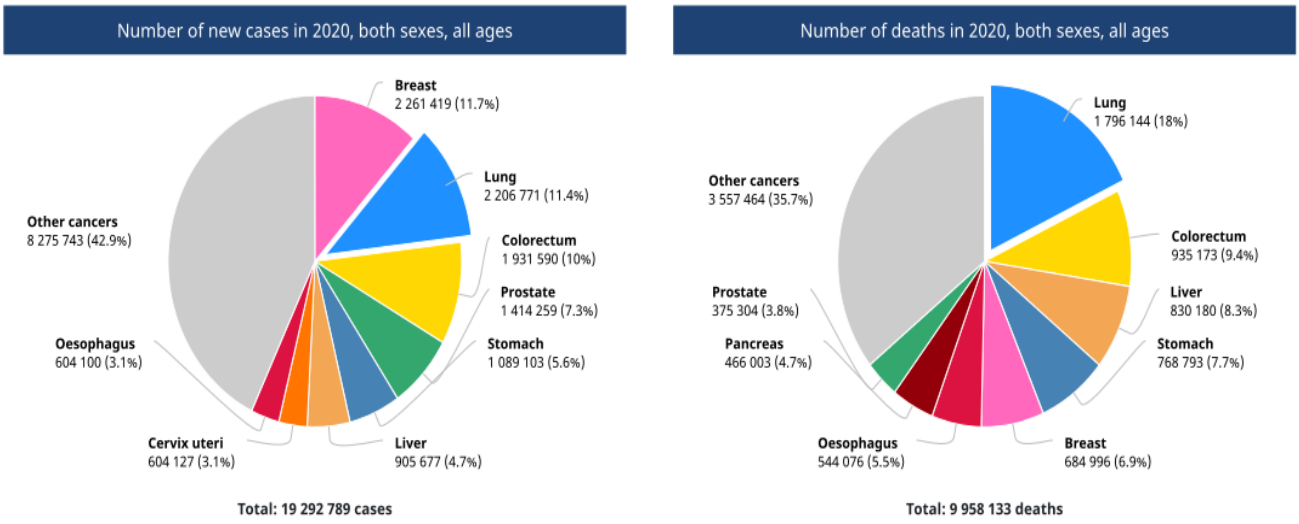
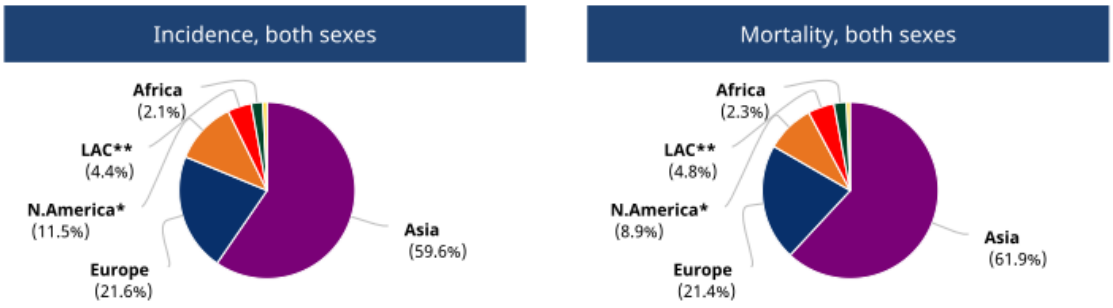


Figure 1. The number of new cases and mortality associated to lung cancer in 2020.[1]



Population	Number
Asia	1 315 136
Europe	477 534
*Northern America	253 537
**Latin America and the Caribbean	97 601
Africa	45 988
Oceania	16 975
Total	2 206 771

Population	Number
Asia	1 112 517
Europe	384 176
*Northern America	159 641
**Latin America and the Caribbean	86 627
Africa	41 171
Oceania	12 012
Total	1 796 144

Figure 2. The number of new cases and mortality associated to lung cancer in Asia.[1]

