EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AND CARCINOEMBRYONIC ANTIGEN (CEA) RELATIONSHIP OF LUNG ADENOKARSINOMA IN SAIFUL ANWAR HOSPITA MALANG

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Abstract: EGFR mutations is associated with sensitivity to tyrosine kinase inhibitors (TKI's) therapy which are found in Lung Adenocarcinoma. *There are some limitations in detecting EGFR mutation. CEA is also expected to predict treatment efficiency of EGFR-TKI's therapy. In this study, we investigated the relationship between serum Carcinoembryonic antigen (CEA) and Epidermal Growth Factor Receptor (EGFR) Mutations in Lung Adenocarcinoma patient. Methods : The research was conducted in Dr. Saiful Anwar General Hospital Malang. From May 2014 to November 2015, 54 lung adenocarcinoma patients who had underwent measurements of EGFR mutation and serum CEA level were retrospectively recruited. None of them had surgery, radiotherapy, chemotherapy and targeted therapy. EGFR mutation was detected using PCR, serum CEA levels were analyzed using electrochemical luminescence. Result: Abnormal serum levels of CEA were significantly associated with EGFR mutation (95% CI, P=0,043) with an odds ratio of 3.4 (95% CI: 1.010-11.451). The area under the ROC curve for CEA was 0.558 (95% CI, P=0.078). Conclusion: Serum CEA is associated with mutation of EGFR in lung adenocarcinoma patients.*

Keywords : *Lung cancer, adenocarcinoma, EGFR, CEA*

INTRODUCTION

Lung cancer is one of the leading causes of cancer deaths in the world in both men and women. Lung cancer is divided into two main types namely, Lung Cancer Small Cell Carcinoma (LCSCC) and Lung Cancer Non-Small Cell Carcinoma (LCNSCC). LCNSCC accounts for 80% of all lung cancers with adenocarcinoma as the most common type of histology.[1-3]

The main risk factor for lung cancer is smoking. Other factors are also known as factors that affect the development of lung cancer are exposure to radon gas, asbestosis, air pollution and genetic factors. [1-4]

About 60% of LCNSCC patients are diagnosed when the disease is already advanced. Current therapies include surgery, radiotherapy and chemotherapy. The therapy is given based on the patient's lung cancer degree. Single or combination chemotherapy with other therapeutic modalities such as radiotherapy or surgery provides unsatisfactory results in improving the patient's quality of life. In addition, the presence of toxicity and resistance to chemotherapy drugs also limits the use of therapy.[5,6]

The challenge in terms of the implementation of LCNSCC is also caused by the lack of a clear understanding of the mechanism of abnormality that occurs in lung cancer. Recent studies have found that there are genetic predisposers that play a role in controlling cell survival. These irregularities increase cell division and induce tumors. One of the pathways that can be deviated is the epidermal growth factor receptor (EGFR). EGFR is a transmembrane receptor of tyrosine kinase protein that can be encountered in normal epithelial, mesenchymal and neurogenic tissues. EGFR's excessive expression is thought to play a role in the development of lung cancer.[4,7]

Mutations occurring in EGFR are common in Asian ethnic and adenocarcinoma lung cancer patients about 51.4%, whereas sex and smoking status are not significantly associated with the mutations. EGFR mutations are related to the sensitivity of tyrosine kinase inhibitor (TKI) therapy. However, there are limitations in detecting mutations in EGFR. The best specimens for EGFR mutation were obtained from surgery. However, 70-80% of LCNSCC patients can not undergo surgery while diagnosed, and biopsies also present a high risk of bleeding in advanced cancers. Therefore, an easier and safer way of estimating the mutation is needed[1,8,9]

Several studies have considered some tumor markers to estimate the success of therapy with EGFR-TKI, such as carcinoembrionic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), carbohydrateantigen 19-9 (CA19-9) and CA125. CEA itself has been widely studied and found that CEA can predict the success of therapy with TKI. CEA levels can describe the growth, recurrence and spread of tumors. However, it is not understood whether there is a relationship between EGFR mutations and elevated serum CEA levels.[6, 10]

Until now, there has been no research conducted at Saiful Anwar Malang Hospital, regarding the relationship between EGFR mutation and elevated serum CEA levels. Therefore, in this study we would examine the relationship between EGFR mutation and serum CEA levels and also a CEA diagnostic test of EGFR mutation in patients with pulmonary adenocarcinoma. Saiful Anwar Malang, so it is expected to be a consideration for patients to receive EGFR-TKI therapy for patients who are unlikely or unable to conduct EGFR mutation examination.

