

REVIEW

OPEN ACCESS

Full open access to this and thousands of other papers at <http://www.la-press.com>.

Gemcitabine: Efficacy in the Treatment of Advanced Stage Nonsquamous Non-Small Cell Lung Cancer

Hidetoshi Hayashi, Takayasu Kurata and Kazuhiko Nakagawa

Department of Medical Oncology, Kinki University School of Medicine, Osaka-Sayama, Japan.

Corresponding author email: t-kurata@med.kindai.ac.jp

Abstract: Lung cancer is the leading cause of cancer-related death in many countries. Approximately half of the patients with non-small cell lung cancer have advanced disease and systemic chemotherapy, especially platinum-based doublets, is currently the standard treatment. Several trials have recently indicated the importance of histological subtype for treatment with molecular target chemotherapy and pemetrexed. Over the last decade, gemcitabine, a pyrimidine nucleoside antimetabolite, has been one of the most effective agents for patients with advanced non-small cell lung cancer. It is unknown whether histological type is a predictor of the outcome of treatment with this agent. This is a review of the past trials and reviews of first-line treatment for advanced NSCLC, focusing on efficacy and safety of treatment with gemcitabine according to histological subtype.

Keywords: gemcitabine, chemotherapy, non-small cell lung cancer, histology elderly patients

Clinical Medicine Insights: Oncology 2011:5 177–184

doi: [10.4137/CMO.S6252](https://doi.org/10.4137/CMO.S6252)

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.



Overview

Lung cancer is the leading cause of cancer-related death in many countries. The disease can be classified into two types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for 80%–85% of all cases. Approximately half of the patients with NSCLC have advanced disease. The standard therapy for patients with good performance status (PS) is systemic chemotherapy. Based on the results of a meta-analysis, cisplatin (CDDP)-based doublets are considered the best available therapy for patients with metastatic NSCLC, because of the moderate improvement in survival.¹ Several new agents with significant activity against NSCLC, such as paclitaxel, docetaxel, vinorelbine, and gemcitabine, have been introduced and any of these agents used in combination with a platinum agent was shown to improve the outcome compared to older agents² and each regimen provided a similar survival outcome.^{3,4} Unfortunately, the tumor recurs in almost all patients. Relapsed patients who still have a good PS receive second-line chemotherapy, which is considered a standard of care. Docetaxel, pemetrexed, and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), including erlotinib and gefitinib, are used in this setting.

Gemcitabine (2',2'-difluoro 2'-deoxycytidine, dFdC) is an analogue of Ara-C from which it structurally differs due to fluorine substituents on position 2' of the furanose ring.⁵ Despite structural and pharmacological similarities to Ara-C, gemcitabine displays distinctive characteristics of cellular pharmacology.⁶ In *in vitro* and phase I studies, gemcitabine has shown activity against many kinds of tumors, especially NSCLC.^{7–10} The evidence of its potent antitumor activity in a wide spectrum of tumor models has been successfully confirmed in clinical practice. Today gemcitabine is indicated for patients with pancreatic cancer, bladder cancer, breast cancer, malignant mesothelioma, and ovarian cancer besides those with NSCLC. Several early phase II studies of single-agent gemcitabine were performed in chemo-naïve patients with advanced NSCLC utilizing the weekly schedule (days 1, 8 and 15) with a 30-minute infusion, repeated every four weeks at a dose of 800–1,250 mg/m². Objective response rate of 20%–25% and a median survival of 9 months were observed. Moreover, phase II trials with gemcitabine plus CDDP demonstrated that response rates of 40%

to above 50% were favorable.^{11,12} These findings lead to phase III trials, in which superiority of gemcitabine plus CDDP for chemo-naïve patients with advanced NSCLC in terms of both overall survival (OS) and quality of life benefit when compared with platinum alone or in combination with etoposide.^{13,14} Therefore, gemcitabine/CDDP is widely used in clinical practice all over the world, and in several countries has become a most popular combination regimen for the treatment of advanced NSCLC.

More recently, some molecular targeted agents have been developed for the treatment of NSCLC. A large, randomized phase III study showed clear efficacy by adding bevacizumab, which inhibits vascular endothelial growth factor (VEGF), to the combination platinum based chemotherapy.^{15,16} In addition, EGFR-TKIs were very effective in a special molecularly defined population of patients harboring EGFR somatic mutations.^{17,18} In this way, much interest is concentrated on the development of molecular target agents and of personalized treatment on the basis of their molecular characteristics.

