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Original Research Article

Comparison of gemcitabine/carboplatin versus paclitaxel/cisplatin for the management of non-small cell lung cancer

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Abstract

Purpose: *To determine the comparative efficacy and toxicity of gemcitabine/carboplatin and paclitaxel/cisplatin in patients with completely resected stage IIa - IIIa non-small cell lung cancer (NSCLC).*
Methods: *Sixty eligible NSCLC patients treated in Funan County People's Hospital were enrolled and assigned to two groups by randomization (n = 30 each). One group (CG group) received the combination of gemcitabine and carboplatin, while the second group (CP group) received a combination of cisplatin and paclitaxel. Efficacy was assessed based on 2-year progression-free survival, while adverse reactions were recorded to assess the toxicity of the chemotherapy treatments.*
Results: *No marked difference was found in the 2-year relapse-free survival in the two groups with similar clinical baseline characteristics after follow-up (60 % in CG group vs. 56.67 % in CP group, p = 0.826). Specifically, no significant difference was found between the two groups with regard to incidence of local metastases, distant metastases, or brain tissue metastases within 2 years, and there were no treatment-related deaths. CG group was more likely to develop leukopenia (93.33 % vs. 63.33 % for CP group, p = 0.04), but no significant difference was observed for other adverse effects such as anemia, vomiting, and nausea.*
Conclusion: *This study shows that adjuvant treatment using carboplatin and gemcitabine produces the same therapeutic efficacy as cisplatin and paclitaxel, but exhibits higher toxicity levels than the latter.*

Keywords: *Non-small cell lung cancer, Carboplatin, Gemcitabine, Cisplatin, Paclitaxel, Metastasis, Leukopenia*

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INTRODUCTION

Globally, the incidence and mortality rates of lung cancer are the highest amongst all cancer types [1]. About 50 % of NSCLC patients are in stage IV upon diagnosis, and symptomatic treatment and symptom relief are generally prescribed for these patients [2]. However, surgical resection is the more common option in clinical practice for early-stage NSCLC patients. It was found that about 30 - 70 % of NSCLC patients experience recurrence and metastasis after surgical

resection, and almost 80 % of NSCLC patients at stage IIIa experience distant micrometastases, leading to limited overall survival time [3]. Tumor cells may have spread to lymph nodes at an early stage, and spread of malignant cells in the peripheral blood may be the main cause of premature death after complete resection.

Therefore, combined chemotherapy has higher benefits when compared to single treatment alone [4]. Based on evidence from large prospective studies and meta-analyses, platinum-based adjuvant chemotherapy regimens are the standard treatment for completely resected stage II or III NSCLC, and they can reduce the risk of postoperative recurrence and metastasis and prolong postoperative survival time [5]. In addition to efficacy, toxicity profile is a key factor that must be considered during selection of a chemotherapy regimen. Despite the proven efficacy of platinum-based adjuvant chemotherapy, some concerns have been raised about the toxicity of the drugs used. Cisplatin-based adjuvant therapy has been widely used to treat postoperative NSCLC and has been shown to be effective in improving outcomes and survival in several studies [6]. Carboplatin-based therapy is also believed to have the same efficacy as cisplatin-participating regimens in patients who cannot tolerate cisplatin [7].

The present study was designed to compare the efficacy and toxicity of adjuvant treatment of gemcitabine and carboplatin versus paclitaxel and cisplatin in patients with post-complete resection IIa-IIIa NSCLC, and to provide a basis for the selection of chemotherapy regimens for such patients.

METHODS

Patients

Sixty patients who were newly diagnosed as NSCLC from June 2018 to June 2019 were allocated into CG and CP groups by randomization, with 30 in each group. CG group received gemcitabine combined with carboplatin, and CP group received paclitaxel combined with cisplatin. The study was carried out with the approval of the Ethics Committee of Funan County People's Hospital. The participants provided signed informed consent before participating in the research.

This study was conducted in conformity with the guidelines of Declaration of Helsinki [8]. Patients aged 18 - 80 years, with pathological staging at IIa-IIIa based on the 8th edition of the AJCC (American Joint Committee on Cancer) [9] were included. Patients with good function of other organs were also included. Patients who were pathologically diagnosed as NSCLC and received a complete resection of the lesion and surgery for mediastinal lymphoma, and who had not received other adjuvant chemotherapy were included. Patients with a history of malignancy, active uncontrollable infection, and prior chemotherapy, radiotherapy, or immunotherapy were excluded.

