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Response Rate, Side Effect and Reduction in Tumor Size of Vinorelbine, Gemcitabine and Taxanes as First Line Setting of Advanced Squamous Cell Carcinoma of the Lung

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Abstract

Background: Squamous-cell carcinoma (SCC) of the lung is a kind of non-small-cell lung carcinoma. Cytotoxic chemotherapy has been found to deliver benefits to patients in advanced disease settings.

Objective: To compare response rate and side effects between first-line chemotherapies vinorelbine, gemcitabine, and taxanes in patients with metastatic SCC of the lung.

Patients and Methods: This is a retrospective study including 45 patients with metastatic lung SCC. All patients had received platinum-based doublet chemotherapy for 4-6 cycles. Patients were allocated into three groups based on the additional treatment protocol, with fifteen patients per group. A reduction in tumor size was assessed from tumor measurements for patients who had at least two evaluable assessments with computed tomography. The side effects of each drug were evaluated.

Results: The reduction in tumor size in the gemcitabine, taxan, and vinorelbine arms was -5.59±35.62 cm3, 1.3±39.98 cm3 and -10.55±14.62 cm3, respectively, with no significant differences. The response rates in the taxan, gemcitabine, and vinorelbine arms were 73.33%, 80%, and 86.67%, respectively, with no significant differences. The side effects, including nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy, were, in particular, more common in patients in the taxan arm than in other arms, with significant differences.

Conclusion: The three therapeutic arms, vinorelbine, gemcitabine, and taxanes, had similar efficiency based on response rate, with a mild preponderance of vinorelbine.

Keywords: Squamous-cell carcinoma,vinorelbine, gemcitabine,taxanes

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Introduction

Lung cancer stands as the leading cause of cancer-related fatalities worldwide. Among non-small cell lung cancer (NSCLC) cases, squamous cell carcinoma (SCC) comprises nearly 30% [1], with Iraq experiencing approximately 1250 new cases annually and over 400,000 cases globally. SCC remains strongly associated with cigarette smoking

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[2]. The primary pulmonary symptoms typically include cough, dyspnea, and hemoptysis [3].

The most recent (eighth) edition of the lung cancer stage classification (TNM) is used for non-small and small cell lung cancer, as well as carcinoid tumors. Surgical resection is the standard of care for stage I and II non-small cell lung cancers [4]. In the case of stage III disease, treatment decisions usually depend on the status of mediastinal lymph nodes to determine the inclusion or exclusion of surgery with adjuvant chemotherapy and/or radiotherapy [5].

Metastatic lung SCC is treated with cytotoxic chemotherapy, primarily utilizing a platinum-based doublet. These regimens employ either cisplatin or carboplatin as the platinum backbone, while drugs such as paclitaxel, nabpaclitaxel, docetaxel, vinorelbine, or gemcitabine serve as the cytotoxic partners [6]. Taxanes and vinorelbine drugs belong to the group of mitotic spindle chemotherapies [7].

Nivolumab improved overall survival compared to second-line docetaxel therapy, regardless of programmed death-ligand 1 (PD-L1) immunohistochemistry expression [8]. The Food and Drug Administration (FDA) has specifically approved nivolumab for the treatment of advanced SCC patients who have progressed after platinum-based chemotherapy [9].

The gemcitabine drug belongs to the group of chemotherapy-named antimetabolites, and the length of time that the cells are exposed to the drug is directly proportional to its killing potential [7]. Assessment of the response to treatment can be done through RECIST criteria [10, 11].

This study aims to assess the response rate, side effects, and reduction in tumor size of first-line chemotherapy vinorelbine doublet, gemcitabine doublet, and taxanes doublet for patients with metastatic SCC of the lung in Iraqi patients.

Patients and Methods

The Study Population

This is a retrospective study including 45 patients with metastatic pulmonary SCC confirmed by histopathological biopsy. Those patients were attending the Oncology Teaching Hospital in Baghdad during the period from the first of January 2020 to the thirty-first of June 2020. Patients with SCC confirmed by histopathology of trans-bronchial or trans-thoracic biopsies of the lung and metastases samples, which identified CT examination, were eligible for the study. The study included ECOG Performance Status (PS) ≤1, adequate hematopoietic, liver, and renal functions, and stage IV tumor SCC. Conversely, those with Performance Status (PS) 2 or more, inability or refusal to perform informed consent, patients treated with other chemotherapy or immunotherapy protocols, patients diagnosed with other primary malignancies in another site, and patients with metastatic lung cancer from other primary cancers were excluded from the study. The approval of the concerned health authority was obtained before data collection.

