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EFFICACY OF GEFITINIB AND ERLOTINIB IN NON-SMALL-CELL LUNG CARCINOMA

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Abstract

Lung cancer is a type of cancer that often occurs after breast cancer and prostate cancer. Lung cancer is one of the main causes of mortality in men and women in the United States. Non-small cell carcinoma is the most common type of lung cancer, complying more than 85% of all lung cancers. The anti-cancer therapy that is currently developing is inhibiting the work of EGFR, one of which is the tyrosine kinase inhibitor that works in the intracellular. Gefitinib and Erlotinib are two epidermal growth factor receptors tyrosine kinase inhibitors) with similar mechanism and nearly the same clinical efficacy in non-small cell carcinoma. There is no data in the Regional Public Hospital Dr Soetomo that compares the efficacy of gefitinib and erlotinib so that this study aims to compare the efficacy of gefitinib and erlotinib in the Non-small cell carcinoma that treated at One-Roof Oncology Poly Regional Public Hospital Dr Soetomo Surabaya, East Indonesia referral hospital.

Methods: This study is an analytical study by means of retrospective cohort design. This study involved 94 patients who met the inclusion criteria. Patients who did not complete the data as well as drug side effects that cause epidermal growth factor receptors tyrosine kinase inhibitors therapy to be changed or their doses permanently changed are not included in this study. This research was conducted at the One-Roof Oncology Poly Dr. Soetomo Surabaya, Indonesia from January 2016 to August 2018.

Results: Based on the results of the chi-square test on drug response, side effects, Progression Free Survival and Overall Survival in both groups showed that the value of p> 0.05.

Conclusion: The efficacy between gefitinib and erlotinib is not different in non-small cell carcinoma lung cancer patients in the Poli oncologi Satu Atap Regional Public Hospital Dr. Soetomo Hospital Surabaya.

Keywords: *gefitinib, erlotinib, lung cancer, tyrosine kinase inhibitor.*

Introduction

Lung cancer is a type of cancer that often occurs after breast cancer and prostate cancer. Lung cancer is one of the main causes of mortality in men and women in the United States [*Murray J, Nadel J, 2005; Bogdanowicz B et al., 2017*]. Based on data from the American Cancer Society in 2016, the incidence of the new cases of lung cancer is estimated as many as 224,390 new cases or 14% of all cancer cases and an estimated mortality rate caused by lung cancer is equal to 158,080 or 27% of all causes of death by cancer [*Society A, 2016*]. Whereas lung cancer ranked first among the 5 most common cancers in men with 25,322 cases and women ranked last among the 5 most common cancers with 9374 cases in Indonesia based on the 2014 Cancer Country Profile data published by WHO (2017). Lung cancer deaths ranked second in men at 21.8% and fourth in women at 9.1%. This incidence is related to the number of smoking habits in men that is greater than women. Most lung cancer patients that come to the hospital were diagnosed with an advanced stage which is around 57%, with a survival rate of 1 and 5 years is 26% and 4%, while those diagnosed at an early stage are only around 15% with a 5-year survival rate of 54 % [*Society A, 2016*].

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WHO divides lung cancer into 2 classes based on biology, therapy, and prognosis, namely small cell carcinoma type lung cancer and non-small cell carcinoma lung cancer (NSCLC). This lung cancer is the most common type, which is more than 85% of all lung cancers, which consist of non-squamous carcinoma (adenocarcinoma, large cell carcinoma, and other cell types) and squamous cell carcinoma (epidermoid). Adenocarcinoma is the most common type of lung cancer in the United States and is the most frequent cell type in nonsmokers. Pathway epidermal growth factor receptor (EGFR) plays an important role in cell growth and proliferation, and often deregulates human epithelial cancers including non-small cell carcinoma lung cancer through increased protein expression, increased gene codes, and activates mutations to occur in angiogenesis, tumorigenesis and apoptotic barriers [*Gridelli C et al., 2011*].

