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ORIGINAL ARTICLE

Gemcitabine combined with cisplatin as adjuvant chemotherapy for non-small cell lung cancer: A retrospective analysis

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Abstract

Background: This study was conducted to evaluate the value of gemcitabine combined with cisplatin as adjuvant chemotherapy for radical resection of non-small cell lung cancer.

Methods: Data of 100 patients who had undergone radical resection of non-small cell lung cancer and were treated with cisplatin/gemcitabine as adjuvant chemotherapy between June 2007 and December 2010 at the Chinese Academy of Medical Sciences were reviewed.

Results: The median age was 59 years (range 36–73); 82% of the patients were male. Forty-two percent had adenocarcinoma and 55% had squamous cell carcinoma. Most patients had pathologic IIB (29%) and IIIA (44%) stage disease. Eighty-five percent of patients completed four cycles of chemotherapy, with 76% completing the planned full dose. The main reason for a reduced gemcitabine dose in 13 patients was grade 3/4 neutropenia or thrombocytopenia. The median dose and dose intensity were 8377.1 mg/m^2 and 708 mg/(m^2/week) for gemcitabine and 293.38 mg/m^2 and 25.24 mg/(m^2/week) for cisplatin, respectively. During follow-up the median disease-free survival was 33.8 months (95% confidence interval [CI] 15.938–51.676). Patients with squamous cell carcinoma (hazard ratio [HR] 0.404, 95% CI 0.241–0.676; $P = 0.001$) and pathologic stage I (HR 4.379, 95% CI 1.721–11.142; $P = 0.002$) achieved better disease-free survival. The survival rates at one, two, and five years were 94%, 77%, and 55%, while the survival rates without recurrence were 64%, 53%, and 39%, respectively.

Conclusion: As an adjuvant chemotherapy regimen, gemcitabine with cisplatin is well tolerated. Patients with squamous cell carcinomas or pathologic stage I achieve better results.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Non-small-cell lung cancer (NSCLC) represents 80–85% of all lung cancers and surgery remains the best curative treatment option for patients who are diagnosed at an early stage (stage IA–IIIA). Unfortunately, only 20–25% of patients with NSCLC are eligible for surgical resection at presentation.[2] Despite complete resection, the risk of recurrence remains high, with disappointing five-year survival rates ranging between 67% and 23% for pathological stage IA and IIIA, respectively.[3]

Theoretically, chemotherapy can eliminate residual small metastases after surgery, thus reducing the risk of recurrence and improving survival. Adjuvant chemotherapy has now been adopted as the standard of care in patients with stage II, III, and high-risk IB (e.g. tumors >4 cm), primarily based on large positive randomized trials of platinum doublets (e.g. ANITA, CALGB 9633, IALT, and JBR.10) and a meta-analysis (the LACE meta-analysis of the five

largest cisplatin-based studies), with a five-year absolute benefit of 5.3% ± 1.6%.[4–9] Although the benefit of adjuvant chemotherapy has been demonstrated, long-term follow-up in some randomized trials (CALGB 9633 and IALT) failed to maintain statistically improved survival over time.[6] The cisplatin/vinorelbine (NP) combination as the standard regimen was associated with considerable toxicity, with more than 80% of patients experiencing grade 3/4 toxicities, and only 50% and 65% patients in the ANITA and JBR.10 studies, respectively, completing four cycles of chemotherapy.[4,8] Hence, there is a need for newer, more effective, and less toxic methods for adjuvant chemotherapy.

Gemcitabine, a novel generation of cytosine nucleoside derivatives, has a wide-spectrum of antitumor activity. The superiority of gemcitabine-containing regimens in efficacy and toxicity over other regimens has been shown in several studies and it has proven to be one of the best regimens for the treatment of advanced NSCLC.[10–13] Although there is limited prospective phase III clinical trial data, several phase II clinical trials have shown beneficial efficacy and reduced toxicity of cisplatin/gemcitabine as adjuvant chemotherapy.[14–17] Therefore, we reviewed the charts of 100 patients to investigate the efficacy and toxicities of cisplatin/gemcitabine as adjuvant chemotherapy for patients with completely resected NSCLC.

