ACADEMIC HOSPITAL JOURNAL

Volume 6, No. 2, September 2024

ISSN 2615-6253 (ONLINE)
ISSN 2615-6245 (PRINT)

A Study on Lung Cancer Chemotherapy Regimen Administration at Universitas Gadjah Mada Academic Hospital

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Publish: September 2024

Abstract

Background: One of the main ways to treat lung cancer is through chemotherapy regimens. Due to the complexity of lung cancer pathophysiology, the variability of chemotherapy given tends to cause drug interactions and toxicity in patients.

Objective: This study aims to determine the characteristics of lung cancer patients and identify chemotherapy administration patterns based on the NCCN therapy guidelines, identify interactions and side effects of chemotherapy that occur in patients diagnosed with lung cancer who are undergoing outpatient therapy at the Universitas Gadjah Mada Academic Hospital.

Method: This research was carried out with a case-series design, namely by conducting a study using descriptive methods that provide an overview of patient characteristics, chemotherapy regimen patterns and their conformity to NCCN guidelines, potential drug-drug interactions (DDIs), and the incidence of side effects experienced by patients. Data was collected retrospectively through medical records of lung cancer patients undergoing outpatient treatment in the period April 2022 – April 2023 who met the inclusion and exclusion criteria.

Result: There were a total of 27 patients in this study with patient characteristics predominantly in the elderly age range (> 60 years), 18 patients (66.7%), with exon 19 mutation NSCLC lung cancer type (n = 13; 92.6%), stage IV (n = 25 ; 92.6%), as well as non-smoking patients (n = 15 ; 55.6%). Chemotherapy regimen patterns at Gadjah Mada University Academic Hospital for lung cancer patients included afatinib (n = 14; 51.9%), gefitinib (n = 12; 44.4%), and cisplatin pemetrexed (n = 1; 3.7 %) with conformity reaching 100% in the accuracy of indications, dosage and usage information. In this study, it was identified that there were 2 Potential DDIs that occurred in 1 patient (3.7%) with respective risks, namely C and B which included cisplatin-furosemide and cisplatin-ondansetron interactions. Side effects were known to occur in almost all patients (n = 23; 85.2%) where side effects in the form of skin toxicity and diarrhea were the two most frequently identified types of side effects with a percentage of 59.3% (n = 16). and 40.7% (n = 11).

Conclusion: More than 90% of NSCLC showed exon 19 mutation. The most chemotherapy given to the patients was afatinib. There was a potential interaction between cisplatin and either furosemide or ondansetron.

Keywords: Chemotherapy Regimen, Lung Cancer, Tyrosine Kinase Inhibitors

1. INTRODUCTION

Lung cancer is the type of cancer with the highest incidence in Indonesia in 2018 with a total of 30,023 sufferers. In 2020, lung cancer was the fourth cause of death in Indonesia, namely 11.2% of total deaths (1,2). Lung cancer refers to a disease resulting from the presence of a malignant tumor in one or both parts of the lung organ which can occur due to the development of abnormal cells in the lung organ itself or as a result of cancer metastasis from other organs (3).

One of the main ways in treating lung cancer is through administering a chemotherapy regimen taking into account the type of lung cancer, stage, and analysis of mutation biomarkers. The two main types of lung cancer

include NSCLC (non-small cell lung cancer) and SCLC (small cell lung cancer). In NSCLC lung cancer, identification of mutation biomarkers can be done in the genes EGFR, ALK, KRAS, ERB2 (HER2), BRAF, NTRK1/2/3, and MET. Patients identified as having mutations in EGFR receive Tyrosine Kinase inhibitors (TKIs)-based chemotherapy as first-line, namely afatinib and gefitinib (4,5).

Not many studies in Indonesia primarily discuss, identify, or evaluate therapy patterns and the suitability of administering lung cancer chemotherapy regimens in Indonesia. However, there is a survey at RSUD Dr. Moewardi showing that in 2010 - 2011, lung cancer patients undergoing inpatient therapy received chemotherapy regimens primarily based on cisplatin and paclitaxel (6). However, with the continuing development of recommendations for lung cancer management, new research is needed to see how the treatment and progress of lung cancer patients develop.