The anti-cancer therapy that is currently developing is inhibiting the work of EGFR, one of which is the tyrosine kinase inhibitor (TKI) that works in the intracellular. The working principle of EGFR TKI is to compete with ATP to bind to the intracellular domain of EGFR catalytic tyrosine kinase thereby inhibiting cancer cell proliferation and inhibiting tumor angiogenesis in Large doses, types of EGFR mutations, EGFR polymorphisms, and gastric pH affect the success of EGFR TKI therapy. Gefitinib and Erlotinib are two EGFR TKIs that have the same mechanism and almost the same clinical efficacy in non-small cell carcinoma lung cancer [*Ettinger D et al., 2015*]. Gefitinib administration at a dose of 250 mg per day is the minimum effective dose which is one-third of the maximum tolerated dose while erlotinib at a dose of 150 mg per day is a maximum tolerated dose so that the said biological activity of erlotinib at standard doses may be higher than gefitinib [*Hidalgo M et al., 2001; Baselga J et al., 2002*]. In RSUD Dr. Soetomo Surabaya, using EGFR TKI therapy since 2012 through health insurance covered by the government. There is no data in the RSUD Dr Soetomo comparing the efficacy of gefitinib and erlotinib so that this study aims to compare the efficacy of gefitinib and erlotinib in the non-small cell carcinoma lung cancer treated at the One Roof Oncology (POSA) Dr Soetomo Surabaya, East Indonesia referral hospital.

Material and Methods

This study is an analytical study using a retrospective cohort design. This study involved patients with a diagnosis of lung cancer who were treated at RSUD Dr. Soetomo Surabaya, Indonesia starting in January 2016 until August 2018. The inclusion criteria of this study were patients who had been diagnosed with definite NSCLC based on histopathological results, with EGFR common mutation, IIIA disease stage and above, had never received any systemic therapy for NSCLC before, and have at least one tumor or a lesion that can be measured. Patients who do not have complete data as well as drug side effects that cause EGFR TKI therapy to be changed or their doses permanently changed are not included in this study. The instrument used in this study is the patient's medical record and the results of a thoracic CT scan. The data used are secondary data from the results of history, physical examination, and investigations found in the medical record, both before gefitinib or erlotinib (baseline) and evaluation, including baseline thoracic CT scan and CT scan evaluation every 3 months. This study used a total sampling technique to obtain 211 patients but who met the inclusion criteria as many as 94 patients. In this study, Kolmogorov-Smirnov test was carried out to determine the data distribution on the gefitinib group and the Shapiro-Wilk test in the erlotinib group and continue with Mann Whitney to statistical analysis. There was significant difference if p value <0.05.

Results

Number of subjects: Patients involved in this study were initially 211 patients but were selected based on the inclusion criteria established in this study. Patients who were unable to continue this study were 117 patients. This is mostly dominated due to incomplete basic data and research support. Various influencing factors include the absence of a CT scan evaluation, the number of visits is only 1, the patient does not take medication and various other factors that influence the results of this study. At the end of this study, the number of patients involved was as many as 94 patients.

The Characteristics of subjects: The characteristics of 94 patients involved in this study can be seen in table 1.

In table 1, it can be seen that the subjects in terms of gender were dominated by female, namely

61.3% in the gefitinib group and 52.6% in erlotinib. The youngest patient profile was 22 years and the oldest was 85 years with a mean of 56 years for gefitinib and 59 years for erlotinib. Another profile showed that most of the non-small cell carcinoma lung cancer patients with EGFR mutations were nonsmokers in both the gefitinib and erlotinib groups, with 44 patients (58.7%) and 10 patients (52.6%) respectively.

Table 1.