Early Detection of Lung Cancer

Lung cancer screening is recommended for individuals who are at a high risk but do not exhibit any signs or symptoms. In cases where an individual is diagnosed with lung cancer but remains asymptomatic, earlier detection of the disease may be possible. When lung cancer is detected in its early stages, still in limited size and not having metastasis, the probability of successful treatment is high. However, typically, lung cancer symptoms do not manifest until the disease has progressed to an advanced stage. Even when symptoms arise, many people mistakenly attribute them to other conditions, causing diagnosis to be delayed.[7]

The use of a low-dose computed tomography (LDCT) scan helps to detect abnormal areas in the lungs that may be cancerous. In contrast to chest X-rays, annual LDCT scans prior to the onset of symptoms has been shown to reduce the mortality rate associated with lung cancer.[8-10]

Hospital Admission of Patients in Advanced Stage

According to global statistics from 1990–2010, it was revealed that 43% of lung cancer patients were diagnosed with stage IV tumors, with a low 5-year survival rates of 10% for stage IVA and 0% for stage IVB (Figure 3).[11] In Surabaya, nearly 80% of lung cancer patients were diagnosed with stage IV tumors according to the data obtained from RSUD Dr. Soetomo in 2016-2018 (Figure 4).[12]

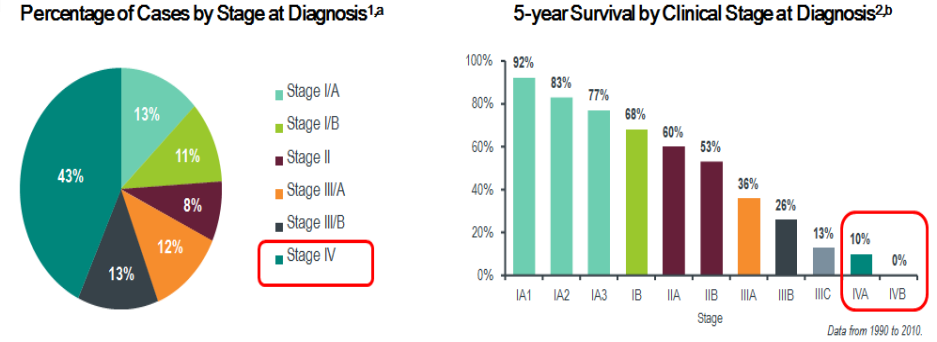


Figure 3. Global lung cancer staging at diagnosis and 5-year survival by stage.[11]

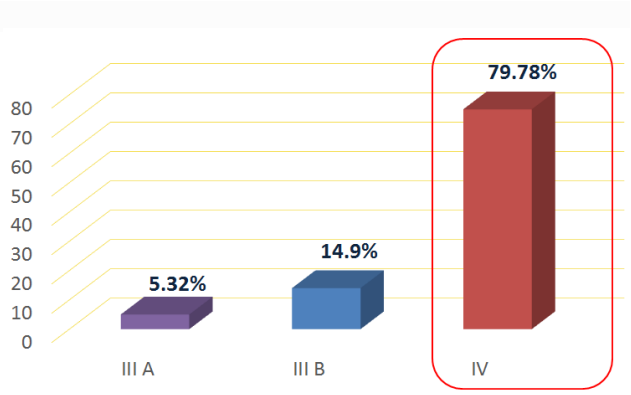


Figure 4. Lung cancer staging at diagnosis in RSUD Dr. Soetomo Surabaya between 2016-2018.[12]

Chemotherapy of Lung Cancer

Platinum-based chemotherapy is widely regarded as the gold standard of therapy for patients with advanced lung cancer across the world. A meta-analysis study by the Non-Small Cell Lung Cancer Collaborative Group in 1995 reported, that chemotherapy using platinum agents resulted in a significant enhancement in patient survival rates as compared to merely optimal supportive care (one-year survival rate of 15% vs 5%).[13]

Despite improvements in survival rates, nearly all patients experience relapse and even leading to death due to recurrent or relapsed NSCLC. Long-term survivors endure significant pulmonary, cardiovascular, and nervous system side effects while receiving treatment.[14]

Chemotherapy not only eliminates cancer cells, but also affects actively proliferating normal cells, such as hematopoietic cells in the bone marrow. Stem cells that secrete granulocytes, erythrocytes and platelets in the peripheral circulation will be harmed as well.[15,16] Therefore, further research and new discoveries are required for treatment approaches that are projected to reduce the problem of adverse survivorship bias and improve the quality of life for lung cancer patients.