With the complexity of therapy and the high prognosis of lung cancer, the limitations of research in Indonesia are partly due to the limited number of health service providers or hospitals in Indonesia that include polyoncology services or oncology outpatient services . In D.I. Yogyakarta itself has at least 4 hospitals that are recorded as having services for lung cancer patients (7).

2. MATERIALS AND METHODS

a. Research Design

This study was conducted with a case-series research design with retrospective data collection with ethical clearance number KE/FK/2032/EC/2023. Data collection was carried out through the patient's electronic health record (EHR) at the Medical Records Department at Universitas Gadjah Mada Academic Hospital.

b. Population and Sample

The subjects in this study included all outpatients who were diagnosed with lung cancer in the period April 2022 – April 2023 who met the inclusion and exclusion criteria. The inclusion criteria were as follows: patients with a primary diagnosis of lung cancer, those receiving a chemotherapy regimen with indications for lung cancer management, and those with complete records of chemotherapy regimens and being able to be monitored through the Universitas Gadjah Mada Academic Hospital's electronic health record (EHR) system. The exclusions that apply to this study include patients with lung cancer as a result of metastasis from other types of cancer.

c. Analysis Method

The data obtained is presented descriptively including patient characteristics (age, gender, smoking/not smoking), disease characteristics (cancer type, EGFR mutation, stage, and comorbidities), use of chemotherapy (chemotherapy regimen, dose, description of use), and suitability of chemotherapy based on suitability to NCCN guidelines. This study refers to the NCCN Oncology Small Cell Lung Cancer guideline version 2.2024 and Non-Small Cell Lung Cancer, version 3.2022 is reviewed from the accuracy of indications, doses, and information on the use of chemotherapy.

In this case, we also reviewed other guidelines, namely those of BC Cancer and the European Society of Medical Oncology (ESMO), as well as related literature, provided that it does not conflict with the therapeutic instructions contained in the NCCN.

Drug interactions or Potential Drug-Drug Interactions (DDIs) in this study are interactions that occur either between chemotherapy regimens or between chemotherapy regimens and other treatment regimens and do not include interactions between each non-chemotherapy treatment regimen. Identification of DDIs is done through the drug interaction checker feature on the Lexicomp® website.

The incidence of side effects is the occurrence of side effects that occur or are suspected to be related to the management of administering chemotherapy regimens to lung cancer patients which are recorded during the administration of chemotherapy regimens through an assessment of the Naranjo logarithm with reference to patient complaint data, laboratory data, and doctor's diagnosis.

3. RESULT

This study aimed to evaluate and identify patterns of chemotherapy use in lung cancer patients, along with assessments of the accuracy of administration, identification of potential drug interactions, and identified side effects experienced by patients. The selection results showed that 27 out of 33 lung cancer patients met the inclusion and exclusion criteria. A total of 6 patients were excluded due to incomplete EHR data and the administration of primary chemotherapy not for lung cancer. The elderly variable 66.7% (N = 18) is the highest number of characteristics of lung cancer patients (**Table I**).

Table I. Characteristics of Lung Cancer Patients

Demographic Variables	Frequency (n)	Percentage (%)
Age		
Adults (20 – 40 Years)	1	3.7
Middle Age (40 – 60 years)	8	29.6
Elderly (>60)	18	66.7
Gender		
Man	14	51.9
Woman	13	48.1
Smoker		
Ever/Smoker	3	11.1
Do not smoke	15	55.6
Not identified	9	33.3

The main chemotherapy regimen for lung cancer patients at Universitas Gadjah Mada Academic Hospital uses a biomolecular regimen pattern that includes Tyrosine Kinase Inhibitors (TKI) in the form of afatinib (44.44%; n = 12 patients) and gefitinib (51.85%, n = 14) and molecular chemotherapy using cisplatin–pemetrexed (3.70%; n 36 = 1 patient). Universitas Gadjah Mada Academic Hospital has implemented a mutation identification system in lung cancer patients to perform biomolecular chemotherapy.