Characteristics of NSCLC patients who received gefitinib and erlotinib therapy

	Gefitinib	Erlotinib	Total
Age (Years)			
Median	56	59	56
Range	35-85	22 - 76	22 – 85
Gender – amount (%)			
Female	46 (61.3%)	10 (52.6%)	56 (59.6%)
Male	29 (38.7%)	9 (47.4%)	38 (40.4%)
Smoking History – amount (%)			
Smoker	31 (41.3%)	9 (47.4%)	40 (42.6%)
Non Smoker	44 (58.7%)	10 (52.6%)	54 (57.4%)
Initial treatmentWHO PS – amount (%)			
0	40 (53.3%)	11 (57.9%)	51 (54.3%)
1	30 (40%)	8 (42.1%)	38 (40.4%)
2	2 (2.7%)	0	2 (2.1%)
3	3 (4.0%)	0	3 (3.2%)
Tumor Histological Features			
Adenocarcinoma	73 (97.3%)	19 (100%)	92 (97.9%)
Squamosa	1 (1.3%)	0	1 (1.1%)
Adenosquamosa	1 (1.3%)	0	1 (1.1%)
Stage of disease at diagnosis			
IIIA	5 (6.7%)	0 (0%)	5 (5.3%)
IIIB	11 (14.7%)	3 (15.8%)	14 (14.9%)
IV	59 (78.7%)	16 (84.2%)	75 (79.8%)
Histology Samples			
Mass in lungs	60 (80%)	15 (78.9%)	75 (79.8%)
Metastasis	15 (20%)	4 (21.1%)	19 (20.2%)
Samples collection method			
FNAB	54 (72%)	14 (73.7%)	68 (72.3%)
FOB	7 (9.3%)	3 (15.8%)	10 (10.6%)
Pleural fluid cytology	14 (18.7%)	2 (10.5%)	16 (17%)
EGFR Mutation			
Exon 19	46 (61.3%)	12 (63.2%)	58 (61.7%)
Exon 21 L858R	27 (36%)	7 (36.8%)	34 (36.2%)
Exon 21 L861Q	2 (2.7%)	0	2 (2.1%)

The initial PS score when getting the EGFR TKI therapy mostly was 0 in both groups, 40 patients (53.3%) in gefitinib and 11 patients (57.9%) in erlotinib while the initial PS of 1 was 30 patients (40%) in gefitinib and 8 patients (42.1%) in erlotinib. The initial PS score of 4 was not found in both groups. The most histological features of the tumor were adenocarcinoma of 73 patients (97.3%) in gefitinib and 19 patients (100%) in erlotinib. In the gefitinib group, there was 1 patient with histology of adenosquamous and 1 patient with squamous. Stage IV is the highest stage in both the gefitinib and erlotinib groups, namely 78.7% and 84.2%. The second most common stage was stage IIIB at 14.7% in gefitinib and 15.8% in erlotinib, while stadium IIIA was 6.7% in gefitinib and none in erlotinib.

Histological samples originated from pulmonary masses were 60 patients in gefitinib and 15 patients in erlotinib, while those from metastasis were 15 patients from gefitinib and 4 erlotinib patients. The sampling method with FNAB was the most commonly used method in both groups, namely 54 patients (72%) in gefitinib and 14 patients (73.3%) in erlotinib. In sampling with cytology method as much as 14 patients in gefitinib and 2 patients in erlotinib while with Fiber Optic Bronchoscopy (FOB) for 7 patients in gefitinib and 3 patients in erlotinib. Exon deletion 19 mutations were the most EGFR mutations in both groups, both in gefitinib and erlotinib by 61.3% and 63.2%. In the erlotinib group, there were no exon 21 L861Q mutations while the gefitinib group had 2.7%.

Treatment Response: Giving EGFR TKI as the first line in lung cancer patients with a positive EGFR mutation, the response was including subjective, semi-subjective and objective responses. In this study, subjective and semi-subjective responses were assessed 3 months after receiving EGFR TKI therapy. Subjective responses were assessed based on changes in EQ5D, semi-subjective responses were assessed based on changes in performance score and weight while objective responses were assessed based on RECIST. In this study, there were 2 patients who could not be assessed for changes in EQ5D, performance score and weight because the two patients received EGFR TKI therapy for the first few months in an-

other hospital. The following is an overview of the EGFR TKI treatment response as the first line in both groups of patients.