Methods

Patient selection

Eligible patients had undergone complete surgical resection (R0 resection) and were pathologically documented with stage IB, IIA, IIB, or IIIA NSCLC at the Chinese Academy of Medical Sciences between June 2007 and December 2010. Other eligibility criteria included: aged 18–75; Eastern Cooperative Oncology Group (ECOG) Karnofsky performance status (KPS) ≥ 70; no previous chemotherapy or postoperative radiation therapy; and adequate hepatic, renal, and bone marrow function.[18] Cases with severe postoperative complications, active infections, concomitant malignancy, clinically significant cardiac dysfunction or neurological/psychiatric disorders were excluded. Written informed consent was obtained from each patient before treatment commenced.

Therapeutic regimens

Gemcitabine was administered at a dose of 1250 mg/m^2 in 100 mL of normal saline solution by 30 minute intravenous infusion on days 1 and 8 in combination with cisplatin administered at a dose of 80 mg/m^2 on days 2–4. The treatment was repeated every three weeks for a total of four courses. Toxicities were assessed before and in the middle of each cycle of chemotherapy according to National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0.

The scheduled day 8 gemcitabine was delayed until recovery (no longer than two weeks) if the patient had a leukocyte count $<2.0 \times 10^9$/L, an absolute neutrophil count $<1.5 \times 10^9$/L, or a platelet count $<100 \times 10^9$/L, and/or other non-hematologic toxicities > grade 2. If these parameters did not sufficiently improve, the day 8 gemcitabine dose was not administered. Dose modification was required according to toxicities. If toxicities persisted after a two-week delay, treatment was discontinued.

Statistical analysis

Disease-free survival (DFS) was calculated from the date of resection to the date of progression, including locoregional and distant recurrence. Overall survival (OS) was defined from the date of resection to the date of death or last known contact. The terminal event for OS analysis was death attributable to cancerous or non-cancerous causes. The primary endpoint of this study was DFS, while the second endpoints were OS and adverse events. DFS and OS curves were generated using the Kaplan–Meier method, and a log-rank test was used for comparison. Hazard ratios (HRs) for univariate and multivariate survival analyses were calculated using the Cox proportional hazard model. Statistical analysis was performed at the last study follow-up date (December 2016) using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). A P value of <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

A total of 100 patients were enrolled in the study; 82 (82%) were male. The median age was 59 years (range 36–73). Nighty-nine patients (99%) had an ECOG KPS ≥ 80. The proportions of adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma were 42%, 55%, 2%, and 1%, respectively. Most patients had pathologic IIB (29%) and IIIA (44%) stage disease, with the remainder at IA (2%), IB (14%), IIA (6%), and IIIB (5%). Surgical methods included sleeve resection (12%), pneumonectomy (14%), and lobectomy (73%). Patient characteristics are summarized in Table 1.

Chemotherapy compliance

One hundred patients completed a total of 372 cycles of chemotherapy, and the median number of cycles was four (range 1–4). Eighty-five percent of patients completed the

Table 1 Patient characteristics

Characteristic	No. of patients (%)
No. of patients	100
Median age (years)	59 (range 36–73)
Gender	
Male	82 (82%)
Female	18 (18%)
ECOG KPS	
90	60 (60%)
80	39 (39%)
70	1 (1%)
Smoking history	
Never smoked	19 (19%)
Ever smoked	81 (81%)
Pathology	
Adenocarcinoma	42 (42%)
Squamous carcinoma	55 (55%)
Adenosquamous	1 (1%)
Large cell lung cancer	2 (2%)
Disease stage	
IA	2 (2%)
IB	14 (14%)
IIA	6 (6%)
IIB	29 (29%)
IIIA	44 (44%)
IIIB	5 (5%)
Type of surgery	
Pneumonectomy	14 (14%)
Lobectomy	73 (73%)
Sleeve resection	12 (12%)
Wedge resection	1 (1%)

ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status.

four cycles of chemotherapy, with 76% completing the planned full dose. Five patients discontinued cisplatin and completed the treatment with carboplatin because of grade 3 gastrointestinal reactions, including two patients after the first cycle, two after the second, and one after the third cycle. Three patients only completed one course of chemotherapy, including two patients who refused to continue chemotherapy because of grade 2 gastrointestinal reactions caused by gemcitabine, and one who continued treatment at another hospital. One patient suffered acute myocardial infarction after the first cycle of chemotherapy; therefore, the treatment was discontinued. Treatment was ceased in one patient because a T wave change was observed in electrocardiogram results. Four stage III patients experienced recurrence after two to three cycles of cisplatin/gemcitabine treatment. The gemcitabine dose was reduced in 13 patients because of grade 3/4 myelosuppression, mainly neutropenia and thrombocytopenia. The median dose and dose intensity were 8377.1 mg/m^2 and 708 mg/(m^2/week) for gemcitabine and 293.38 mg/m^2 and 25.24 mg/(m^2/week) for cisplatin.