On the other hand, tumor histology has not been recognized as a consistent prognostic factor in patients with NSCLC so far.¹⁹ Recently, a preplanned subset analysis by histology in a large phase III trial demonstrated longer survival for pemetrexed/CDDP-treated than for gemcitabine/CDDP-treated patients with non-squamous NSCLC histology, while patients with squamous cell carcinoma treated with pemetrexed/CDDP had a shorter survival than those treated with gemcitabine/CDDP.²⁰ This finding indicated that histology could serve as a predictor of the outcome of NSCLC patients treated with pemetrexed. However, it is unknown whether histology serves as a predictor for patients treated with other cytotoxic chemotherapies.

Here we will briefly review the role of gemcitabine as a treatment option for NSCLC, especially focusing on histological subtypes. Association of efficacy or safety with histological subtype will be discussed in the whole population and elderly patients.

Gemcitabine Combined with a Platinum Agent as First-Line Treatment

In the ECOG 1594 trial, the combination of gemcitabine plus CDDP was compared to other standard



doublets. This phase III trial demonstrated equivalent response rates among the three experimental arms, including docetaxel/CDDP, paclitaxel/CBDCA and gemcitabine/CDDP, compared with the control arm of paclitaxel/CDDP. In the groups of patients assigned to a regimen of gemcitabine/CDDP, gemcitabine at a dose of 1000 mg/m², was administered on days 1, 8, and 15 and CDDP, at a dose of 100 mg/m², was administered on day 1 of a four-week cycle. The median time to progression in the gemcitabine/CDDP group was 4.2 months and significantly better compared with that of the control arm, which was 3.4 months. Although there were no significant differences in the response rate or OS among the three experimental-treatment groups, there was a trend for an improvement of the 1 and 2-year survival in the gemcitabine/CDDP arm. Moreover, a meta-analysis was performed to evaluate the treatment effect of gemcitabine plus a platinum agent, either CDDP or CBDCA, on advanced NSCLC.²¹ Thirteen trials that met the inclusion criteria were selected if there was a comparison between gemcitabine plus platinum with any non-gemcitabine platinum-containing regimen. The protocol for the meta-analysis was finalized in August 2002 and individual patient data were obtained from the principal investigators for seven of the 13 trials. Overall, the median OS was 9.0 months for the gemcitabine-based treatment arms and 8.2 months for the comparator group and the estimated pooled HR for OS was 0.90 (95% CI: 0.84–0.96, $P < 0.001$) in favor of gemcitabine based regimens. Comparing the first- and second generation platinum-based comparator regimens, the HR was 0.84 showing a significant gain with gemcitabine-based regimens, while the differences were not significant when compared to the third-generation agent comparators. There was an also significant decrease in the risk of disease progression in favor of gemcitabine-platinum regimens, HR 0.88 (95% CI: 0.82–0.93, $P < 0.001$). Sub-group analysis indicated a significant PFS benefit for patients assigned to gemcitabine-platinum treatment even compared to third-generation agent plus platinum regimens. Thereafter, several trials which aimed to quantify the treatment effect of gemcitabine plus a platinum agent were performed, however, none of the trials showed a significant improvement of OS.

Efficacy of Gemcitabine-Platinum Chemotherapy by Histological Subtype

In ECOG 1594, a subgroup analysis to compare the efficacy in different histological subtypes was also conducted.²² Of 1139 eligible patients, adenocarcinoma was the most common histological type ($n = 647$; 56.8%), followed by squamous cell carcinoma ($n = 224$; 19.7%) and large cell carcinoma ($n = 74$; 6.5%). Not otherwise specified (NOS) cases were also included in this trial ($n = 194$; 17.0%). No difference in OS and PFS was observed among the four histological subtypes, regardless of treatment arm. There were no survival differences either among the four regimens of chemotherapy in each histological subtype (Table 1). In the squamous cell carcinoma and large cell carcinoma subgroups, patients treated with gemcitabine/CDDP appeared to have a longer OS compared to other regimens, while patients with adenocarcinoma in the paclitaxel/CDDP arm showed a better survival, although the difference was not statistically significant.

Other retrospective analyses of three-arm randomized trials comparing paclitaxel/CBDCA, gemcitabine/CDDP, and vinorelbine/CDDP explored the potential predictive and prognostic role of histology.²³ Pairwise comparisons of histological subtypes demonstrated a survival advantage for squamous cell carcinoma over adenocarcinoma ($P = 0.0021$), however, histology was not predictive of treatment effect for either OS or time to progression.