Based on table 2, it can be concluded that there was no difference in drug response in the group that receiving Gefitinib and Erlotinib therapy.

Side Effects: The comparison test results using chi-square obtained values> 0.05 on all side effects due to treatment so that it can be concluded that there were no significant differences in the gefitinib and erlotinib groups (Table 3).

Progression Free Survival dan Overall Survival: Before analyzing the differences between progression-free-survival and overall survival from the administration of EGFR TKI therapy to patients with NSCLC, first the normality test was carried out. The normality test results will be used to determine the methods that will be used to determine the significance between the group. For this study, Kolmogorov-Smirnov test was carried out to determine the data distribution on the gefitinib group and the Shapiro-Wilk test in the erlotinib group. The following are the normality test results of progression-free survival and overall survival in NSCLC patients who received gefitinib and erlotinib (Table 4).

Table 2

Subjective, semi-subjective and objective responses of patients who received gefitinib and erlotinib therapy

EQ5D Score	Gefitinib	Erlotinib	Value
Subjective Response			
Decrease	21 (28.8%)	2 (10.5%)	
No changes	38 (52.1%)	14 (73.7%)	0.382
Increase	14 (19.2%)	3 (15.8%)	
Semi-Subjective Response			
Performance status (PS)			
Improved	15 (20.5%)	1 (5.3%)	
No changes	49 (67.1%)	15 (78.9%)	0.188
Worsen	9 (12.3%)	3 (15.8%)	
Weight			
Increase	32 (43.8%)	9 (47.4%)	
No changes	19 (26%)	3 (15.8%)	0.887
Decrease	22 (30.1%)	7 (36.8%)	
Objective Response			
Partial response	30 (40%)	10 (52.6%)	
Stable disease	26 (34.7%)	4 (21.1%)	0.576
Progressive disease	19 (25.3%)	5 (26.3%)	

Table 3

Side effects of Gefitinib and Erlotinib in patients

	Gefitinib	Erlotinib	Value
Rash			
No Occurence	6 (8%)	1 (5.3%)	
1st Degree	60 (80%)	15 (78.9%)	0.571
≥ 2nd Degree	9 (12%)	3 (15.8%)	
Diarrhea			
No Occurence	45 (60%)	13 (68.4%)	
1st Degree	28 (37.3%)	5 (26.3%)	0.684
≥ 2nd Degree	2 (2.7%)	1 (5.3%)	
Paronychia			
No Occurence	58 (77.3%)	11 (57.9%)	
1st Degree	15 (20%)	8 (42.1%)	0.191
≥ 2nd Degree	2 (2.7%)	0	
Stomatitis			
No Occurence	69 (92%)	16 (84.2%)	
1st Degree	6 (8%)	3 (15.8%)	0.380

From the normality test results of progression-free survival and overall survival in the gefitinib group, P <0.05 was obtained. Based on these results it can be concluded that the gefitinib group is normally distributed while the erlotinib group also had a normal distribution (p> 0.05) so that Mann Whitney variance test will be carried out. In the Mann Whitney statistical test results, a value of > 0.05 was obtained so that it can be concluded that in progression-free survival, gefitinib therapy did not provide a significant difference compared to erlotinib. The Mann Whitney test results in regards to OS concludes that there was no significant difference in OS value of gefitinib therapy compared to erlotinib, with value >0.05.

Discussion

Based on the result of this study, the efficacy of both drugs showed no significant difference. This can be seen from the results of progression-free survival and overall survival which showed a value of >0.05, meaning that the therapies from both gefitinib and erlotinib are similar. To determine the efficacy of gefitinib and erlotinib can be seen based on the value of progression-free survival and OS. The results of this study are lower than in previous studies. In the WJOG 5108L study, progres-

Table 4.