Treatment schedule

Patients in this study underwent 4 cycles of adjuvant chemotherapy. In CG group, carboplatin was administered at an area under the concentration-time curve (AUC) of 6.0 mg/mL per min on the first day of a 21-day cycle, and gemcitabine (1000 mg/m^2) was administered on days 1 and 8 of the cycle. In CP group, paclitaxel (200 mg/m^2) and cisplatin (80 mg/m^2) were administered on the first day of the 21-day cycle. Treatment was repeated every 21 days for a maximum of 4 cycles. After completion of adjuvant therapy, clinical examinations and chest X-rays and CT examinations were carried out every 3 months with a follow-up of 1 year.

Assessment of treatment efficacy

Efficacy was assessed according to the 2-year progression-free survival (PFS). The 2-year PFS was defined as the percentage of recurrence-free patients within 2 years after surgical resection. Recurrence was categorized as local, distant, and brain tissue metastases. Local metastasis: metastasis to supraclavicular lymph nodes, mediastinal lymph nodes, pleural effusion, bronchial stump, and ipsilateral lung. Distant metastasis: metastasis to contralateral lung, bone, liver, adrenal gland and other organs except brain. Simultaneous local and distant metastases were regarded as distant metastases. Brain metastases were specified as a special group.

Treatment toxicity

Adverse reactions reported by patients and documented by doctors in a 2-year follow-up were recorded to assess the toxicity of the chemotherapy regimen. According to the National Cancer Institute Common Terminology Criteria for Adverse Events [10], the adverse reactions were classified into hematologic toxicity (leukopenia, anemia, thrombocytopenia and neutropenia) and non-hematologic toxicity (fatigue, anorexia, nausea, vomiting, diarrhea, constipation, neurological symptoms, alopecia,

myalgia, infection, ALT elevation, hyperbilirubinemia and creatinine increase).

Leukopenia refers to the number of white blood cells in peripheral blood continuously less than 4 × 10^9/L. Anemia refers to hemoglobin in blood below the normal limits (120 g/L for adult male and 110 g/L for non-pregnant adult female). Thrombocytopenia refers to the blood platelet count < 100 × 10^9/L. Neutropenia refers to the neutrophil count less than 2.0 × 10^9/L. The adverse reactions were scored according to the severity on a scale of 0 - 4, with 4 being the most severe.

Statistical analysis

Chi-square test was applied to assess the significant difference between the two groups of categorical variables, and Student *t*-test was applied to assess the count variables. Calculations were performed using Statistical Package for Social Sciences (SPSS), version 18.0. $P < 0.05$ was regarded as statistically significant.

RESULTS

Baseline demographic profile of patients

The two groups showed no marked difference in terms of demographic characteristics (the age, gender, marriage and smoking status), disease associated characteristics (pathological stages, surgical procedures and NSCLC histology), and clinical variables before administration of adjuvant chemotherapy (the hemoglobin concentration, platelet count, blood albumin concentration, the estimated glomerular filtration rate, and weight loss) ($p > 0.05$) (Tables 1 and 2), which excluded possible influencing factors.

Table 1: Patient demographic characteristics and clinical variables

Variable	Group CP (n=30)		Group CG (n=30)		*P*-value
	Median	***Interquartile range (%)***	***Median (n)***	***Interquartile range (%)***	
Age (years)	65	57-71	63	58-68	0.645
Gender					0.382
Male	18	60	21	70	
Female	12	40	9	30	
Married	19	63.33	17	46.67	0.245
Smoking status					0.673
Never smoker	5	16.67	7	23.33	
Ex-smoker	25	83.33	22	73.33	
Current smoker	0	0	1	3.33	
Hemoglobin (g/L)	128	116-139	125	115-140	0.654
Anemia*	10	33.33	11	36.67	0.432
Platelet count (×10^9/L)	176	148-245	(×10^9/L)	156-243	0.01
Albumin (g/L)	36	31-38	35	30-39	0.642
Hypoalbuminemia*	14	46.67	15	50	0.518
eGFR (ml/min/1.73m^2)	87	72.3-100.4	84	67.9-101.6	0.345
Chronic kidney disease*	4	13.33	3	10	0.421
Weight loss (%)	4.2	1.6-8.6	4	1.8-8.3	0.378

