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Original Article

Correlation between chemotherapy cycles and performance status based on ECOG in non-small cell lung cancer patients

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Abstract

Background: Tumor-infiltrating Lymphocytes (TILs) have prognostic value on HER2 positive breast cancer (BC). The absence of standardized method for evaluating TILs causes variations in results of previous studies. This study is performed to evaluate the prognostic value of TILs in HER2 positive BC treated with trastuzumab-based adjuvant therapy using standardized method recommended by the *International TILs Working Group*.
Aim: To analyze the prognostic value of TILs in HER2 positive BC patients receiving trastuzumab-based adjuvant therapy at Dr. Sardjito General Hospital, Yogyakarta and to analyze proportion differences between high TILs (≥30%) and low TILs (<30%).
Methods: This is a retrospective cohort study on HER2 positive, stage 1-3 BC patients who received trastuzumab-based adjuvant therapy. Histopathology slides from 6 hospitals/laboratories were analyzed by two pathologists.
Results: 73 data were available for analysis. TILs stroma <30% was 65,8% and most patients received combination of anthracyclines, taxanes and trastuzumab (67,1%). There was no difference of overall survival between high and low TILs (p log rank: 0,331).
Conclusion: The proportion of HER2 positive breast cancer with high TILs was lower than those with low TILs. HER2 positive BC with high TILs did not show better overall survival compared to those with low TILs. Our study did not support the theory that different TILs score has prognostic value in HER2 positive breast cancer. Since no formal recommendation for a clinically relevant TIL threshold has been given, further study with bigger samples and better concordance rate among pathologists should be done.

Keywords: *adjuvant, breast cancer, HER2, trastuzumab, tumor-infiltrating lymphocytes*

Abstrak

Latar belakang: Prevalensi kejadian kanker paru adalah 14,3% pada laki-laki dan 8,4% pada perempuan. Rokok merupakan salah satu penyebab kanker paru. Dan kemoterapi merupakan tatalaksana lanjutan pada KPKBSK dan berpengaruh pada *performance status* pasien.
Tujuan: Penelitian ini bertujuan untuk mengetahui hubungan siklus kemoterapi terhadap *performance status* berdasarkan ECOG pada pasien kanker paru jenis karsinoma bukan sel kecil (KPKBSK) di RSUD dr. Zainoel Abidin Banda Aceh tahun 2017-2020.
Metode: Ini merupakan penelitian analitik observasional dengan desain *cross sectional*. Dengan *total sampling*. Dan data bersumber dari rekam medis sebanyak 164 subjek.
Hasil: Hasil penelitian menunjukkan 57% pasien KPKBSK setelah kemoterapi menunjukkan *performance status* yang stabil, sedangkan 41% menurun. Karboplatin + paclitaxel merupakan regimen yang paling banyak digunakan (43%), dengan rata-rata PFS < 1 tahun dan OS < 2 tahun.
Kesimpulan: Berdasarkan analisa bivariat dengan menggunakan metode spearman, didapatkan nilai p < 0,05 dengan nilai R 0,367 yang menandakan terdapat hubungan antara jumlah siklus kemoterapi terhadap *performance status* berdasarkan ECOG pada pasien KPKBSK di RSUD dr. Zainoel Abidin dengan koefisien korelasi rendah.

Kata Kunci*: kanker paru karsinoma bukan sel kecil, performance status, siklus kemoterapi.*

Background

Lung cancer is the main malignancy in the world which has a large proportion (11.4%) along with breast cancer (11.7%), colorectal cancer (10 %), prostate cancer (7.3%), and abdominal cancer (5.6%).[1] With a comparison of the incidence of lung cancer in men by 14.3% and in women by 8.4%.[2] Apart from that, lung cancer in Indonesia is also one of the highest causes of death from cancer. From WHO data in 2020, it was found that the total incidence of lung cancer was 34,783 cases (8.8%) which was dominated by men as many as 25,943 cases of lung cancer.[3] In the province of Aceh itself, there was an increase in the incidence of cancer from 2013 which was around 1.3% to 2% in 2018.[4]

Various risk factors have been studied in determining the prognosis of lung cancer, one of which is smoking. Active smokers and passive smokers can also get harmful carcinogenic effects from cigarette smoke. In addition, age, genetics, occupation, delay in diagnosis and low response of cancer cells to available cytostatic drugs are the main reasons for the poor prognosis of lung cancer.[5,6]