The Study Groups

A history and physical examination were done for all the patients, including TNM staging. Every patient was given platinum-based doublet chemotherapy, according to national comprehensive cancer network guidelines [12], with 4-6 cycles of

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carboplatin AUC 5 i.v. over 60 minutes (manufactured by the Hospira) combined with one of the following drugs (groups):

Group A: 15 patients treated with vinorelbine (manufactured by Ebewe Pharma) at 25 mg/m^2 on days 1 and 8 i.v. over 5–10 minutes.

Group B: 15 patients treated with gemcitabine (manufactured by Ebewe Pharma) 1000 mg/m^2 days 1 and 8 i.v. over 30 minutes.

Group C: 15 patients treated with taxanes: paclitaxel (manufactured by Hospira) 175 mg/m2 i.v. over 3 hours or docetaxel (manufactured by Pfizer) 75 mg/m^2 IV over 60 minutes.

Treatment was postponed for about 1 week for patients with neutropenia, thrombocytopenia, or anemia and hemoglobin less than 9 mg/dl. Treatment was stopped if the patient experienced complications, progression, or a decrease in his performance status.

Evaluation of Response

Patient responses were assessed in accordance with the RECIST guidelines, utilizing clinical evaluations and conventional CT scans conducted every three treatment cycles. A complete response was defined as the complete vanishing of all target lesions. Progressive disease was identified by a minimum 20% rise in the sum of the longest diameters of the target lesions or the presence of one or more new lesions. Additionally, the side effects associated with each treatment protocol were evaluated.

Statistical Analysis

The SPSS software (ver. 24) was used for all statistical analysis. Continuous data underwent a normality test, and if they had a normal distribution, they were expressed as mean and standard deviation (SD). These data sets were then analyzed using the Student t-test or analysis of variance (ANOVA) as required. Non-normally distributed data were presented as median and range and were analyzed with the Mann-Whitney U test or Kruskal-Wallis as required. Categorical variables were presented as numbers and percentages and were analyzed using the Chi-square (χ^2) test. The Spearman's correlation test was utilized to explore potential correlations between tumor reduction and other continuous variables. A p-value ≤ 0.05 was considered significant.

Results

Demographic characteristics of patients

The study included a total of 45 patients with pulmonary SSC treated with three types of anticancer drugs. The mean ages of Taxan, gemcitabine, and navelbine arms were 58.93±10.4 years, 62.07±13.63 years, and 66.0±9.91 years, respectively, with no significant differences (p-value = 0.413). The vast majority of the patients (84.44%) were males, who were distributed evenly between the three groups. The total male-female ratio was 1: 0.18. The male-to-female ratio in taxan, gemcitabine, and navelbine was 1:0.25, 1:0.15, and 1:0.15, respectively. The three arms were comparable regarding body mass index (BMI) with no significant differences. Smokers accounted for 80%, 86.67%, and 60% of patients in taxan, gemcitabine, and navelbine, respectively, with no significant differences. Most patients had a zero ECOG score Table (1).

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Table (1): Demographic characteristics of the patients.

Variables	Taxan (n=15)	Gemcitabine (n=15)	Navelbine (n=15)	p-value
Age, years				
Mean±SD	58.93±10.4	62.07±13.63	66.0±9.91	0.413
Range	42-74	21-75	43-80	
Gender				
Male	12(80%)	13(86.67%)	13(86.77%)	0.844
Female	3(20%)	2(13.33%)	2(13.33%)	
BMI, kg/m^2				
Mean±SD	23.48±3.65	25.0±3.6	24.41±6.21	0.332
Range	19.2-33.6	18.4-31.7	20.12-28.7	
Smoking				
Never	3(20%)	2(13.33%)	6(40%)	0.209
Ex/current	12(80%)	13(86.67)	9(60%)	
ECOG				
Zero	5(33.33%)	8(53.33%)	5(33.33%)	0.435
One	10(66.67%)	7(46.47%)	10(66.67%)	

Therapeutic and clinical characteristics of patients

Hypertension was more frequent among patients in the taxan arm (40%) than in either the gemcitabine arm (13.33%) or the navelbine arm (0%), with a significant difference (p value 0.014). Patients in the taxan arm had remarkably smaller initial and final tumor sizes (25.85±23.44 cm3 and 27.16±34.28 cm3, respectively) than those in the gemcitabine arm (42.26±33.18 cm3 and 47.86±43.8 cm3, respectively) or the navelbine arm (45.15±36.67 cm3 and 34.6±30.94 cm3, respectively). However, the differences were not significant. Patients in all arms mostly received 6 cycles of treatment or, less commonly, 4 cycles Table (2).