The normality test results of PFS and OS of patients who received gefitinib and erlotinib therapy

Variable	progression-free -survival		overall survival	
	Gefitinib	Erlotinib	Gefitinib	Erlotinib
Normality Test	*Kolmogorov – Smirnov*	*Shapiro – Wilk*	*Kolmogorov – Smirnov*	*Shapiro – Wilk*
n	58	14	38	9
Value	0.002	0.515	0.001	0.656
Results	Abnormal	Normal	Abnormal	Normal
		months		
Range	2-18	2-14	3-24	3-15
Median	6	7	8	10
Mean	7.0	7.14	9.05	9.56
St.Dev	3.902	3.880	4.306	4.246
Value	0.825		0.559	

sion-free survival of gefitinib was 8.3 months and erlotinib was 10 months [*Yoshida T, 2013*]. From other studies, the value of progression-free survival in gefitinib was 10.4 months and erlotinib was 13 months [*Yang J et al., 2017*]. The value of progression-free survival in gefitinib was 11.7 months and erlotinib 9.6 months [*Lim S et al., 2014*]. but obtained a 7-month median progression-free survival result [*Fatmawati F, 2016*]. Until the end of this study, there were still 17 gefitinib patients and 5 erlotinib patients who had not experienced progression of the disease.

The results of this study in terms of progression-free survival and low overall survival showed no significant differences when compared with previous studies. This can be caused by large differences in the number of samples of the two groups so that there are a wide bias and wider standard deviation. The range of progression-free survival and overall survival duration that is too far away in one group causes a wide bias and standard deviation so that the comparison test results are not significantly different. The low survival rate contrasts with PS at the beginning of therapy which shows the patient's condition is good before getting EGFR TKI therapy, this can be due to the influence of the subjectivity of PS assessment performed by the examiner on lung cancer patients. In addition, compliance also affects EGFR TKI therapy.

Tumor response, improvement in symptoms and conditions in non-small cell carcinoma lung cancer patients who received gefitinib have been observed since early 1999. Retrospective analysis of the IPASS study showed significant predictions of activation of the EGFR gene mutation in the patient's ORR and progression-free survival that treated with gefitinib. The results showed that the amplification of the EGFR gene was weakened. Although the benefits of amplification in patients continue to be observed, this is only seen in patients who activate mutations in the EGFR gene in the amount of 77% of patients with amplification. Patients without activation of the EGFR gene mutation did not benefit from gefitinib therapy with RR 1% and progression-free survival was longer if the patient received chemotherapy [*Knetki-wróblewska M et al., 2012; Bogdanowicz B et al., 2017*].

In the FIRST-SIGNAL study, regardless of the EGFR mutation, the median progression-free survival was 6.1 months for gefitinib compared to 6.6 months for chemotherapy (cisplatin and gemcitabine). progression-free survival in the first year in the gefitinib group was 20.3% compared to 5% in the chemotherapy group. The OS is almost the same in both groups. In the subgroup with the EGFR mutation, the median progression-free survival was significantly higher in patients with gefitinib ie 8.4 months compared with 6.7 months and the proportion of patients without 1-year progression was 34.6% with gefitinib versus 14.3% with chemotherapy [*Gridelli C et al., 2011*].

A meta-analysis of 4 randomized studies, comparing the efficacy of gefitinib and chemotherapy as first-line therapy was published. Of the 2000

patients who were the subjects of the study, 75% were women and 86% were non-smokers. Prediction values of mutation activation in the EGFR gene are listed in the ORR and progression-free survival. The ORR value in patients with activation of the EGFR gene mutation that received gefitinib compared to platinum chemotherapy was 73% and 38% respectively. progression-free survival values also increased significantly in patients treated with gefitinib, which was 55% lower than platinum chemotherapy [*Knetki-wróblewska M et al., 2012*]. Recent studies report favorable results for the use of gefitinib in EGFR patients with positive mutations that are contraindicated for other forms of chemotherapy (elderly or PS 3-4); RR is 66% and OS median is 17.8 months. This suggests that therapy with gefitinib is effective for patients with EGFR mutations and is not suitable for other forms of standard chemotherapy for several other reasons such as old age or poor PS [*Araki T et al., 2012*].