Toxicity

All patients were evaluable for toxicities (Table 2). The observed toxicities were mild and patients showed good compliance to treatment. Grade 3/4 hematological adverse effects included neutropenia (27.5%), thrombocytopenia (9.9%), leukopenia (9.0%), and anemia (1.1%). The 3/4 non-hematological adverse effects consisted mainly of nausea/vomiting, which occurred in 13.5% patients. There was low incidence of other mild adverse effects, such as fatigue, rash, constipation, hepatic dysfunction, and alopecia. No treatment-related death occurred.

Survival

During a median follow-up duration of 73.1 months, 62 patients experienced recurrence and there were 51 death events (14 patients were alive with recurrence, 48 deaths occurred after recurrence, and 2 deaths not caused by cancer).

Table 2 Worst adverse events by NCI grading†

Adverse events	No.‡	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicities					
Leukocytopenia	89	20 (22.5%)	26 (26.2%)	8 (9.0%)	0
Neutropenia	91	12 (13.2%)	27 (29.7%)	22 (24.2%)	3 (3.3%)
Anemia	91	29 (31.9%)	9 (9.9%)	3 (3.3%)	0
Thrombocytopenia	91	5 (5.5%)	11 (12.1%)	8 (8.8%)	1 (1.1%)
Non-hematologic toxicities					
Nausea/vomiting	96	29 (30.2%)	53 (55.2%)	12 (12.5%)	1 (1.0%)
Fatigue	100	19 (19%)	0	0	0
Constipation	100	8 (8%)	0	0	0
Rush	100	3 (3%)	0	0	0
Liver dysfunction	91	3 (3.3%)	2 (2.2%)	0	0
Tinnitus	100	2 (2%)	0	0	0
Alopecia	100	2 (2%)	1 (1%)	0	0

†National Cancer Institute (NCI) Common Terminology Criteria, version 2.0. ‡The number of adverse events with records.

The major sites of tumor recurrence were distant metastases (51/62), and the rate of recurrence was higher in patients with advanced stage disease. Thirty-six patients recurred in the first year, 11 in the second, and only three had recurrence over five years after surgery. The survival rates at one, two, and five years were 94%, 77%, and 55%, while the survival rates without recurrence were 64%, 53%, and 39%, respectively.

The median DFS was 33.8 months (95% confidence interval [CI] 15.938–51.676), while the median OS was not reached (Fig 1). We analyzed the effects of several possible factors, including age, gender, ECOG KPS, smoking history, pathology, stage, chemotherapy cycle, and surgery method on DFS. The results of the Cox model are shown in Table 3. Univariate analysis demonstrated that compared to adenocarcinoma, squamous carcinoma was associated with better survival (hazard ratio [HR] 0.404, 95% CI 0.241–0.676; $P = 0.001$). When compared to stage I, stage III was a risk factor for DFS (HR 4.379, 95% CI 1.721–11.142; $P = 0.002$). Multivariate analysis also showed that squamous carcinoma (HR 0.499, 95% CI 0.273–0.912; $P = 0.024$) and stage I (HR 4.192, 95% CI 1.544–11.380; $P = 0.005$) were potential protective factors. Other factors were not significantly associated with DFS in either univariate or multivariate analyses (Fig 2).