Table (2): Therapeutic and clinical characteristics of the patients.

Variables	Taxan (n=15)	Gemcitabine (n=15)	Navelbine (n=15)	p-value
Comorbidities				
No comorbidity	7(46.67%)	12(80%)	10(66.67%)	0.158
Hypertension	6(40%)	2(13.33%)	0(0%)	**0.014**
Diabetes mellitus	1(6.67%)	1(6.67%)	2(13.33%)	0.760
Ischemic heart disease	2(13.33%)	1(6.67%)	5(33.33%)	0.139
Others	2(13.33%)	0(0%)	0(0%)	0.123
Initial tumor size, cm^3				
Mean±SD	25.85±23.44	42.26±33.18	45.15±36.67	0.142
Range	2.0-99.75	14.94-127.6	3.48-120.96	
Final tumor size, cm^3				
Mean±SD	27.16±34.28	47.86±43.8	34.6±30.94	0.386
Range	0-144.9	0-142.74	0.5-101.92	
Treatment cycles				
4	2(13.33%)	4(26.67%)	2(13.33%)	0.544
6	13(86.67%)	11(73.33%)	13(86.67%)	

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Reduction in tumor size

The reduction in tumor size (based on CT scan examination) in the Navelbine arm was -5.59±35.62 cm^3 (range -85.74-52.6 cm^3), compared with -1.3±39.98 cm^3 (range -111.27-90.51 cm^3) in the gemcitabine arm and 10.55±14.62 cm^3 (range -9.75-34.0 cm^3 in the Taxan arm. Despite this variation, the Kruskal-Wallis test revealed no significant differences in the reduction of tumor size between the three arms Figure (1).

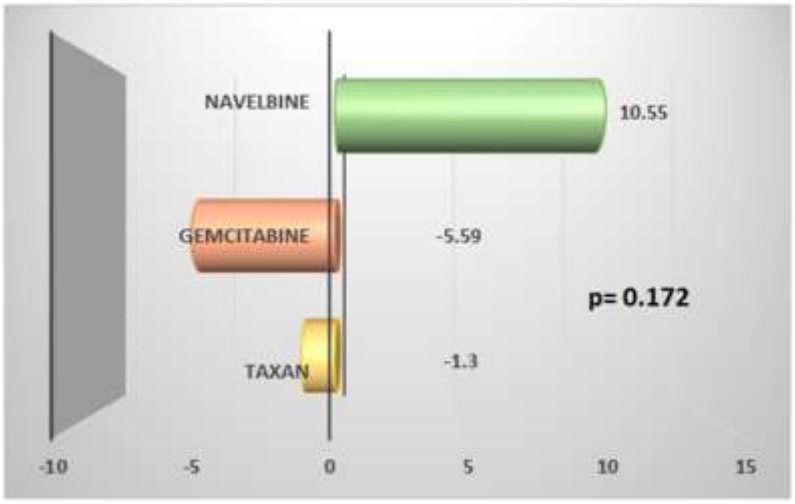

Figure (1): Reduction in tumor sizes in three treatment protocols.

Response to treatment

The response to treatment was almost compatible between the three arms, with some preponderance to the navelbine arm, in which there were only 2 (13.33%) non-responders compared to 4 (26.67%) among the taxan arm and 3 (20%) among the gemcitabine arm, with no significant differences Figure (2). Interestingly, there were only two patients with complete remission: one in the taxan arm and the other in the gemcitabine arm Figure (2).