Table 2. Disease Characteristics

Patient characteristic	Frequency (n)	Percentage (%)
Comorbidity	n = 27	
With Comorbidity	12	44.0
Without comorbidity	15	56.0
Comorbid diseases	n = 18	
Cardiovascular	9	50.0
Diabetes mellitus	3	17.0
Pneumonia	2	11.0
Hernia Nucleus Pulposus (HNP)	1	6.0
Benign Prostate Hyperplasia (BPH)	1	6.0
Hemiplegia	1	6.0
Cancer type	n = 27	
NSCLC	27	100
SCLC	0	-
EGFR mutation type	n = 27	
Wild Type	1	3.7
Single Variant	25	92.6
Double Variant	1	3.7
Stage	n = 27	
III	2	7.4
IV	25	92.6
NSCLC type	n = 27	
Adenocarcinoma	25	92.6
Adenosquamous	2	7.4
EGFR mutation location	n = 26	
Exon 18	2	7.4
Exon 19	13	48.1
Exon 20	1	3.7

Exon 21	9	33.3
Exon 18 and 21	1	3.7

An assessment of the indications for the use of lung cancer chemotherapy (**Table 3**) shows that mutations in EGFR in exons 18, 19, 20, and 21 can be given chemotherapy based on tyrosine kinase inhibitors (TKIs), including gefitinib and afatinib. They were given chemotherapy regimens for EGFR wild type based on molecular chemotherapy, including cisplatin, pemetrexed, and various other combinations.

Table 3. Suitability of Chemotherapy Indications

EGFR mutation	***NCCN Guidelines***	**Patient Number**	**Chemotherapy given**	**Accordance/ No**
Exon 18	**EGFR Exon 18 G719X** TKI Inhibitors : erlotinib, gefitinib, afatinib, and dacotinib	2, 25	afatinib	Accordance
Exon 19	**EGFR Exon 19 *Deletion*** TKI Inhibitors : Afatinib, Erlotinib, Dacomitinib, gefitinib	10, 13, 21	afatinib	Accordance
		4, 7, 12, 14, 15, 16, 18, 19, 22, 26	gefitinib	Accordance
Exon 20	**EGFR Exon 20 p. S7681 & *Exon 20 Insertion mutation* except for p.A763_Y764insF** TKI Inhibitosr: afatinib, erlotinib, gefitinib, osimertinib **EGFR Exon *20 Insertion mutation*** Amivantamab-vmjw, mobocertinib	5	afatinib	Accordance
Exon 21	**Exon 21 L858R & Exon 21 L861Q** TKIs inhibitors: afatinib, erlotinib, gefitinib, osimertinib	6, 9, 17, 20, 23, 24	afatinib	Accordance
		1, 8, 11	gefitinib	Accordance
Exon 19 and 21	**EGFR Exon 19 Deletion** TKIs Inhibitor: Afatinib, Erlotinib, Dacomitinib, gefitinib **Exon 21 L858R & Exon 21 L861Q** TKIs inhibitors: afatinib, erlotinib, gefitinib, osimertinib	3	gefitinib	Accordance
Wild Type	**Performance status 0 - 1** cisplatin/pemetrexed **Performance status 2** carboplatin/pemetrexed **Performance status 3 - 4** supportive care	27	cisplatin/ pemetrexed	Accordance

The results of the drug interaction assessment were that DDIs were identified in only 1 patient (3.7%) with the cisplatin–pemetrexed chemotherapy regimen (**Table 4**).

Table 4. Potential Drug-Drug Interaction Chemotherapy

Patient Number	*Drug-drug interaction*	Description	Severity level	*Reliability rating*	risk
27	Cisplatin-Furosemide	Furosemide increases the nephrotoxic and ototoxic effects of cisplatin	*Moderate*	*Fair*	C (therapy monitor)
	Cisplatin-Ondansentron	Ondansetron increases serum cisplatin concentration	*Minor*	*Fair*	B (No adjustment required)

A total of 73 cases of side effects were identified in this study. The most common side effects were skin reactions with symptoms such as reddish skin, acne, itching, dry skin, peeling, soreness, spots and ulcers (59.3%) in 16 lung cancer patients (Table 5). Researchers did not observe the severity of the 12 side effects found.