In addition to the speed and accuracy of diagnosis, the management of the patient is very important to note. Actions taken in lung cancer patients in the form of chemotherapy.[7] Chemotherapy is the main treatment for small cell carcinoma and advanced treatment for non-small cell carcinoma. Chemotherapy is one type of treatment used in lung cancer patients. Chemotherapy is carried out to kill cancer cells with anti-cancer drugs which must be evaluated after two to three cycles of chemotherapy or even four to six cycles with a distance of each cycle is 21 to 28 days and before doing chemotherapy the doctor must confirm the histology of the cancer cells whether small cell carcinoma or non-small cell carcinoma (NSCLC).[8] Chemotherapy has side effects that can be in the form of a worsening of the biological, physical, social status, functional status of the patient and the *performance status of the* patient.[7]

Information regarding the relationship between chemo-therapy cycles and performance status based on ECOG in non-small cell carcinoma (NSCLC) lung cancer patients at dr. Zainoel Abidin Banda Aceh is not widely known. In Aceh Province itself, especially at the Regional General Hospital, dr. Zainoel Abidin Banda Aceh which is a regional referral hospital, information about the relationship between chemotherapy cycles and performance status based on ECOG in non-small cell carcinoma (NSCLC) lung cancer patients at dr. Zainoel Abidin Banda Aceh is not widely known because no research has been done on this relationship. Based on the background described above, the researchers to examine the relationship between chemotherapy cycles and performance status based on ECOG in non-small cell carcinoma (NSCLC) lung cancer patients at dr. Zainoel Abidin Banda Aceh in 2017-2020.

Methods

This research is an analytic observational with a cross sectional design. This study looked at the correlation between the number of chemotherapy cycles and the performance status of lung cancer patients with non-small cell carcinoma in RSUD dr. Zainoel Abidin Banda Aceh Year 2017-2020. The research data collection was carried out from September 2 to September 17, 2021.

The sample population in this study were lung cancer patients with non-small cell carcinoma and undergoing chemotherapy at RSUD dr. Zainoel Abidin. The sample in this study was selected by the method, non-probability sampling namely total sampling. The data used in this study is secondary data using patient medical records.

Data analysis was carried out univariate and bivariate. Univariate analysis was carried out on variables from the results of the study resulting in the frequency distribution of each variable studied including age, gender, diagnosis, TNM staging, lung cancer stage, cycles the patient go through, performance status of the patient for each cycle undertaken, and the chemotherapy regimen used. Meanwhile, bivariate analysis was used to assess the correlation between the number of chemotherapy cycle the patient go through and the patient's performance status which would be proven using the statistical test *Spearman Rank* ($p<0.05$).

Results

Based on research that has been conducted using secondary data in the form of patient medical records, it was found that a total of 164 patients with non-small cell carcinoma who go through chemotherapy met the inclusion and exclusion criteria.

Patient Characteristics

Based on the results of the study, the frequency distribution of the characteristics of research subjects based on age and gender can be seen in table 1.

Table 1. Characteristics of Non-small Cell Lung Cancer Patients (N=164).

	N	%
Gender		
Male	139	85%
Female	25	15%
Age (Years)		
<30	5	3.04
31-40	7	4.26
41-50	25	15.24
51-60	69	42.08
61-70	43	26.22
>70	15	9.16

Characteristics of lung cancer patients with non-small cell carcinoma by age found that the highest number of study subjects was aged >40 years, namely 152 patients with a percentage of 92.7% with the most age range being 51-60 years, namely 69 subjects (42%).

Based on gender, it was found that the male sex occupied more than half of the total number of subjects, namely 85% or as many as 139 patients. This is thought to occur due to the high prevalence of smoking in men compared to women globally, and judging from the typical risk factors for lung cancer including tobacco smoking, family history of malignancy, previous lung disease, and exposure to second hand smoke, radon, asbestos, arsenic, air pollutants, or occupational carcinogens are one of the causes of the difference in the incidence of these cancers. Different subtypes of lung cancer have different epidemiology and different prognoses.[9]

Distribution of the incidence of non-small cell lung cancer presented that data shows majority of the study subjects were diagnosed with lung cancer. Squamous cell carcinoma or as many as 136 patients and 17% of the subjects were diagnosed with adenocarcinoma. Table 2 describes the characteristics of patients based on their diagnosis and treatment options.