*Anemia = Hemoglobin < 120 g / L in males, < 110 g / L in females; Hypoalbuminemia = albumin < 35 g / L; chronic kidney disease = eGFR < 60 mL / min / 1.73 m^2

Table 2: Disease associated characteristics of patients

Variable	Group CP (n=30)		Group CG (n=30)		*P*-value
	Median (n)	***Interquartile range (%)***	***Median (n)***	***Interquartile range (%)***	
Pathological stage					0.734
IIa	5	16.67	6	20	
IIb	13	43.33	15	50	
IIIa	12	40	9	30	
Surgical procedure					0.419
Lobectomy	24	80	22	73.33	
Pneumonectomy	6	20	8	26.67	
NSCLC histology					0.473
Squamous cell	7	23.33	8	26.67	
Adenocarcinoma	12	40	12	40	
Adenosquamous	1	3.33	2	6.67	
Not otherwise specified	8	36	7	23.33	
Others	2	6.67	1	3.33	

Table 3: Non-mortality outcomes observed in 2-year follow-up

Non-mortality outcomes	Group CP (n=30)		Group CG (n=30)		*P*-value
	Median (n)	*Interquartile range*	*Median (n)*	*Interquartile range (%)*	
Locoregional	6	20	5	16.67	0.752
Distant, excluding brain	4	13.33	5	16.67	0.879
Brain	3	10	4	13.33	0.726
Relapse-free	17	56.67	16	53.33	0.826
Hospitalizations	6.2	3-8	5.9	2-8	0.352
Length of stay in days	28.5	12-34	27.6	13-33	0.407
Outpatient visits	21.3	7-27	20.8	8-26	0.342

Treatment efficacy and recurrence

The non-mortality outcomes of patients in the 2-year follow-up are shown in Table 3. Specifically, the non-mortality events included locoregional recurrence, distant metastasis (brain metastases were listed separately) and relapse-free survival. The two groups showed no marked difference in terms of local metastasis rate (20 % vs. 16.67 %, p = 0.752), distant metastasis rate (13.33 % vs. 16.67 %, p = 0.879), and brain metastasis rate (10 % vs. 13.33 %, p = 0.726). No marked difference was found in the 2-year relapse-free rate (56.67 % vs. 53.33 %, p = 0.826). In addition, the times of hospitalizations and outpatient visits, as well as the length of stay, were documented, which showed no difference between the CP and CG groups.

Adverse reactions

In 2-year follow-up, patient-reported and doctor-documented adverse reactions were recorded to evaluate the toxicity of chemotherapy treatment. Specifically, these events included hematologic toxicity (leukopenia, anemia, thrombocytopenia, neutropenia), and non-hematologic reactions (fatigue, anorexia, nausea, vomiting, diarrhea, constipation, neurologic symptoms, alopecia, myalgia, infection, elevated ALT, hyperbilirubinemia, and elevated creatinine). The total numbers of reported cases of different degrees of adverse events in two groups are listed in Table 4. Mild events were more often reported, and there were a few events of degree 4.

To better compare the toxicity of two therapeutic regimens, the occurrence of the main toxicity-related events (including leukopenia, neutropenia, anemia, nausea and vomiting), was recorded, including Grade 3 / 4 toxicity and total grade (0 to 4) toxicity, respectively. Table 5 listed the amounts of reported toxicity-related events in two groups, and the P-values were calculated in comparing the occurrence. Figure 1 directly showed the comparative numbers of Grade 3 / 4 main toxicity-related events in the two groups. In terms of Grade 3 / 4 toxicity, the CG group was more prone to neutropenia (8 vs. 16, p = 0.02), shown in Figure 1 B.