Table 5. Side Effects of Chemotherapy

Occurrence of ADRs	Patient Code	N	%
Hepatotoxic	1[a], 8[a]	2	7.4
Diarrhea	1,[a] 2[b], 5[b], 6[b], 7[a], 8[a], 10[b], 15[b], 20[b], 21[b], 24[b]	11	40.7
Skin Toxicity	1[a], 2[b], 3[a], 4[a], 5[b], 6[b], 7[a], 8[a], 10[b],12[a], 13[b], 14[a], 15[b], 18[a], 20[b], 23[b]	16	59.3
Mucositis of the mouth and throat	2[b], 5[b], 7[a], 10[b], 13[b], 15[b], 20[b], 21[b], 23[b], 24[b]	10	37.0
Edema with symptoms of swelling in certain organs such as the hands, feet and face	2[b], 3[a], 19[a], 21[b]	4	14.8
Hyperuricemia	3[a]	1	3.7
Complaints of nausea, vomiting and decreased appetite	4[a], 10[b], 18[a], 27[c]	3	11.1
Nail toxicity	5[b], 7[a], 10[b], 13[b], 15[b], 20[b]	6	22.2
Anemia	5[b], 6[b], 7[a], 17[b]	4	14.8
Dyspepsia	7[a], 12[a], 17[b]	3	11.1
Neuropathic Pain	7[a], 8[a], 10[b], 24[b]	4	14.8
Symptoms of heart palpitations	16[a]	1	3.7
No side effects occurred	9[a], 11[b], 12[b], 25[b] 26[b]	5	18.5

a: patients with the gefitinib chemotherapy regimen**, b:** patients with the afatinib chemotherapy regimen, **c:** patients with the cisplatin–pemetrexed chemotherapy regimen

Skin reactions were a side effect that occurred in 16 out of 27 patients. Naranjo's assessment showed that all patients who experienced side effects from skin reactions received probable scores ranging from 5 – 8 (**Table 6**).

Table 6. Identification of Side Effects Based on the Naranjo Score

Side effects	*Probable* (n;%)	*Possible* (n;%)
Hepatotoxic	2;100	0
Diarrhea	9;81.8	2;18.2
Skin Toxicity	16;100	0;0
Mucositis of the mouth and throat	10;100	0;0
Edema with symptoms of swelling in certain organs such as the hands, feet, and face	4;100	0;0
Hyperuricemia	0;0	1;100
Complaints of nausea, vomiting, and decreased appetite	4;100	0;0
Nail toxicity	6;100	0
Anemia	4;100	0
Dyspepsia	2;66.7	1;33.3
Neuropathic Pain	3;75	1:25
Symptoms of heart palpitations	1;100	0;0

4. DISCUSSION

a. Patient and Disease Characteristics

The high incidence in the elderly is caused by the accumulation of oncogenic mutations through DNA damage after exposure to carcinogens over a long period. In addition, through the mechanism of reducing the elimination of cells that have been damaged either by a decrease in immune system function, it becomes a contributor to the incidence of lung cancer in elderly patients (8,9).

Lung cancer patients identified in this study were known to be non-smokers or at least had a record of not smoking in the EHR system with a percentage of 55%. The hazard ratio (HR) value for participants who were smokers and heavy smokers was 14.54 (95% CI, 12.47 – 16.94) and 17.80 (95% CI, 15.23 – 20.81), which shows smoking status is independently associated with a higher risk of lung cancer (10).

Non-small cell Lung Cancer (NSCLC) is a type of cancer found in all lung cancer patients in this study and is the most common type of cancer in other studies. (11-13). A total of 92.6% or 25 patient cases identified in this study were in stage IV and 2 in stage III. In Table II, it was identified that 96.30% (n = 26) of lung cancer patients had EGFR mutations and one other patient was diagnosed with wild-type lung cancer. In this study, no other mutation markers were found. In this case, based on the patient's medical records and interviews with medical staff (pharmacists), hospitals. Universitas Gadjah Mada Academics Hospital has implemented identification standards for Genomic Biomarkers both EGFR and other biomarkers (ALK) as operational standards for lung cancer diagnosis. Of the 27 lung cancer patients who were all diagnosed with NSCLC cancer type, 92.6% (n = 25) of the patients had adenocarcinoma type and 7.4% (n = 2) of the other patients were diagnosed with adenosquamous type. The percentage of cancer patients who had mutations in exons 18, 19, 20, 21, and 18 and 21 was 7.4% (n = 2); 48.1% (n = 13); 3.7% (n = 1); 33.3% (n = 9); and 3.7% (n = 1).