Targeted Therapy of Lung Cancer

Non-Small-Cell Lung Cancer (NSCLC) is a prevalent type of lung cancer, accounting for approximately 80% of all reported lung malignancy cases and characterized by a poor 5-year survival rate. Numerous genetic and epigenetic abnormalities have been discovered in the development of NSCLC types.[17] Oncogenic driver mutations are primarily responsible for the activation of chemical signaling pathways that result in uncontrolled cell growth and proliferation which attributed to these abnormalities. Several mutation drivers, such as genes encoding for the epidermal growth factor receptor (EGFR), K-ras (KRAS), anaplastic lymphoma kinase (ALK), and others, have been identified in cases of NSCLC. A variety of targeted therapies, including EGFR tyrosine kinase inhibitors and ALK inhibitors, have demonstrated significant clinical success in treating NSCLC patients with the corresponding gene mutations.[18,19]

1. EGFR mutation-targeted therapy

   Epidermal growth factor receptor (EGFR) is a cell surface protein that promotes cell growth and division. Sometimes, individuals with NSCLC have an excessive number of EGFR, which accelerates cell growth. Drug agents that inhibit EGFR signals to cue cells to grow are known as EGFR inhibitors. Some of EGFR inhibitors are employed in the treatment of NSCLC, including erlotinib, afatinib, gefitinib, osimertinib, and dacomitinib.[20-22]

   EGFR inhibitors have frequently demonstrated to reduce tumor size that can persist for several months or beyond. Eventually, however, the efficacy of these pharmaceutical agents diminishes for the majority of patients because cancer cells develop another mutation in the EGFR gene known as the T790M mutation.[20-22]

2. ALK rearrangement-targeted therapy
   Approximately 5% of individuals with NSCLC have ALK gene rearrangements. These alterations are frequently observed in nonsmokers or younger light smokers with adenocarcinoma subtype. ALK gene rearrangements produce abnormal ALK proteins which in turn promote the proliferation and metastasis of cancer cells. ALK-targeted therapy includes crizotinib, seritinib, alectinib, brigatinib, and lorlatinib.[20,21]

   The administration of these drugs to NSCLC patients with ALK gene alterations is frequently reduce the size of the tumors. Although this drug may help when chemotherapy has been ineffective, it may also be used directly as a substitute for chemotherapy in people with confirmed ALK gene rearrangements.[20,21]

Immunotherapy of Lung Cancer

Immunotherapy refers to the administration of pharmaceutical agents with the aim of enhancing the body immune system to recognize and eliminate malignant cells effectively. The crucial feature of immune system is the capacity to combat abnormal cells in the body. Immune cells, for this purpose, use checkpoint proteins that act as switches, that must be activated or deactivated to initiate the attack mechanism of the immune response. Cancer cells occasionally use these checkpoint proteins to evade the attack of host's immune system. The class of pharmaceuticals that specifically target checkpoint proteins are referred to as Immune Checkpoint Inhibitors.[23]

1. PD-1/PD-L Inhibitor
   Nivolumab, pembrolizumab, and cemiplimab are drugs that target PD-1, a protein on immune cells (T cells) that prevent these cells from attacking other cells in the body. Atezolizumab and durvalumab are pharmaceutical agents that specifically bind to PD-L1, a protein associated with PD-1, which is expressed on some tumor cells and immune cells. By inhibiting PD-1/PD-L1, these pharmaceutical agents have the capacity to augment the immune response against cancer cells, resulting in the reduction in size or deceleration of tumor progression. In some cases, before either of these drugs can be administered, a laboratory test is required to confirm the presence of PD-L1 expression, indicating that the drug will be more effective.[20,21]