The BR.21 study was a randomized, double-blind phase III trial that tested the efficacy of erlotinib with placebo in patients with advanced stage non-small cell carcinoma lung cancer and refractory chemotherapy. In the study, RR in the erlotinib group was 8.9% and less than 1% in the placebo group; the median response duration was 7.9 and 3.7 months, respectively. OS scores were 6.7 months in erlotinib and 4.7 months in placebo ($p<0.001$). The one-year survival rate was 31% in erlotinib and 21% in placebo. The value of Objective Responses (OR) was more frequent in women (14% vs 6%; $p<0.0065$) and in patients with adenocarcinoma, compared with other histologies (14% vs 4.1%; $p< 0.0001$), at patients without a smoking history (25% vs 4%; $p< 0.0001$) [*Ricciardi S et al., 2011*].

The TRUST study analysis confirmed that erlotinib was an effective and well-tolerated choice in advanced NSCLC patients with progression-free survival and overall survival values in the study of 3.25 months and 7.9 months while the Disease Control Rate (DCR) was 69%. Research on the use of erlotinib with East and Southeast Asian patient populations compared to the population of the TRUST study, obtained progression-free survival values of 5.78 months in East and Southeast Asia, 2.92 months in non-East and Southeast Asia, 3.25 months in the global population. The OS scores were 14.7 months, 6.8 months and 7.9 months, respectively. ORR was significantly higher for East and Southeast Asian patients (27%), compared with non-East and Southeast Asian patients (10%) or the overall global population (13%) [*Reck M et al., 2010; Wu Y et al., 2012*].

This study is a retrospective study that uses medical record data as a source of data retrieval, so it has limitations to confirm doubtful data, especially in patients who have died. The doctor on duty at POSA is a resident of Pulmonology and Respiratory Medicine department, which the shift changes each month according to the schedule so that the data is collected by a different doctor every month. The subjectivity factor of the doctor greatly influenced data collection for this study. In this study, there was a significant difference in the number of patients. This can be caused by gefitinib being approved by government health insurance.

Conclusion

There were no significant differences in terms of efficacy between gefitinib and erlotinib in non-small cell carcinoma lung cancer patients at the one-roof poly oncology (POSA) RSUD Dr. Soetomo Surabaya. Future studies are expected to use a prospective cohort design so that the data obtained is more accurate. Patients included in the study sample are followed prospectively by a doctor, or the author himself, so that they can see first-hand, the complaints and changes in the patient's condition, timely CT scans and educate patients on EGFR TKI therapy compliance so that the outcome can be more optimal.

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KOMITE ETIK PENELITIAN KESEHATAN
RSUD Dr. SOETOMO SURABAYA

KETERANGAN KELAIKAN ETIK
(" ETHICAL CLEARANCE ")

0658/KEPK/IX/2018

KOMITE ETIK RSUD Dr. SOETOMO SURABAYA TELAH MEMPELAJARI SECARA SEKSAMA RANCANGAN PENELITIAN YANG DIUSULKAN, MAKA DENGAN INI MENYATAKAN BAHWA PENELITIAN DENGAN JUDUL :

" PERBANDINGAN EFIKASI GEFITINIB DAN ERLOTINIB PADA PASIEN KANKER PARU JENIS KARSINOMA BUKAN SEL KECIL DI POLI ONKOLOGI SATU ATAP RS DR SOETOMO SURABAYA "

PENELITI UTAMA : Dr. Laksmi Wulandari, dr., Sp.P(K), FCCP
PENELITI LAIN : L. Afrita Amalia Laitupa, dr.
UNIT / LEMBAGA / TEMPAT PENELITIAN : RSUD Dr. Soetomo