In this research, it was discovered that the majority of patients identified, namely 56% (n = 15) had no comorbidities identified during the research data collection period, while 44% (n = 12) of patients had identified comorbidities which included types of disease in the cardiovascular system. , diabetes, pneumonia, HNP, BPH, and hemiplegia were recorded in 50.0% each (n = 9); 17.0 % (n = 3); 11.0% (n = 2); 6.0% (n = 1); 6.0% (n = 1); and 6.0% (n = 1) of patients.

b. Overview and Suitability of Chemotherapy

Based on the cancer therapy guidelines by NCCN version 3.2023 (13 April 2023), the identification of DNA biomarker mutations in lung cancer is part of the therapy management which is the gold standard in lung cancer therapy management. According to NCCN, gene mutations in the genes encoding EGFR, KRAS, ALK, ROS1, BRAV, NTR1/2/3, MET, RET, and HER2 are biomarkers for the development of lung cancer. Therefore, biomolecular therapy in this case works specifically on markers in the form of proteins/receptors. In this case, molecular chemotherapy such as cisplatin, carboplatin, and pemetrexed remains the treatment for lung cancer therapy, provided that no mutations are found in DNA biomolecule marker tests or as first-line therapy for certain biomarker mutations (4).

Assessment results related to the use of chemotherapy in lung cancer patients in Universitas Gadjah Mada Academic Hospital reached 100% in this study, both for accuracy of indications, as well as accuracy of dosage and information on how to use it. The high rate of accuracy in administering chemotherapy regimens for lung cancer is expected to provide clinical outcomes in the form of improving the quality and survival of lung cancer patients. In this case, research at Dr. Soetomo Hospital Surabaya showed the use of tyrosine kinase in 63 patients with median Progression Free Survival and Overall Survival values of 8.3 months (95% CI: 6.50 – 10.2) and 16 months (95% CI: 11.9 – 20.2) (14).

In the assessment regarding indications and how to use chemotherapy regimens, researchers identified the doses and usage procedures given to lung cancer patients, in this case in the gefitinib regimen, all patients received a dose of 250 mg tablets once a day and were given information to drink 2 hours after eating. or on an empty stomach. Considering that both afatinib and gefitinib interact with food it can reduce Cmax and AUC values by up to 50% and 39% (15). Apart from that, in the regimen of oral administration of afatinib chemotherapy, all patients were given a dose of 40 mg tablets 1 x 1 on an empty stomach or 2 hours before/after meals. There was an identification of an adjustment in the form of a dose change in a patient with code number 26, namely a change in dose from 40 mg 1 x 1 to 30 mg 1 x 1 due to drug intoxication requiring a dose reduction. Dosage changes in the form of increasing the dose of afatinib were also known in patients with code number 9 who initially received a dose of 20 mg 1 x 1 to 40 mg 1 x 1 on the second administration of the drug. According to the researchers' considerations, a doctor can increase the dose by looking at the patient's ability to tolerate afatinib to tolerate drug intoxication. The change in the regimen for patients with code 16 was in the form of changing the regimen of gefitinib 250 1 x 1 to afatinib 40 mg 1 x 1 which was given at the second administration of chemotherapy. Any changes, including adjustments to the dose and regimen, are still appropriate and in line with recommendations by the NCCN guidelines.