2. CTLA-4 Inhibitor
   Ipilimumab and tremelimumab are likewise immune-stimulating medications, however they act by blocking CTL-4, another protein on T cells that helps to maintain the cells under control. These medications are not typically used as monotherapy, but rather in combination with PD-1 inhibitors (ipililumab with nivolumab, tremelimumab with durvalumab).[20,21]

Conclusion

The treatment of lung cancer, particularly the NSCLC type, is a challenge that is rapidly developing in the field of modern medicine. In the past, this condition was considered as a homogeneous disease, and all patients were treated in the same way. All stage IV NSCLC patients were treated exclusively with chemotherapy without patient selection based on histology or other biomarkers.

The application of platinum-based doublet chemotherapy was shown to increase overall survival for several months, while the level of toxicity continued to rise.[24] The implementation of personalized medicine for lung cancer therapy is driven by this factor. Collins described personalized medicine as an approach to guide clinical decisions associated to disease prevention, diagnosis, and treatments according to individual's genetic profile.[25] The patient's genetic profile can assist clinicians decide on the best course of treatment, including as the right dose or regimen.

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Manuscripts are submitted through online submission; Please register/make an account first (don't forget to checklist "Author" in "Register as" field, when you fill/edit your profile). After you have an account, please do log in, then in your profile, you can click "New submission", follow the step for uploading your manuscript. If you have any difficulty please contact submission@inajcc.com for help.

The maximum file size for the manuscript is 5MB, full-resolution photographs should be uploaded separately as supplementary files.

Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. Accepted manuscripts become the permanent property of The Indonesian Journal of Cancer Control without permission from the publisher.

Author Responsibility

All accepted manuscripts are subject to copy editing. The author is responsible for all statements in his work.

Manuscript Preparation

All manuscripts should be prepared in accordance with "Uniform Requirements for Manuscript Submission to Biomedical Journals" (also known as "Vancouver Style"), as agreed by the International Committee for Medical Journal Editors. The entire manuscript must be typewritten, double spaced, on white bond paper, 216 x 279 mm (8 ½ x 11 in.) or ISO A4 (212 x 297 mm), with margins of at least 25 mm (1 in.), including the abstract, footnotes, references, figure legends and tables (superscript). If a word processor is used, do not justify lines.

All manuscripts should include (1) title page, (2) short title page, (3) abstract in English (4) body of paper, (5) acknowledgements, (6) references, (7) tables, (8) figure legends, and (9) clear photocopies of figures and illustrations. Manuscripts should be consistent in style, spelling, and use of abbreviations. Slang, medical jargon, and obscure abbreviations are to be avoided. The word count should not exceed 5000 words including figures and tables.

Abstract and key words

Provide an abstract (250 words maximum) of the article. Original articles consist of statements of the problem (background), method of study, findings and conclusions. Observation and others (review article) consists of statement of the problem and the way of study performed. Abstract replaces the summary. Key words must be included after abstract and maximal 5 words.

References

List references in consecutive numerical order (not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications should not be listed as references. Reference to journal articles should include: (1) authors (abbreviation of middle name), (2) title, (3) journal name (as abbreviated in Index Medicus), (4) year, (5) volume number, (6) inclusive page numbers. References to book should include: (1) author[s], (2) chapter title (if any), (3) editor (if any), (4) title of book, (5) city of publication, (6) publisher, and (7) year. Volume and edition numbers, specific pages, and name of translator(s) should be included when appropriate.

Further explanation and examples could be seen, e.g., in the file "Quick references guide to Vancouver citing & referencing style" (Vancouver - Citing and referencing - Library guides at Monash University), that can be obtained from the Monash University site.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The material has not been previously published and is not under simultaneous consideration for publication elsewhere
2. The submission file is in Microsoft Word.
3. Where available, URLs for the references should be provided.
4. The text is single-spaced; uses a 10-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.
6. The manuscript has been structured based on the template.
7. For original article, ethical clearance and informed consent statement must be included in the submission.
8. For case report, patient's informed consent must be included in the submission.
9. Ethics Statement, Authorship Agreement and Copyright Statement forms must be filled and submitted together with the manuscript.
10. Each author and co-author(s) must have an active e-mail and register it during the submission process.
11. Provide a cover letter for submission.