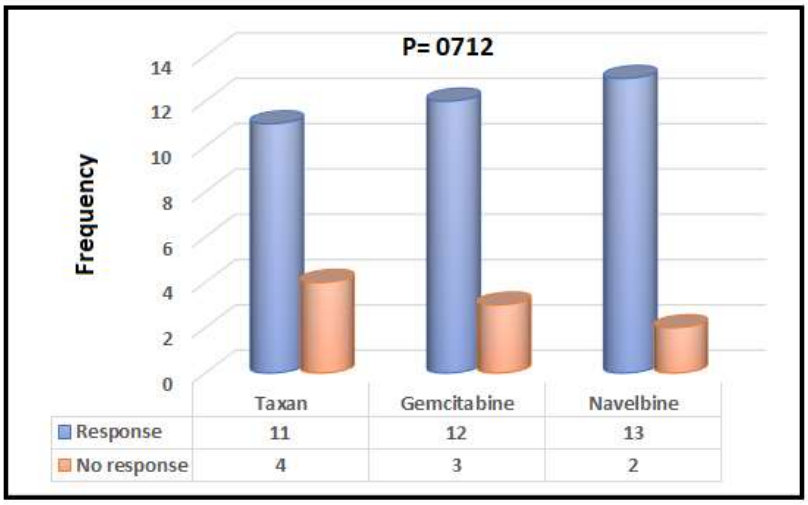

Figure (2): Response rate in the three treatment protocols.

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Correlation of tumor reduction with other variables: Spearman's correlation test was used to explore the possible correlation between tumor reduction and other continuous variables. In general, none of the included variables had a significant correlation with tumor reduction Table (3).

Table (3): Spearman's correlation between tumor reduction and other continuous variables.

Variable	Taxan		Gemcitabine		Navelbine	
	r	p-value	r	p-value	r	p-value
Age	-0.03	0.915	0.154	0.584	0.068	0.327
BMI	0.106	0.706	154	0.584	0.057	0.840
No. of cycles	0.074	0.734	0.267	0.337	0.277	0.317
ECOG score	0.006	0.982	-0.436	0.3104	0.345	0.208

Association of tumor reduction with gender, smoking, and co-morbidity: Similarly, there was no significant effect of gender, smoking habit, or the presence of co-morbidity on the reduction rate Table (4).

Table (4): Association of tumor reduction with gender, smoking, and comorbidities.

Variables	Taxon	Gemcitabine	Navelbine
Gender			
Males	-0.171±44.92	-8.34±37.67	9.52±13.93
Females	-5.84±7.34	12.22±0.37	17.29±23.63
p-value	0.448	0.171	0.800
Smoking			
Yes	-5.77 ±37.89	634±395	8.87±14.14
No	-4.44±23.2	1090±155.6	13.08±16.31
p- value	0.438	0.865	0.554
Comorbidity			
Yes	-2.91±60.1	10.07±12.89	10.26±22.27
No	0.1±9.83	-9.51±38.74	10.71±10.59
p-value	0.613	0.312	0.768

* Non-parametric Mann Whitney test was used for comparison

Side effects of the treatment

A total of 14 side effects were reported for the three treatment arms., eight of which differed significantly between different arms. Nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy were, in particular, more common in patients in the taxan arm than in the gemcitabine or vinorelbine arms, with significant differences (P<0.05). On the other hand, vomiting was significantly associated with the gemcitabine arm, while fatigue and constipation were more common with gemcitabine and vinorelbine than taxan, with significant differences (P<0.05) Table (5).

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Table (5): Side effects of the three treatment arms, Baghdad, 2020.

Effects	Taxan (n=15)	Gemcitabine (n=15)	Navelbine (n=15)	p-value
Leukopenia	5(33.33%)	6(40%)	6(40%)	0.083
Neutropenia	10(66.57%)	6(40%)	6(40%)	0.182
Nausea	9(60%)	5(33.33%)	7(46.67%)	0.016
Vomiting	6(40%)	13(86.67)	6(40%)	0.022
Alopecia	14(93.33%)	1(6.67)	1(6.67)	<0.001
Diarrhea	8(53.33%)	0(0%)	0(0%)	<0.001
Arthralgia	8(53.33%)	0(0%)	0(0%)	<0.001
Peripheral neuropathy	12(80%)	0(0%)	6(40%)	<0.001
Anemia	12(80%)	14(93.33%)	8(53.33%)	0.271
Hematuria	0(0%)	2(13.33%)	0(0%)	0.198
Thrombocytopenia	0(0%)	1(6.67)	0(0%)	0.455
Pain	0(0%)	1(6.67)	1(6.67)	0.079
Fatigue	0(0%)	3(20%)	4(26.67%)	<0.001
Constipation	0(0%)	4(26.67%)	3(20%)	0.002

Discussion

According to the outcomes of the existing study, there were no significant differences in the reduction of tumor size between taxan, gemcitabine, and navelbine, nor in the response to treatment. In line with these results, there are many studies worldwide [13-15]. In one study, gemcitabine/cisplatin was compared with some standard protocols [13]. The study demonstrated almost similar response rates among the three experimental arms: cisplatin/docetaxel, carboplatin/paclitaxel, and gemcitabine/cisplatin, compared with cisplatin/paclitaxel. However, the gemcitabine/cisplatin arm was associated with a longer time-to-disease progression compared with cisplatin/paclitaxel. Furthermore, there was also an improved 2-year survival with this arm.