RESEARCH METHODS

This research was conducted in Saiful Anwar Malang Hospital from May 2014 to November 2015. This study retrospectively involved 54 patients with adenocarcinoma lung cancer who had

undergone EGFR mutation and CEA levels. The patients involved had not undergone surgery, radiotherapy and previous chemotherapy. EGFR mutations are detected using PCR. CEA levels were analyzed using electrochemical luminescence. The relationship between EGFR mutation and CEA levels was tested with Chi square. Diagnostic test analyzes were performed to obtain the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of serum CEA levels against epidermal growth factor receptor (EGFR) mutations in adenocarcinoma lung cancer patients at Dr. Saiful Anwar Malang Hospital.

RESULTS AND DISCUSSION

Data processing in this study was conducted in January to February 2016, secondary data taken from medical records of lung cancer patients treated at Pulmonology Division Saiful Anwar Hospital Malang. To determine the frequency of EGFR mutations, data from medical records of patients undergoing EGFR examination from 2013 to 2015 is taken, to see the association of EGFR mutation and CEA levels, accuracy, sensitivity, specificity, positive predictive value and negative predictive value of CEA serum levels against mutations of EGFR, secondary data were taken as many as 54 medical records that meet the inclusion criteria.

Table 1 shows the characteristics of the study subjects. Subjects aged ≥18 years, with an average age of 56.93. Distribution of research subjects are group by age, most in the age group ≤ 65 years as many as 155 people (78.86%), while the age group ≥ 65 years as many as 29 people (20.14%). By sex, the highest in the male sex group were 77 people (53.47%) and 67 people (46.53%) were women.

Table 1 Sample Charactheristics

Variable	
Age	N : 144
Mean	56.93
≤ 65 years old	115 (78.86%)
≥ 65 years old	29 (20.14%)
Sex	N : 144
Male	77 (53.47%)
Female	67 (46.53%)
CEA serum level	N : 54
Normal (< 5)	21 (38.89%)
Abnormal (>5)	33 (61.11%)

Based on the results of medical record data, it can be described frequency of EGFR mutation as in table 2

Table 2 EGFR mutation frequency

EGFR	Frequency	Percentage %
Wildtype	89	61.8
EGFR mutation	55	38.2
Total	144	100

Based on Table 2, patients with EGFR mutation were 55 people or 38.2% of 144 patients and wildtype were 89 people or 61.8% of 144 patients. Among these mutations, 32 patients had mutations

in exons 19, 18 people had mutations in exon 21 L858R, 5 people mutated on exon 21 L861Q, 1 person mutated on exon 18G719C and 1 person had double mutation in exon 19 and exon 21 L858R . The distribution of EGFR mutation status is shown in figure 1.

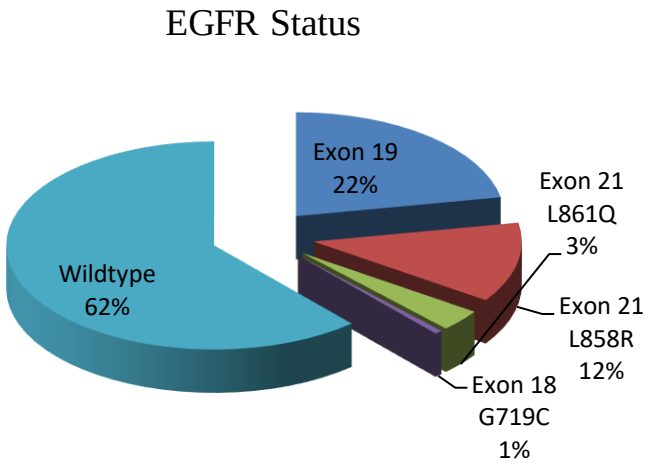

Figure 1 EGFR status diagram in patients with lung cancer adenocarcinoma at Saiful Anwar Hospital, Malang. In 144 cases, 22% (32 of 144 people) had mutation in exon 19, 12% (18 of 144 people) mutations in exon 21 L858R, 3% (5 of 144 people) had exon mutations 21 L861Q, 1% (1 of 144 people) had exon 18 G719C mutation, and 62% (89 of 144 persons) is wildtype. (Source: Secondary Data Research).

In Table 3, it was seen that of 144 people, patients who had EGFR mutation with female gender were 29 people or 20.14%, while there were 26 or 18.06% male gender patients had EGFR mutations.