Download article submission kit/template here

Instructions For Authors

Article Type (10 pt, colored gray 50%, bold, underlined)

Article title (First letter capitalized, 14 pt, bold, centered, max 15 words)

(one blank line, 14 pt)

First Author, Second Author, Third Author, etc. (12 pt)

(one blank line, 12 pt)

1. Department, Faculty, University, Address, City, Zip Code, Country (10 pt)
2. Research Group, Institution, Address City, Zip Code, Country (10 pt)

(one blank line, 12 pt)

Email: author@address.com (10 pt, italic, underlined)

(two blank line, 12 pt)

Abstract (12 pt, bold)

(one blank line, 12 pt)

Abstract must be written in English and should not exceed 250 words. The font is Arial size 9 with single spacing. Original articles consist of statements of the problem (background) including aim of the journal, method of study, results and conclusions. Case reports consist of background, case illustration, discussion and conclusion. Observation and others (review article) consists of statement of the problem and the way of study performed.

(one blank line, 12 pt)

Keywords: (10 pt, bold, italic) *maximum 5 words in English must be provided in alphabetical order, chosen according to the Medical Subject Headings (MeSH) terms* (10 pt, italic)

(three blank line, 12 pt)

Submission Requirements (12 pt, bold)

(one blank line,10 pt)

Manuscripts are submitted through online submission; Please register/make an account first (don't forget to checklist "Author" in "Register as" field, when you fill/edit your profile). After you have an account, please do log in, then in your profile, you can click "New submission", follow the step for uploading your manuscript. If you have any difficulties please contact submission@inajcc.com for help.

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It must be stated that all the protocols for research project have been approved by the Ethic Committee of the institution. Research that includes human subjects must preserve anonymity of the subjects and a statement that all subjects gave informed consent. Case reports should include informed consent by the patient.

Background (12 pt, bold)

(one blank line, 10 pt)

All manuscripts should be prepared in accordance with "Uniform Requirements for Manuscript Submission to Biomedical Journals" (also known as "Vancouver Style"), as agreed by the International Committee for Medical Journal Editors. The entire manuscript must be typewritten in two columns with Arial font size 10, single spaced, left and right aligned, on one sided page with white bond paper, 216 x 279 mm (8 ½ x 11 in.) or ISO A4 (212 x 297 mm), with margins of at least 25 mm (1 in.), including the

abstract, footnotes, references, figure legends and tables (superscript). All pages must be numbered on bottom right-hand corner. If a word processor is used, do not justify lines.

Generally, the body of paper should be divided in sections with these following headings: **Background, Methods, Results, Discussion,** and **Conclusion**. Acknowledgements must be written if present.

Parts of Manuscript (12 pt, bold)

(one blank line, 10 pt)

All manuscripts should include (1) title page, (2) short title page, (3) abstract, in English and Indonesian (4) body of paper, (5) acknowledgements, (6) references, (7) tables, (8) figure legends, and (9) clear photocopies of figures and illustrations.

Original Articles

a. Abstract: maximum 250 words, single spaced, divided by subheadings Background, Methods, Results, and Conclusion. Key words must be included below the abstract maximal 5 words.
b. Background: 1-3 paragraphs consists of the background of the study, objectives of the study, and hypothesis which will be proved with the study. Background should show the importance of the study, novelty of the manuscript and the gap analysis.
c. Methods: explains the details on how the study was conducted. Statistical methods of the study must be explained in this section including the software used. Statistical terms, symbols and abbreviations should be defined clearly.
d. Results
e. Discussion
f. Conclusion: conclusion related to the objectives of the study

Case Report

a. Abstract: maximum 250 words, single spaced, divided by subheadings Background, Case Illustration, Discussion and Conclusion.
b. Background: explanation of the main problem and the purpose of the case report. Brief description of the background of the study.
c. Case Illustration
d. Discussion
e. Conclusion

Review Article or Special Article

a. Abstract: maximum 250 words, single spaced, consists of summary of the problem considered and how the study was performed
b. Background: consist of 1-3 paragraphs
c. Content: consists of comprehensive analysis of the topics.
d. Conclusion

Result (12pt, bold)

(one blank line, 10 pt)

Data presented in the result must have been processed, and can be presented in forms of tables or figures.