Table 4: Adverse reactions reported in 2-year follow-up

Variable	Degree of toxicity				
	0	1	2	3	4
Hematologic toxicity					
Leukopenia	13	12	23	12	0
Anemia	15	23	13	9	0
Thrombocytopenia	52	2	6	0	0
Neutropenia	12	9	15	19	5
Non-hematologic toxicity					
Fatigue	29	31	0	0	0
Anorexia	48	7	5	0	0
Nausea	5	45	6	4	0
Vomiting	47	9	3	1	0
Diarrhea	49	2	9	0	0
Constipation	52	4	3	1	0
Neuropathy, sensory	34	15	9	2	0
Alopecia	54	5	1	0	0
Myalgia	40	12	6	1	1
Infection	56	2	2	0	0
ALT elevation	53	3	2	2	0
Hyperbilirubinemia	59	1	0	0	0
Creatinine increase	58	1	1	0	0

Table 5: Comparison of main toxicity-related events in two groups

Parameter	Grade 3/4 toxicity			Total grade toxicity		
	CP	***CG***	***P--value***	***CP***	***CG***	***P-value***
Leukopenia	5	7	0.621	19	28	0.04
Neutropenia	8	16	0.02	20	28	0.08
Anemia	4	5	0.528	20	25	0.26
Nausea	2	2	0.872	25	30	0.71
Vomiting	0	1	0.308	8	5	0.463

The occurrence of Grade 3 / 4 toxicity of leukopenia (Figure 1 A), anemia (Figure 1 C), nausea (Figure 1 D) and vomiting (Figure 1 E) in both groups exhibited no statistical difference ($p > 0.05$). As for total grade toxicity, the CG group was more prone to leukopenia (19 vs. 28, $p = 0.04$), as shown in Figure 2 A. No statistical difference was observed in the occurrence of all grade toxicity of neutropenia (Figure 2 B), anemia (Figure 2 C), nausea (Figure 2 D) and vomiting (Figure 2 E).

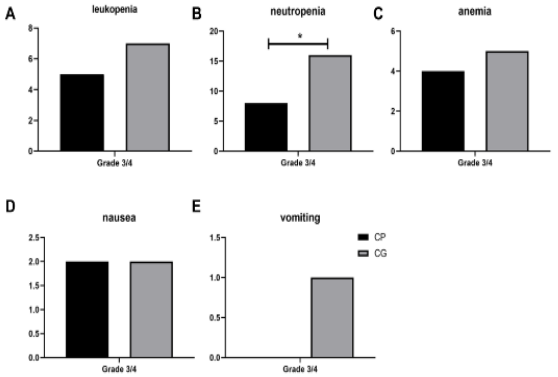

Figure 1: Comparison of Grade 3 / 4 toxicity events between CP and CG. (A) Leukopenia. (B) Neutropenia. (C) Anemia. (D) Nausea. (E) Vomiting. *$P < 0.05$

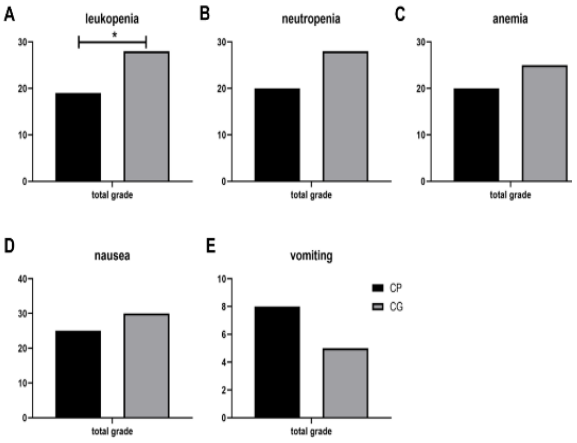

Figure 2: Comparison of all grades of toxicity events between CP and CG. (A) Leukopenia. (B) Neutropenia. (C) Anemia. (D) Nausea. (E) Vomiting. *$P < 0.05$

DISCUSSION

In this study, the CP regimen was similar to that of the CG in terms of the 2-year PFS, but was slightly better than the CP regimen in terms of bone marrow transplantation-related adverse effects. While previous retrospective studies may have introduced selection bias, this study is a prospective trial with no significant bias for participants included in the study, and the conclusions are more convincing. The findings suggest that carboplatin in combination with gemcitabine achieved a similar efficacy as paclitaxel in combination with cisplatin, but with more incidence of leukopenia-related adverse effects, providing a basis for the selection of adjuvant chemotherapy after NSCLC surgery.

Many randomized phase III researches have compared the effect of a combined therapy of platinum and newer agents in NSCLC treatment. Dual regimens of platinum and next-generation anticancer drugs have been recognized as the standard chemotherapy regimen for advanced NSCLC [11]. However, the efficacy of platinum-based chemotherapy in patients with postoperative NSCLC was controversial. A previous cohort study suggested that platinum-based chemotherapy may be beneficial for the survival of NSCLC patients [12].