In another trial, the gemcitabine/paclitaxel combination protocol was found to have an equivalent result to paclitaxel/carboplatin in terms of the patient's response [14]. A further study demonstrated equivalent efficacy between gemcitabine/vinorelbine and carboplatin/paclitaxel in previously untreated patients with advanced NSCLC [15].

In contrast, one study compared gemcitabine "1000 mg/m^2 days 1 and 8" plus carboplatin (300 mg/m^2) against cisplatin (first-generation). The study established that gemcitabine/carboplatin was associated with improved 1-year survival but had a comparable toxicity profile [16].

In a study assessing the effectiveness of navelbine on a total of 202 patients diagnosed with advanced NSCLC, there were no statistically significant differences between NC and PC regarding response rate (28% vs.

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25%), survival (8 months in both groups), or 1-year survival rate (38% vs. 36%) [17].

In a separate study conducted in Japan, 602 patients with advanced SCC were allocated to: NC (navelbine 25 mg/m^2 plus cisplatin 80 mg/m^2), PC (paclitaxel 200 mg/m^2 and carboplatin), IC (irinotecan 60 mg/m^2 plus cisplatin 80 mg/m^2), or GC (gemcitabine 1000 mg/m^2 plus cisplatin 80 mg/m^2). The study found no considerable differences in response rates among patients in the four treatment groups [18].

However, in a phase three trial involving 612 patients with advanced NSCLC, three different chemotherapeutic regimens were compared: Navelbine only (N), NC (navelbine 30 mg/m^2 plus cisplatin 120 mg/m^2), or vindesine and cisplatin. The NC regimen demonstrated statistical superiority over both N alone and the vindesine combination regarding response rate (30% vs. 14% vs. 19%) and survival (40 weeks vs. 31 weeks vs. 32 weeks) [19].

These variations in the results can be attributed to several factors, the most important of which are the patient's demographics, genetic factors, the presence of comorbidities, and treatment schedules.

In a comparative study investigating navelbine and taxanes, a total of 1218 patients diagnosed with advanced NSCLC were allocated to: NC (navelbine 25 mg/m^2 and cisplatin 100 mg/m^2), DC docetaxel 75 mg/m2 plus cisplatin 75 mg/m^2, or DCb docetaxel 75 mg/m^2 plus carboplatin. The results revealed no significant differences in these variables between the VC and DCb groups. However, patients who received DC exhibited better outcomes in terms of survival (11.3 months for DC vs. 10.1 months for VC) and the 2-year survival rate (21% vs. 14%) [20].

In another trial, 153 patients with NSCLC were allocated to have cisplatin plus oral navelbine (NC) or cisplatin plus pemetrexed (PC); after 4 cycles, patients achieving at least disease stabilization received single-agent maintenance with oral NC or with PC. Treatment consequences, in terms of disease control and survival, were equivalent between the two arms [21].

Furthermore, the current findings support a meta-analysis that indicated comparable survival outcomes between carboplatin-based doublets and more recent non-platinum doublets [22]. However, they do not confirm the results of Tan et al.'s study [23], which suggested that NG was superior to NC.

In another trial, there was a tendency towards elongated PFS with PC compared to PG (4.2 months versus 3.5 months, p = 0.044), while GC showed a PFS of 5.1 months [24]. Notably, nearly one-third of the patients in this trial were treated with second-line chemotherapy, predominantly platinum-based (86%), after receiving non-platinum-based first-line chemotherapy.

In the current study, nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy were more common in the taxan arm than in the gemcitabine or navelbine arms, with significant differences. Vomiting was significantly associated with the gemcitabine arm, while fatigue and constipation were more common in gemcitabine and navelbine than taxan, with significant differences.