Table 3 Association of EGFR mutation and Sex

Sex	EGFR				Total	%	
	Wildtype		Mutation				
	F	%	F	%	F		
Female	38	26.39	29	20.14	67	46.53	
Male	51	35.42	26	18.06	77	53.47	*p 0.241*
Total	89	61.81	55	38.19	144	100	

p : < 0,05

Based on the results of statistical tests obtained that the results p value of 0.241 and $\chi 2$ = 1,375, the value of $\chi 2$ tables with degrees of freedom = 1, the error rate of 5% is 3.841, then the value of $\chi 2$ = 1.375 smaller than the value of $\chi 2$ table = 3.841 or p = 0.241> 0.05 (α = 5%). So it can be concluded that there is no significant relationship between sex with EGFR mutation.

Table 4 shows that 54 people divided into 4 groups, ie patients who did not have EGFR or wildtype mutation with CEA <5 levels were 16 people or 29.63%, and CEA> 5 levels were also 16 or 29.63%, patients with mutations EGFR with CEA level <5 were 5 people or 9.26%, and CEA> 5 were 17 people or 31.48%.

Table 4 Association of EGFR mutation and CEA serum level

EGFR	CEA				Total	%	
	≥ 5		< 5				
	F	%	F	%	F		
Mutation	17	31.48	5	9.26	22	40.74	
Wildtype	16	29.63	16	29.63	32	59.26	*p 0.043*
Total	33	61.11	21	38.89	54	100	

p < 0,05

Based on the results of statistical tests, p value result was 0.043 and $\chi 2$ = 4,080, and the value of $\chi 2$ tables with degrees of freedom = 1 with a 5% error rate is 3.841, therefore the value of $\chi 2$ = 4,080 is greater than the value of $\chi 2$ table = 3.841 or p value = 0.043 <0.05 (α = 5%), so it can be concluded that there is a significant relationship between EGFR mutation and CEA level.

Table 5 Odd Ratio of EGFR mutation and CEA level

		CI 95%	
Variable	Odd Ratio	Lower	Upper
EGFR +/EGFR -	3.4	1.010	11.451

The Odd Ratio table in Table 5 showed that patients with EGFR mutations were at a greater risk of having 3.4 times increased CEA levels than patients without EGFR mutations. Based on the values of the common Odds Ratio on the table, at least patients with EGFR mutations at least 1-fold increased levels of CEA up to 11,451-fold. The diagnostic test results are expressed in 2x2 table, then calculated sensitivity, specificity, accuracy, positive predictive value, and negative predictive value.

Table 6 Sample Distribution in EGFR and CEA test

CEA level	EGFR Mutation	Wildtype	Total
CEA ≥ 5	17 (a)	16 (b)	33
CEA < 5	5 (c)	16 (d)	21
Total	22	32	54

From the analysis it is known that the sensitivity of CEA is 77% and specificity 50%. From the sensitivity results it can be concluded that CEA can detect EGFR mutation of 77%. The CEA specificity of 50% means that the possibility of CEA can detect lung cancer patients without 50% EGFR mutation. A positive predictive value of 53% means that only about 53% of EGFR is actually a mutation. A negative predictive value of 76% means about 76% of EGFR patients with lung cancer adenocarcinoma is completely non-mutated.

From the calculation, the value of AUC (area under ROC curve) is 0.558 or 55%. This figure is very far from 100% which means that the CEA is very weak in determining EGFR mutation. The interpretive value is if AUC> 50.0 - 60.0% is very weak,> 60.0 - 70.0% is moderate,> 80.0 - 90.0% is good,> 90.0 - 100.0% is very good.

In this study we found that patients with EGFR mutation were 55 people (38.2%) of 144 patients and wildtype were 89 people (61.8%) of 144 patients. Among these mutations, 32 patients had mutations

in exons 19, 18 individuals had mutations in exon 21 L858R, 5 had mutations in exon 21 L861Q, 1 person mutated on exon 18 G719C and 1 person had multiple mutations in exon 19 and exon 21 L858R, as shown in Figure 1. The most frequent mutations in this study are exon 19 and 21, for more detail there is 22.2% (32 of 144 people) exon 19 mutations, 12.5% (18 of 144 persons) exon 21 L858R mutations, 3.4% (5 of 144 people) exon 21 L861Q mutations, 0.6% (1 of 144 people) exon 18 G719C mutations, and 61.8% (89 of 144 people) wildtype. This is in accordance with the previous findings. There are three types of mutations of EGFR commonly found, among others: (a) deletions in exon 19, which is the most frequent mutation that is about 46% of all EGFR mutations, (b) mutations in exons 18, 20, or 21, which is the second most common mutation, found in about 41% of cases of all EGFR mutations, including single nucleotide substitution L858R at exon 21, (c) duplication / insertion on exon 20.[3,11-13]