Discussion (12pt, bold)

(one blank line, 10pt)

Discussion should focus on the study/case. The correlation between the result and hypothesis should be explored. The result should be compared with other studies. The implication of the study, both theoretically and implementation, should be discussed.

Tables and Figures (12pt, bold)

(one blank line, 10pt)

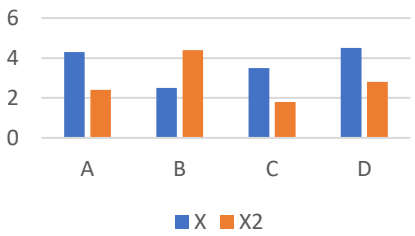
Tables should be self-explanatory and numbered consecutively based on the order of appearance (Table 1, Table 2, etc). The data contained in the tables must not be duplicated within text and figures. Tables should be written with Arial font size 10 pt, single spacing. Tables should be cited accordingly unless it is original. The title should be positioned above the table, in a center justified manner like the following example.

Table 1. Title of the Table
(one blank line, 10pt)

	A	B
A	1	2
B	3	4
C	5	6

Table content source and additional explanation (font 10)

Figures should be numbered consecutively based on the order of appearance (Figure 1, Figure 2, etc) Images must be supplied as JPEG or GIF files with minimum size of 500 KB. All figures must be supplied as a separate file with each figure labeled as Figure 1, Figure 2, etc. Images should be cropped sufficiently to prevent recognition of the subject. The use of eye bar is acceptable. Figures should be cited accordingly unless it is original. The consent from the subjects/patients whose images are used is needed. The title should be positioned below the figure, in a center justified manner like the following example.



(one blank line, 10pt)

Figure 1. Title of the Figure
(two blank line, 10pt)

Acknowledgements (12pt, bold)

(one blank line, 12pt)

Only written if present. People who are contributed to the study but does not meet the criteria for authorship must be acknowledged and listed. The source of funding, financial grants, and conflict of interest must be acknowledged and listed.

Conflict of Interests (12pt, bold)

(one blank line, 10pt)

This part should declare authors' conflicts of interest, including sources of support for the work and authors' authority to access the study data.

References (12pt, bold)

(one blank line, 10pt)

References should be done with Vancouver system of referencing. Further explanation and examples could be seen, e.g., in the file "Quick references guide to Vancouver citing & referencing style" (Vancouver - Citing and referencing - Library guides at Monash University), that can be obtained from the Monash University site. In the text, references must be cited using superscript. Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications should not be listed as references. Updated references should always be prioritized.

Examples:

Books

Author 1, Author 2, so on (last name, abbreviated first name). Title of book. Edition. Place of publication: Publisher; Year of publication. Page range.

Book Chapter

Author 1, Author 2, so on (last name, abbreviated first name). Title of chapter. In: Editor 1, Editor 2, so on (last name, abbreviated first name), editors. Title of book. Edition. Place of publication: Publisher; Year of publication. Page range.

Journal

Author 1, Author 2, so on (last name, abbreviated first name). Title of article. Abbreviated journal name. Publication year;volume number(issue number):page range.

Online Journal

Author 1, Author 2, so on (last name, abbreviated first name). Title of article. Abbreviated journal name [Internet]. Publication year [date accessed];volume number(issue number):page range. Available from: Uniform resourced locater (URL) address

Thesis or Dissertation

Author (last name, abbreviated first name). Title. [Paper, thesis, or dissertation]. University place: University name; Year

Proceeding Book

Editor 1, Editor 2, so on (last name, abbreviated first name). editors. Title of article. Conference name, Date, Month, and Year, City, Country. Publication place; Publisher; Publication year.