Table 2. Distribution of Cancer Cell Types, Staging and the Number of Cycles of Chemotherapy received by patients.

	N	**(%)**
Cancer cell type		
Adenocarsinoma	28	17.07
Squamous Cell Carcinoma	136	83.93
Staging		
Stage I	0	0
Stage II	10	6.09
Stage III	48	29.27
Stage IV	106	74.64
Cycle Chemotherapy		
2	6	3.66
3	8	4.68
4	150	91.66

Based on Table 2, it is known that 65% or as many as 108 subjects were first diagnosed at stage IV, 29% at stage III, 6% at stage II, and 0% at stage I. Based on Table 3 it is known that 65% or as many as 108 subjects first diagnosed at stage IV, 29% at stage III, 6% at stage II, and 0% at stage I.

Characteristics of non-small cell lung cancer patients based on the number of chemotherapy cycles the patient go through in table 2 explained that as many as 150 subjects or 91 % of research subjects followed chemotherapy up to cycle 4. This was due to changes in the quality of life of patients and changes in the performance status of patients in each cycle. In lung cancer patients, the number of chemotherapy cycles greatly affects the patient's quality of life. Patients who do not follow chemotherapy cycles up to cycle IV can be caused by a worsening of performance status, patients lost follow-up or because the patient has died.[10]

In this study, the 95 patients who go through chemotherapy until the 4th cycle had normal performance status, 40% with a performance status decreased, namely from performance status 1 to 2, and only 2% an increase in performance status from 2 to 1. This can be influenced by several factors

including age, gender, smoker, cancer stage, and seen of the patient's cancer metastases.

For the frequency distribution of non-small cell lung cancer patients based on the treatment options listed in Table 2, it is known that as many as 72 subjects (43%) were given carboplatin and paclitaxel as a chemotherapy regimen, 31% subjects were given carboplatin and navelbine, and only 1% subjects given the chemotherapy regimen cisplatin and vinoralbin. Other regimens used by doctors in administering chemotherapy include bondronat; docetaxel, cisplatin, 5-fluorouracil; brexel, cisplatin, 5-fluorouracil; gemcitabin, kemobin; and belotaxel.

Carboplatin and paclitaxel are the most widely used regimens. This is in line with the study of Gridelli C, et al., who explained that Paclitaxel/carboplatin was efficacious and well tolerated in 70-year-old patients with squamous NSCLC. These results are based on a previous analysis, which showed that paclitaxel /carboplatin was effective for a subgroup of difficult-to-treat patients.[11]

Table 3. Correlation between chemotherapy cycles and charges in the performance status of subjects

Cycles of Chemotherapy						
Performance status	2	3	4	Total	%	
Decreased	5	8	53	66	40.24	P<0.05
Stable	0	0	95	95	57.93	R 0.67
Increase	0	0	3	3	1.83	

In this study the use of carboplatin, paclitaxel was also associated with the performance status patient's and age. Where patients aged 60 years as many as 19 subjects had performance status 0 and as many as 91 subjects had performance status 1. Patients aged 65 years as many as 12 subjects had performance status 0 and as many as 58 subjects had performance status 1 and patients aged 70 years as many as 8 subjects. have a performance status of 0 and 22 subjects have a performance status of 1. This means that the performance status of patients when using carboplatin, paclitaxel is still said to be good for increasing patient age.[11]

Nathan R, et al conducted 10 trials with a subject of 2,855 patients. With the average results of OS and PFS are 9.8 months and 5.9 months.[12] And in the study of Akamatsu H, et al explained that the average PFS of non-small cell lung cancer patients was 12 months and the average OS of patients was 39 months. With Carboplatin + Paclitaxel, Cisplatin + S-1, and Cisplatin + Vinorelbine.[13]

Correlation between Chemotherapy Cycle and Performance Status in Non-Small Cell Lung Cancer Patients

Statistical tests based on Spearman rank correlation were used to analyze the relationship between the number of chemotherapy cycles and performance status of patients in RSUD dr. Zainoel Abidin, Banda Aceh. The following is the hypothesis for the Spearman rank correlation test:

If p < 0.05 then Ho is rejected Ha is accepted 0.05 then Ho is
If p > accepted Ha is rejected
Meaning:
Ho: There is no relationship between the dependent variable and the independent variable
Ha: There is a relationship between the dependent variable and independent variables

The data in Table 3 shows that subjects who go through 4 cycles of chemotherapy had changes in performance status. Subjects with performance status normal were 95 patients with a percentage of 57%. 32% of patients had decreased performance status and 2% had improved performance status. While in patients who go through 3 cycles of chemo-therapy as many as 8 subjects experienced a decrease in performance status. Then, a 3% decrease in performance status in subjects who go through 2 cycles and seen from the total cycles of patients and also the value of the performance status patient's as much as 57% with performance status normal, 41% experienced a decrease in performance status and only 2% of patients experienced an increase in performance status.

Performance status is said to be normal if it is 0 because the patient can still perform all physical activities without restrictions. It is said to decrease if there is a change in the value of the patient's performance status from 0 to 1 or 1 to 2, this happens because the decreasing performance status of the patient will worsen the quality of life. While the performance status of the patient is said to be increasing if the ECOG score obtained is with a value of 2 to 1 or 1 to 0. Due to the improvement in physical activity that the patient can do.

In the statistical test results using the Spearman method, P value <0.05 and R 0.367 indicated that there was a relationship between the number of chemotherapy cycles and performance status based on ECOG in lung cancer patients with non-small cell carcinoma in RSUD dr. Zainoel Abidin Banda Aceh in 2017-2020 and with a low correlation coefficient. And there is no theory that directly states the relationship between chemotherapy cycles and performance status patient. However, the value of performance status can be used as an outcome for lung cancer patients with non-small cell carcinoma. If the patient's performance status is good, the chemotherapy cycle can be continued until the 6th cycle, but if it gets worse, chemotherapy should be considered. This is done to reduce the side effects of chemotherapy drugs on patients.

Discussion

Data from patient medical records, it was found that a total of 164 patients with non-small cell carcinoma who go through chemotherapy met the inclusion and exclusion criteria. Characteristics of NSCLC patients were dominated by patients aged > 40 years as many as 152 patients or 92.7%, with the highest age range between the ages of 51-60 years with a total of 69 subjects or 42%. This is in line with research conducted by Edi Saputra Saksari's study, with a study sample of 22 lung cancer patients. It was stated that the most patients were aged >40 years as many as 19 patients (86.6%) while age <40 years were 3 patients (13.4%).[14] This is in accordance with Adam Szpechcinski's study, the average age of non-small cell lung cancer patients is 49 to 88 years.[11] This illustrates that with increasing age, the incidence of cancer will increase significantly. The peak was when entering menopause, namely at the age of 50 years.[15]

Based on gender, the results showed that the male gender dominated more than half of the total number of subjects, which was 141 patients or 85%. This is in line with other studies, namely the study of Adam Szpechcinski, et al. It consisted of 37 patients or 56% of non-small cell lung cancer patients were male.[16] Research conducted by Shah DN et al, also showed the same result, where as many 68% of lung cancer patients with non-small cell carcinoma types were male.[14] According to the research of Zhang T, et al in a retrospective study consisting of 381 patients in 2012-2014.[17] Comparison of the incidence of non-small cell lung cancer in men and women is 286/95 patients.[18] This is thought to occur due to the high prevalence of smoking in men compared to women globally, and judging from the typical risk factors for lung cancer including tobacco smoking, family history of malignancy, previous lung disease, and exposure to second hand smoke, radon, asbestos, arsenic, air pollutants, or occupational carcinogens are one of the causes of the difference in the incidence of these cancers.[18]

Conclusion

As many as 57% of cancer patients who go through chemotherapy cycles up to cycle 4 had *performance status* a normal and 41% of patients experienced a decrease in *performance status.* There is a significant relationship between chemotherapy cycles and *performance status* based on ECOG in lung cancer patients with non-small cell carcinoma in RSUD dr. Zainoel Abidin Banda Aceh with P <0.05 and R 0.367.

Suggestions

Because the assessment of *performance status* is a subjective assessment, it is necessary to have a common perception so that there are no differences in the assessment of *the performance status* and can be recorded in full in the patient's medical record.

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