Deletions on exon 19 occur in parts that encode the kinase domain and eliminate four amino acids. The mutation of exon 21 L861Q results from the substitution of leucine into glutamine at position 861, this mutation also occurs in the section that codes the domain kinase. The exonal mutation of 21 L858R occurs due to the substitution of leucine to arginine at position 858, this mutation also occurs in the section that codes the domain kinase. Mutations in exon 18 G719A / C caused by amino acid substitution from glycine to cysteine at position 719, this mutation occurs on the exon 18 that codes the domain kinase. This type of mutation is related to the sensitivity to thyroline kinase inhibitor therapy. Types of EGFR mutations resistant to tyrosine kinase inhibitor therapy include point mutations in exon 19 (D761Y), point mutations in exon 20 (T790M) and exon 20 inserts (D777_N777insNPG). Mutations which is occurring outside the kinase domain are very rare in lung cancer.[3,8,11,13]

Based on the literature, the EGFR mutation rate varies regionally. The rate of mutation in LCNSCC in Asian countries is higher than in western countries which is about 50% while in the West is around 10% .[1,14]

Four of the five lung cancer patients in the United States and Australia who were involved in the study of Shigematsu *et al* were found to have EGFR mutations.[1] This suggests that genetics are more important factor in EGFR mutations than geographically. There have been identified several variations of polymorphisms in the EGFR gene including repeat CA in intron 1 or single nucleotide polymorphisms in the promoter region. Some of these polymorphisms also regulate the level of EGFR expression and their distribution indicates ethnic variation.

This study found that the mutation of EGFR found more in female sex that is equal to 20.14%, while men equal to 18.06%. Although the EGFR mutation was found more in women but in this study there was no significant association between sex and EGFR mutations. This result is similar to the study by Shoji *et al*[14] and Pan *et al*[10] also revealed a similar thing that the rate of EGFR mutation is not related to sex.

Research conducted by Pan YQ[10] and Tukumo M[1] found that the EGFR mutation was significantly higher in women than in men, so it was concluded that EGFR mutations were significantly associated with sex. The role of gender at the EGFR mutation frequency is still not clearly understood. However, it is suspected that there is a role of sex hormones or environmental factors in this case

In this study, there was a significant association between EGFR mutation and serum CEA level (P = 0.043) with odds ratio 3.4 (cutoff value = 5 ng / ml), similar to Pan JB study in 2013 and Pan YQ in 2014. Similarly, research conducted by Wang WT in 2014, revealed that abnormal serum CEA levels before therapy were

significantly associated with EGFR mutation frequency. Shoji et al[14] also reported that there was a positive correlation between CEA levels and EGFR mutation rates in patients with recurrent lung adenocarcinoma.[14,15]

CEA is one type of adhesion protein whose expression can be activated and regulated through P13-K / Akt and STAT 3/5 signal pathways in EGFR. Activation of the P13-K / Akt signal pathway is involved in the regulation of cell differentiation, proliferation and apoptosis. EGFR mutations can cause irregularities in the pathway to decrease the transduction signal and cause antiapoptotic activity in tumor cells. Suspected antiapoptotic signal pathways resulting from deviations on Akt and STAT 3/5 molecular activation may affect CEA expression. In addition, the EGFR mutation undergoes autophosphorylation in the absence of interleukin 3 without EGF stimulation. Presumed continuous signals from EGFR mutations may stimulate antiapoptosis activity, consequently the expression of the CEA protein as an antiapoptosis agent may appear to be elevated in patients with EGFR gene mutations.[14-16]

CEA is one of the proteins that can be affected by activation of the EGFR pathway, then serum CEA levels may be a sign of a mutated EGFR. However, these allegations require further research. Although EGFR and CEA belong to different protein groups, studies in recent years have found that there is a relationship between CEA expression and EGFR mutations. Similarly, research conducted by Abdurahman *et al* in 2015, they found that there was a significant association between EGFR mutation and serum CEA levels, but they suggested to increase the sample size to explain serum CEA determination to be able to replace EGFR testing for carcinoma lung cancer.[6,17]