Besides, three clinical trials investigated the curative effect of platinum-based chemotherapeutic agents in post-surgical resection NSCLC, but the results were mixed, with two trials finding that it improved survival, while the other one did not support this conclusion [13-15]. The choice of chemotherapeutic agents, the pathological stage of the patients included, and the chemotherapy regimen may have led to inconsistent conclusions from these trials.

In a large randomized study, patients with partial resection of NSCLC who underwent platinum-based adjuvant chemotherapy had a 5.4 % increase in a 5-year absolute survival and a 50% 5-year overall survival in contrast to surgery alone [13]. A meta-analysis proposed that cisplatin-based adjuvant chemotherapy could improve survival following complete resection for

state II and III NSCLC [5]. Currently, adjuvant chemotherapy has not been shown to be effective in stage Ib NSCLC, and is not routinely recommended for such early stage patients. However, there is evidence that patients with larger tumors (> 4 cm) can benefit from adjuvant chemotherapy [15]. Therefore, platinum-based adjuvant chemotherapy is currently used primarily in patients with stage II and III NSCLC as well as stage Ib NSCLC following complete resection. The choice of platinum-based adjuvant chemotherapy regimens continues to be an issue for clinicians. Cisplatin has been recommended in the guidelines of the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) as an effective chemotherapeutic agent. Previous evidence suggests that cisplatin-based two-drug regimens have improved patient survival in multiple phase III clinical studies [16], while carboplatin-based two-drug regimens, particularly carboplatin in combination with paclitaxel, have not improved survival [15]. Patients who cannot tolerate cisplatin may be considered for carboplatin-based chemotherapy regimens, as recommended by the NCCN guidelines [16].

Despite lack of studies for the comparison of cisplatin- and carboplatin-based adjuvant therapy, a meta-analysis demonstrated that cisplatin-based regimens induce stronger antitumor effects when compared to carboplatin. However, they are also associated with more adverse effects, such as nausea, vomiting, and impaired renal function [17]. There are contraindications for cisplatin in patients with symptomatic congestive heart failure and renal failure, while carboplatin does not cause these problems. In fact, a meta-analysis suggests that regimens containing gemcitabine have greater superiority for advanced NSCLC [18]. The combined therapy of gemcitabine and carboplatin has been shown to be one of the best treatment options for advanced NSCLC [19]. Nevertheless, severe thrombocytopenia is frequently noted in the three-week dosing schedule of the combination of gemcitabine and carboplatin [20].

Although platinum-based chemotherapy has benefited from the quality of survival of most NSCLC patients, the benefit is limited. The introduction of immune checkpoint inhibitors, in addition to traditional adjuvant chemotherapy, has improved patient survival at a greater level. PD-L1/PD-1 inhibitors, such as atelelizumab, dulvalumab, nabritumomab, and pembrolizumab, have been approved as first- or second-line treatment for patients with metastatic NSCLC or some stage III advanced NSCLC, but data on their safety and curative effect in resectable NSCLC are just emerging [21]. Currently, immune checkpoint inhibitors, a new adjuvant therapy, is being evaluated for safety and efficacy in more than 100 clinical trials for patients with different tumor types as chemotherapeutic agents alone or in combination with chemotherapeutic agents regimens [22]. Therefore, it is important to explore the role of immune checkpoint inhibitors in postoperative adjuvant chemotherapy of NSCLC, which is one of our future research directions.

Limitations of the study

There were some limitations in this study. The number of patients receiving adjuvant chemotherapy was limited to 60, and the follow-up period was short. Therefore, observations of efficacy and toxicity were limited, survival was not documented in the long term, and delayed onset adverse effects were not reported. In addition, it is promising to study the relationship between dose and efficacy of adjuvant drugs. In this study, the commonly recommended clinical doses were used, and stepped doses were not adopted to provide more specific and detailed treatment protocols for postoperative adjuvant chemotherapy.

CONCLUSION

Despite the limitations stated above, the findings of this study show that adjuvant treatment with carboplatin and gemcitabine produces the same therapeutic outcomes as cisplatin and paclitaxel, but with a higher level of toxicity. This may be beneficial for the selection of chemotherapy regimens for NSCLC patients.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Wei Wang and Wenli Li contributed equally to this work.

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