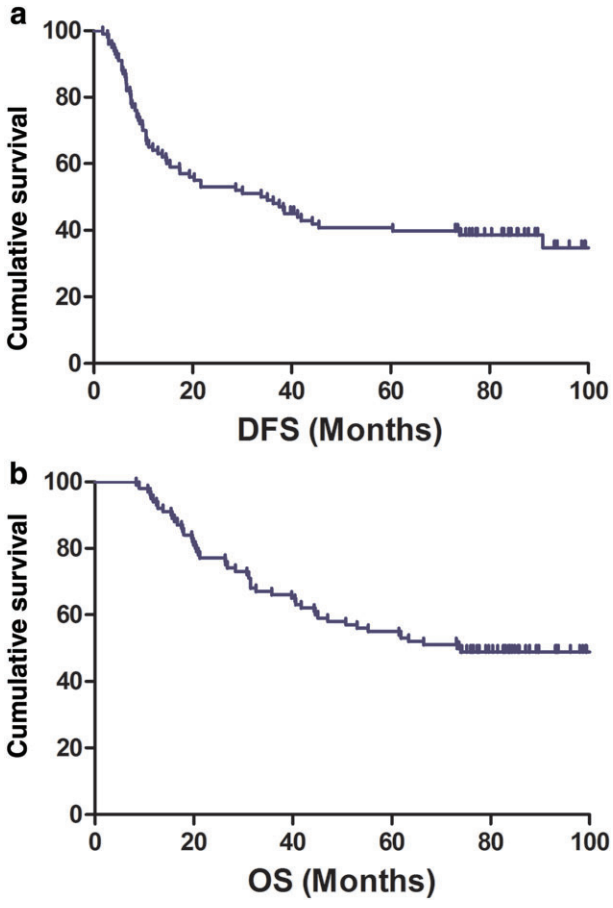

Figure 1 Outcomes of analyses on disease-free survival (DFS) and overall survival (OS). (**a**) DFS and (**b**) OS curves for all patients.

Discussion

Adjuvant chemotherapy is now recommended for patients with stage II and III completely resected NSCLC. On the basis of clinical studies, cisplatin combined with docetaxel, etoposide, gemcitabine, or vinorelbine has been included as adjuvant chemotherapy for all histologies in the National Comprehensive Cancer Network Guidelines (Version 4, 2016; available at http://www.nccn.org/patients).[9] Nonetheless, the optimal regimen is yet to be determined, as long-term side effects have been observed using the older regimens. Analyses of compliance with cisplatin/vinorelbine adjuvant chemotherapy in the ANITA trial and JBR.10 study revealed a less than 65% completion rate of the planned four courses of chemotherapy, and the incidence of grade 3/4 neutropenia was 86% and 73%, respectively.[4,8] The combination of cisplatin/vinorelbine was associated with a negative impact on quality of life, and some treatment-related deaths were observed in these trials.

The efficacy and toxicities of a cisplatin/gemcitabine regimen as postoperative adjuvant chemotherapy for completely resected NSCLC patients can be inferred from several phase II studies. In 2009, Tibaldi *et al.* analyzed the results of 22 consecutive patients treated with cisplatin 80 mg/m^2 on day 1 and gemcitabine 1200 mg/m^2 on days 1 and 8, every three weeks for four planned courses.[14] This was the first study to provide information about the feasibility and tolerability of a cisplatin/gemcitabine combination for the adjuvant treatment of NSCLC. Grade 3/4 neutropenia was reported in only three patients, and nonhematologic toxicities were mild and tolerable. As a direct consequence of good tolerability, the compliance to treatment was optimal and most patients received all four planned courses of chemotherapy, with high delivered dose intensity equal to 97.2% and 87.5% of planned cisplatin and gemcitabine, respectively. Another phase II trial, in which gemcitabine was administered intravenously at a dose of 1000 mg/m^2 and cisplatin at 40 mg/m^2 on days 1 and 8 every four weeks for a maximum of four cycles, showed a relative dose intensity of 97% of planned gemcitabine and cisplatin.[15] The completion rate in this four cycle chemotherapy regimen was higher than in the adjuvant chemotherapy trials previously reported. Grade 3/4 neutropenia occurred in 33% and thrombocytopenia in 20%. Non-hematological adverse effects were extremely rare. The authors proposed that split-dose cisplatin might result in low toxicity and good compliance. The completion rate of four planned courses of chemotherapy in each of these two phase II trials was 95%, and the incidences of