Numerous studies conducted worldwide have yielded somewhat similar findings. One particular study indicated that PC was related

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to higher rates of alopecia and PN compared to NC [25] or GC, as well as higher rates of NAV compared to GP [24].

Toxicities normally linked with paclitaxel-platinum regimens include neutropenia, leukopenia, anemia, and neurotoxicity. In comparison to PG, PC demonstrated generally comparable toxicity profiles [44]. Paclitaxel-carboplatin exhibited lower incidences of neutropenia (50–57% versus 65–76%) and nausea and vomiting (<1–7% versus 12–18%) compared to NC [25], but higher rates of neurotoxicity (13% versus 3%) [17].

In another study, the mixture of vinorelbine (30 mg/m^2 weekly) and cisplatin (100 mg/m^2 every 4 weeks) was associated with hematologic complications such as neutropenia, anemia, and febrile neutropenia [26].

Furthermore, other side effects were reported in various studies. Initially, when gemcitabine was given on days 1, 8, and 15 with a protocol given every 28 days, very high rates of thrombocytopenia fluctuating from 40% to 60% were noted [27]. The relatively low occurrence of thrombocytopenia in the present study may be attributed to the small sample size.

Conclusions

The three therapeutic protocols—vinorelbine, gemcitabine, and taxanes—had similar efficacy, based on response rate, in the treatment of SCC with a mild preponderance of vinorelbine.

Recommendations

Taxane is associated with more frequent side effects, including nausea, alopecia, diarrhea, arthralgia, and peripheral neuropathy.

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Ethical clearance: This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no.2023SAA768).

Conflict of interest: Nil

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معدل الاستجابة والتأثيرات الجانبية وتراجع حجم الورم باستخدام الفينوريلبين والجيمسيتابين والتاكسان كخط أول لعلاج سرطان الخلايا الحرشفية المتقدم في الرئة

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الملخص

خلفية الدراسة: سرطان الخلايا الحرشفية في الرئة هو نوع من سرطان الرئة ذو الخلايا غير الصغيرة. استخدم العلاج الكيميائي السام للخلايا لتحقيق فائدة للمرضى في حالات المرض المتقدمة.

اهداف الدراسة: لمقارنة معدل الاستجابة والآثار الجانبية بين ثلاث علاجات كيمائية اساسية: فينوريلبين، وجيمسيتابين والتاكسان في المرضى الذين يعانون من سرطان الخلايا الحرشفية النقيلي في الرئة.

المرضى والطرائق: شملت هذه الدراسة الاسترجاعية ٤٥ مريضًا مصابين بسرطان الخلايا الحرشفية النقيلي في الرئة. تلقى جميع المرضى علاج كيميائي مزدوج يعتمد على البلاتين لمدة ٤-٦ دورات. قسم المرضى إلى ثلاث مجموعات على أساس بروتوكول العلاج الإضافي لكل مجموعة خمسة عشر مريضا. تم تقييم التراجع في حجم الورم من قياسات الورم للمرضى الذين لديهم على الأقل تقييمين باستخدام التصوير المقطعي المحوسب. كما تم تقييم الآثار الجانبية لكل دواء.

النتائج: بلغ معدل الانخفاض في حجم الورم في أذرع جيمسيتابين وتاكسان وفينوريلبين-٥,٥٩±٣٥,٦٢ سم٢، ١,٣±٣٩,٩٨ سم٢ و-١٠,٥٥±١٤,٦٢ سم٢ على التوالي مع عدم وجود فروق معنوية. وبلغ معدل الاستجابة في أذرع التاكسان والجيمسيتابين والفينوريلبين ٧٣,٣٣٪ و٨٠٪ و٨٦,٦٧٪ على التوالي مع عدم وجود فروق معنوية. كانت الآثار الجانبية بما في ذلك الغثيان، والثعلبة، والإسهال، وآلام المفاصل، والاعتلال العصبي المحيطي، على وجه الخصوص، أكثر شيوعًا في المرضى في ذراع التاكسان مقارنة بالأذرع الأخرى مع وجود اختلافات معنوية.

الاستنتاجات: كانت للعلاجات الكيمياوية الثلاثة: فينوريلبين، وجيمسيتابين، وتاكسانيس، كفاءة مماثلة، بناءً على معدل الاستجابة مع رجحان بسيط للفينوريلبين.

الكلمات المفتاحية: سرطان الخلايا الحرشفية، فينورلبين ، جمسيتابين ، تاكسان

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