DINYATAKAN LAIK ETIK

Berlaku dari : 25/09/2018 s.d 25/09/2019
Surabaya, 25 September 2018
KETUA

(Dr. Elisna Syahruddin, dr., Sp.An, KIC,KAP)
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Improved CiteScore methodology

CiteScore 2020 counts the citations received in 2017-2020 to articles, reviews, conference papers, book chapters and data papers published in 2017-2020, and divides this by the number of publications published in 2017-2020. Learn more >

CiteScore 2020

$$0.3 = \frac{70 \text{ Citations } 2017 - 2020}{220 \text{ Documents } 2017 - 2020}$$

Calculated on 05 May, 2021

CiteScoreTracker 2021

$$0.4 = \frac{85 \text{ Citations to date}}{221 \text{ Documents to date}}$$

Last updated on 06 March, 2022 • Updated monthly

CiteScore rank 2020

Category	Rank	Percentile
Medicine General Medicine	#637/793	19th

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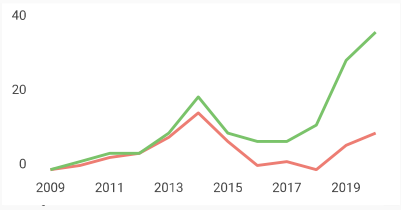
New Armenian Medical Journal

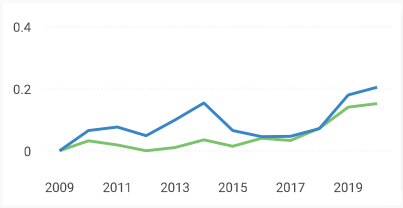
COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
Armenia Universities and research institutions in Armenia	Medicine Medicine (miscellaneous)	UNIPRINT	5

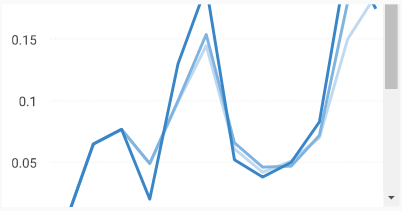
PUBLICATION TYPE	ISSN	COVERAGE	INFORMATION
Journals	18200254, 18290825	2009-2020	Homepage namj.ysmu@gmail.com

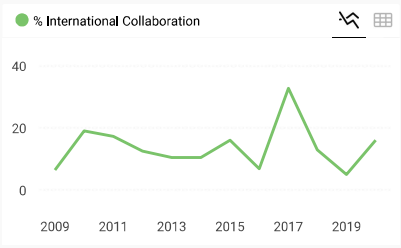
SCOPE

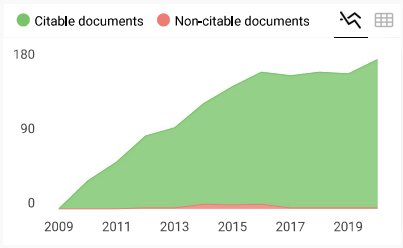
Information not localized

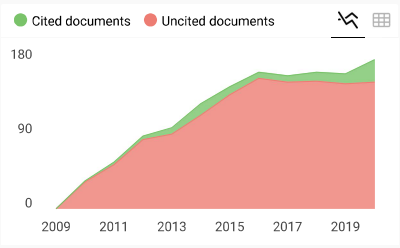


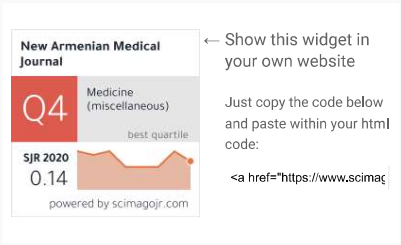


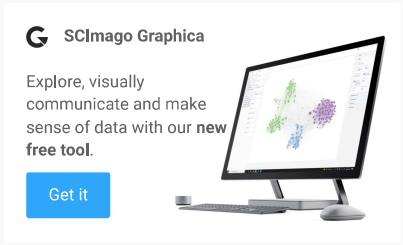












Metrics based on Scopus® data as of April 2021

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