Table 3 Risk factors for DFS in 100 patients

Characteristics	Univariate analysis				Multivariate analysis			
	P	HR	95% CI		*P*	HR	95% CI	
Age (< 65 vs. ≥ 65)	0.844	0.942	0.519	1.709	0.725	0.884	0.445	1.756
Gender	0.167	1.508	0.842	2.701	0.917	1.102	0.174	6.970
Smoking history	0.255	0.713	0.399	1.277	0.968	0.964	0.157	5.936
ECOG KPS (90 vs. 70–80)	0.710	0.907	0.544	1.513	0.592	1.169	0.661	2.069
Pathology								
Adenocarcinoma	0.002	—	—	—	0.049	—	—	—
Squamous carcinoma (vs. adenocarcinoma)	0.001	0.404	0.241	0.676	0.024	0.499	0.273	0.912
Others (vs. adenocarcinoma)	0.238	0.301	0.041	2.205	0.216	0.277	0.036	2.116
Stage								
I	0.000	—	—	—	0.003	—	—	—
II (vs. I)	0.289	1.715	0.632	4.652	0.243	1.878	0.652	5.406
III (vs. I)	0.002	4.379	1.721	11.142	0.005	4.192	1.544	11.380
Chemotherapy cycles (≤ 3 vs. 4)	0.450	0.770	0.391	1.517	0.806	0.898	0.381	2.116
Surgery method								
Pneumonectomy	0.148	—	—	—	0.273	—	—	—
Lobectomy (vs. pneumonectomy)	0.456	0.761	0.371	1.561	0.690	0.840	0.357	1.976
Sleeve resection (vs. pneumonectomy)	0.948	0.969	0.374	2.512	0.507	1.441	0.490	4.240

DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status.

grade 3/4 neutropenia were 18% and 33%, respectively. Furthermore, the CJLSG0503 study showed that adjuvant chemotherapy with a carboplatin/gemcitabine combination regimen also had an acceptable toxicity profile.[16] A randomized trial in 2015 that defined quality of life as the primary end-point found that cisplatin/gemcitabine or cisplatin/docetaxel adjuvant chemotherapy for completely resected NSCLC was well tolerated.[17] These trials indicate that the combination of cisplatin/gemcitabine is a feasible and well-tolerated regimen in an adjuvant setting.

In our study, the combination of cisplatin/gemcitabine also showed good compliance and mild toxicity in Chinese patients. The completion rate of four cycles of chemotherapy was 85%, with 76% of patients completing the planned full dose chemotherapy. Grade 3/4 hematological adverse effects included neutropenia (27.5%), thrombocytopenia (9.9%), leukopenia (9.0%), and anemia (1.1%). The 3/4 non-hematological adverse effects consisted mainly of nausea/vomiting, and occurred in 13.5% of patients. Thus, the cisplatin/gemcitabine combination was associated with less toxicity and better compliance. The median dose and dose intensity were 8377.1 mg/m^2 and 708 mg/(m^2/week) for gemcitabine, and 293.38 mg/m^2 and 25.24 mg/(m^2/week) for cisplatin, equal to 85% and 95% of the planned doses, respectively, consistent with the results of previous studies.

We proposed that pathology and stage were risk factors for DFS based on univariate and multivariate analyses. Our results indicated that squamous carcinoma was associated with better survival (HR 0.404, 95% CI 0.241–0.676; $P = 0.001$), while stage III was a risk factor for DFS (HR 4.379, 95% CI 1.721–11.142; $P = 0.002$) in patients who had undergone radical resection for NSCLC. The JMDB study also demonstrated the superiority of cisplatin/gemcitabine for squamous cell carcinoma, showing a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (10.8 vs. 9.4 months) in subgroup analysis of advanced NSCLC patients.[19] These results may potentially guide the selection of patients most likely to benefit from cisplatin/gemcitabine therapy.

The survival rates in our study at one, two, and five years were 94%, 77%, and 55%, while the survival rates without recurrence were 64%, 53%, and 39%, respectively. The median DFS was 33.8 months (95% CI 15.938–51.676), while the median OS was not reached. The five-year survival data in our study was slightly higher than observed in the ANITA study (51%), but was close to other previous studies (69% in JBR.10, 60% in CALGB9633).[4,6,8] After a median follow-up period of nearly six years, the curative effect of cisplatin/gemcitabine combination treatment has been maintained.