Regarding the function of CEA is still little known, but it has been known as adhesion molecule and involved in cell aggregation. It is well known that CEA has a role in antiapoptotic and prometastasis in colon cancer. In lung cancer, CEA levels are also found to increase especially in the histologic type of adenocarcinoma. In addition, it has been reported that excessive expression of CEA levels may protect tumor cells against apoptosis induced by loss of cell contact with the extracellular matrix and inhibit cell death.[14,15]

Research conducted by Jin et al also found an association between CEA levels and EGFR mutations. In addition, Jin *et al* believes that patients with pulmonary adenocarcinoma with serum CEA ≥20 ng / mL are ideal populations to receive targeted therapy using EGFR-TKI. This is caused by the results of research conducted revealed that the higher levels of CEA, the higher the rate of EGFR mutation. However, there is no clear reason and ground on it. More interestingly, Jin *et al* found that mutations in exon 19 are more closely related to serum CEA levels, presumably this is because the frequency of EGFR mutations in exon 19 is the most common mutation found.[15,18]

This study also looked at sensitivity, specificity, accuracy, positive predictive value, negative predictive value of serum CEA levels against epidermal growth factor receptor (EGFR) mutations. Although the study analysis found a significant association between EGFR and CEA mutations, the CEA sensitivity and specificity of EGFR mutations were found to be low. Based on the analysis, it was found that the sensitivity of CEA was 77% and specificity was 50%. A 77% sensitivity score indicates that out of 100 people with EGFR mutations, CEA can detect an EGFR mutation of 77%. A 50% CEA specificity indicates that of 100 people without EGFR mutation, CEA can detect EGFR without mutation of only 50%. A positive predictive value of 53% means that from 100 patients with CEA> 5 ng / ml only about 53% actually have EGFR mutation, this result is low because

this value is almost equivalent as no mutation. A negative predictive value of 76% means that from 100 people with CEA <5 ng / ml then about 76% of EGFR is completely non-mutated. The obtained value is similar to that of Pan YQ *et al* (2014). Pan YG *et al* found the CEA sensitivity and specificity in estimating EGFR mutation was 76% and 45%, NPP and NPN were 52% and 71%. In this research, the accuracy of CEA examination is 61%, it means the proximity of CEA measurement value to the actual value was 61%.

The ROC curve showed that CEA was not an ideal predictor for EGFR mutation in adenocarcinoma lung cancer at Saiful Anwar Hospital Malang (Area under curve (AUC) 0.558, P = 0.078). The ROC curve presented in Figure 5.6 shows the AUC value was 55%, the figure is very far from 100.0%, so the CEA is considered very weak in estimating the EGFR mutation. This finding is appropriate and even lower with results discovered by Pan YQ *et al* in 2014, which found that CEA may not be the ideal predictor for EGFR mutation with ROC curve of 0.608, P = 0.069. This is due to the expression of CEA levels that can be affected by various causes and from a variety of pathways, a path known today that may affect the CEA is the path of the insulin receptor (IR) as well as the EGFR pathway.

However, this is in contrast to Pan JB *et al*'s findings, where high serum CEA levels are significantly associated with high EGFR mutations and ROC curves suggesting that CEA can be used to estimate EGFR mutations. This difference may be due to the differences in the population involved. The study by Pan JB *et al* involved patients with advanced stage adenocarcinoma lung cancer with high levels of CEA (35-40 ng / ml), whereas in this study involving patients with CEA cutoff point was 5 ng / ml. However, further research is still needed to elucidate whether the serum CEA determination can replace EGFR testing for adenocarcinoma lung cancer patients.[6]

CONCLUSIONS

There are 55 patients (38.2%) of 144 patients with EGFR mutations, and 89 patients (61.8%) for wildtype. Among these mutations, 22% are exon 19 mutations, 27% mutations in exon 21 (24% are in exon 21 L858R, 3% are exon 21 L861Q), 1% are exon 18 G719C mutations, 1% with double mutation (exon 19 and exon 21 L858R). In addition, there was a significant association between EGFR mutation and CEA levels with P = 0.043 and odd ratio 3.4 and no significant association between EGFR and sex mutations.

Sensitivity of CEA levels is 77%, specificity is 50%, positive predictive value is 53%, negative predictive value is 76%, accuracy value is 61%, AUC value is very weak which is 36% (0.558, P = 0.088) so that CEA is not an ideal predictor for EGFR mutation in adenocarcinoma lung cancer in Saiful Anwar Malang Hospital.

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