Administration of cisplatin – pemetrexed to patient no. 27, given in doses of 90 mg and 690 mg administered i.v. using 100 mL 0.9% NaCl solvent. Both are given with a duration of 10 minutes and 4 hours respectively with a cycle carried out every 21 days. Patients during the research implementation period are known to have undergone chemotherapy twice on March 30 and April 19, 2023. The dosage is following the guidelines although further review is still needed regarding the dosage of cisplatin.

c. Potential Drug-Drug Interaction

Potential DDIs that occur include interactions between cisplatin–furosemide and cisplatin–ondansetron. Both interactions have risks C and B so both can be continued and given to patients even though they require monitoring of the cisplatin – furosemide interaction. In patients with TKIs-based therapy regimens, no DDIs were identified (n = 0.0%), so in this case, the researchers believe that administering TKIs-based regimens to lung cancer patients provides the advantage of no interactions with most therapy regimens in lung cancer patients.

A study of potential interactions on TKI-based chemotherapy agents by Ergun et al, (2019) succeeded in identifying interactions in 147 patients or 47.4% of the total 310 cancer patients in which 250 types of interactions were identified (16). Based on the clinical trial report of gefitinib with the brand name Iressa® in 2021, it is clear that the metabolism of gefitinib, which is mainly via CYP3A4, is influenced by drugs that affect this metabolizing enzyme (17). In addition, Gefitinib is known to have potential interactions with drugs that affect the CYP2D6 enzyme, antacids, H2 antagonists, proton pump inhibitors, vinorelbine, and vitamin K antagonists (18). With afatinib, potential interactions that can occur mainly include drugs that affect BCRP/ABCG2, P-glycoprotein/ABCB1, CYP3A4, including aminolevulinic acid, elacestrant, and other drugs (18).

d. Identification of side effects

Identification of side effects in this study provide an overview and findings that can serve as a reference for future research. Additionally, Table 5 and 6 present the results of identifying side effects that occurred in each chemotherapy regimen administered to patients, including afatinib, gefitinib, and cisplatin-pemetrexed.

In this study, the identified side effects included hepatotoxic reactions, diarrhea, skin problems, nephrotoxicity, mucositis, hypoalbuminemia, hypokalemia, edema, hyperuricemia, constipation, nausea/vomiting, nail abnormalities, anemia, dyspepsia, neuropathic pain, arrhythmia, and hyponatremia. The findings of this study show several similarities to those of a study by Sunder et al, (2023) who investigated adverse effects in patients receiving TKIs-based chemotherapy regimens (19). According to this study, patients who received either gefitinib or

afatinib tended to experience side effects such as skin rash, dizziness, decreased appetite, vomiting, neuropathy, arthralgia, stomatitis, paronychia, and dry skin (19).

Based on the data in Table 6, researchers believe that the TKI regimen induces side effects of skin toxicity. This is confirmed by other studies, that in this case, at least 50% of patients who received TKIs-based regimens experienced skin toxicity reactions (20).

Side effects in the form of mucositis in this study were identified in `10 patients or 37% of the total 27 patients included in the study. The quite high number in this study was also reported in other studies, namely 20 – 30% of cancer patients who received TKIs-based therapy (21). All patients identified as experiencing mucositis in table XVII, through the Naranjo assessment, were identified in the probable category. It is known that oral mucositis in cancer patients who receive TKIs-based chemotherapy regimens is caused by toxicity to submucosal basal cells which under normal conditions continue to divide, as well as damage to epithelial cells, so that inflammation occurs which is mediated by activation of NF-kB, IL-1B and IL- 6. With this inflammation, infection and bacterial colonization of the mucosal area in this case become susceptible to occurring (22).

5. CONCLUSIONS

The chemotherapy regimen patterns at Universitas Gadjah Mada Academic Hospital for lung cancer patients included afatinib (n = 14; 51.9%), gefitinib (n = 12; 44.4%), and cisplatin pemetrexed (n = 1; 3.7 %) with 100% conformity in the accuracy of indications, dosage and usage information. This study identified 2 potential DDIs occurred in 1 patient (3.7%) with respective risk categories of C and B which included cisplatin-furosemide and cisplatin-ondansetron interactions. Side effects were observed in almost all patients (n = 23; 85.2%), where side effects in the form of skin toxicity and diarrhea were the two most frequently identified side effects, occurring inof 59.3% (n = 16). and 40.7% (n = 11) of patients, respectively.

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