It is worth mentioning that our study has some distinct features compared to previous reports. First, we used DFS as the primary end point instead of OS. Because of the existence of epidermal growth factor receptor active mutations and anaplastic lymphoma kinase rearrangement, OS might be affected by targeted therapy in further treatment.[20–22] Second, the median follow-up time of our study was nearly six years, so we could gain a better understanding of the effects of cisplatin/gemcitabine as adjuvant chemotherapy on long-term survival. However, our study was a retrospective non-randomized study with an unequal cohort and several variables may affect the progression-free

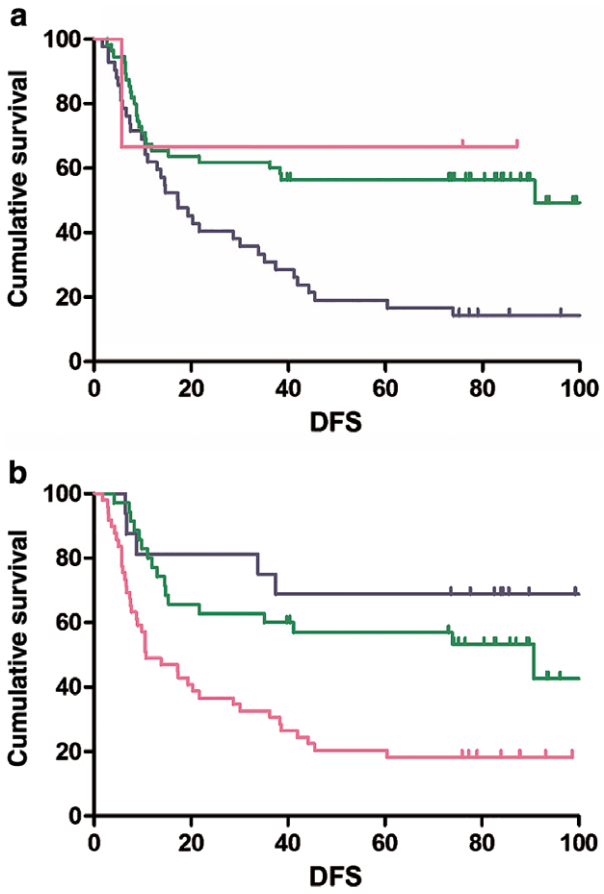

Figure 2 Univariate analysis of pathology and stage showed that squamous carcinoma and stage I were associated with better survival. Univariate analysis between (**a**) adenocarcinoma and squamous carcinoma (hazard ratio [HR] 0.404, 95% confidence interval [CI] 0.241–0.676; $P = 0.001$) (—·—) adenocarcinoma, (—·—) squamous carcinoma, and (—·—) other and (**b**) stage I and III (HR 4.379, 95% CI 1.721–11.142; $P = 0.002$). (—·—) stage I, (—·—) stage II, and (—·—) stage III.

survival outcome. The overall size of our sample was relatively small and some bias in patient selection could not be avoided. Thus, further prospective research involving larger cohorts of patients is required to investigate the efficacy and factors associated with the clinical significance of cisplatin/gemcitabine as an adjuvant regimen in radically resected NSCLC patients.

Adjuvant chemotherapy after radical resection provides an improvement in the cure rate, although recurrence still occurs in a substantial proportion of patients. Ongoing clinical trials are evaluating emerging therapies to improve efficacy and reduce toxicity, aiming to improve patient selection for such therapies.[23,24] Recent studies have explored the role of vascular endothelial growth factor inhibitors (e.g. bevacizumab),[25] epidermal growth factor receptor-tyrosine kinase inhibitors (e.g. erlotinib),[26] immunotherapy (e.g. nivolumab), and predictive biomarkers (e.g. ERCC1)[27] in the adjuvant setting, and have led to marginal advances over the past decade. However, a large number of questions remain unanswered. Considering that many variables may influence final outcomes, patient selection is key to preserving the survival benefit. We hope that with improved techniques for patient selection and more effective, less toxic therapies, more patients with NSCLC can be cured in the near future.

The combination of gemcitabine and cisplatin is feasible and well tolerated in the adjuvant setting for NSCLC. Squamous carcinoma and early stage were potential protective factors for DFS in radically resected NSCLC patients. Further prospective research involving larger cohorts of patients is needed to investigate the efficacy and factors associated with the clinical significance of cisplatin/gemcitabine as an adjuvant regimen in radically resected NSCLC patients.

Disclosure

No authors report any conflict of interest.

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