Other investigators assessed the literature on NSCLC of the last 25 years with a special emphasis on an association between histological subtype, and the efficacy of a specific chemotherapeutic agent.¹⁹ Of 408 publications identified, 11 reported a prognostic association between histology and clinical outcome, showing a relationship between more differentiated histology and better clinical outcome, and a prolonged survival of patients with adenocarcinoma or carcinomas other than squamous-cell carcinoma. Moreover, 7 studies suggested that histological subtype was a predictor of outcome in patients treated with specific cytotoxic chemotherapy regimens. However, the limitation of this analysis is that those data are derived from either an unplanned subset or retrospective analyses not aimed to examine the role of histology. Therefore, no clear conclusions could be drawn.

**Table 1.** Overall survival of histology subgroups in ECOG 1594.

	Chemotherapy	Adenocarcinoma	Squamous-cell carcinoma	Large-cell carcinoma	Others	P value
		N = 647	N = 224	N = 74	N = 194	
OS (months)	Gemcitabine/CDDP	8.1	9.4	9.7	7.9	0.63
	Paclitaxel/CDDP	9.1	6.9	6.1	6.0	0.09
	Docetaxel/CDDP	7.7	8.1	6.8	8.2	0.91
	Paclitaxel/CBDCA	7.6	9.3	8.3	6.9	0.37
	P value	0.39	0.18	0.39	0.82	

More recently, several trials have prompted a renewed interest in the impact of NSCLC histological subtype on efficacy outcomes. Especially, pemetrexed and bevacizumab containing regimens might have a greater impact on adenocarcinoma. Four trials identified a relation between pemetrexed treatment and histology, showing a better outcome in patients with non-squamous cell carcinoma.^{20,24–26}

Of these trials, a pivotal phase III trial comparing gemcitabine/CDDP with pemetrexed/CDDP in 1725 chemotherapy-naïve patients with advanced NSCLC was the first to prospectively assess survival differences according to histology (Table 2).²⁰ Patients were assigned to receive CDDP 75 mg/m² on day 1 plus gemcitabine 1250 mg/m² on days 1 and 8 or CDDP 75 mg/m² and pemetrexed 500 mg/m² on day 1 every 3 weeks, for up to 6 cycles. OS for pemetrexed/CDDP was noninferior to gemcitabine/CDDP (10.3 months for both arms; HR: 0.94; 95% CI: 0.84–1.05) and PFS was 4.8 months for the pemetrexed/CDDP, whereas PFS was 5.1 months for gemcitabine/CDDP (HR: 1.04 95% CI: 0.94–1.15). Response rates were subequal for the two arms (gemcitabine/CDDP: 28.2%, pemetrexed/CDDP: 30.6%). With respect to toxicity, for pemetrexed/CDDP, rates of grade 3–4 neutropenia, anemia, thrombocytopenia ($P < 0.001$), febrile neutropenia ($P = 0.002$) and alopecia ($P < 0.001$) were significantly lower, whereas the rate of grade 3–4 nausea ($P = 0.004$) was higher.

This trial also demonstrated different effects on survival of pemetrexed/CDDP against non-squamous (adenocarcinoma and large-cell carcinoma) versus squamous histology. Patients with adenocarcinoma ($n = 847$) and large-cell carcinoma ($n = 153$) treated with pemetrexed/CDDP showed a significantly better survival compared with those treated with gemcitabine/CDDP (12.6 vs. 10.9 months; HR: 0.84; 95% CI: 0.71–0.99; $P = 0.03$; 10.4 vs. 6.7 months, HR: 0.67; 95% CI: 0.48–0.96; $P = 0.03$, respectively). On the other hand, in patients with squamous cell histology, survival with pemetrexed/CDDP was inferior than with gemcitabine/CDDP ($[n = 473]$: 9.4 vs. 10.8 months; HR: 1.23; 95% CI: 1.00–1.51; $P = 0.05$). The OS for NOS ($n = 252$) did not show a significant difference in survival between the two arms (8.6 vs. 9.2 months; HR: 1.08; 95% CI: 0.81–1.45; $P = 0.586$). Considering histology of non-squamous cell carcinoma (adenocarcinoma and large cell carcinoma, $n = 1252$), pemetrexed/CDDP showed a significantly longer survival (11.0 vs. 10.1 months; HR: 0.84; 95% CI: 0.74–0.96; $P = 0.011$). Same survival difference according to histology has been found in three other trials performed with pemetrexed in advanced NSCLC in different settings.

On the other hand, two phase III trials which evaluated the effects of the angiogenesis inhibitor, bevacizumab, were conducted in patients with advanced

Table 2. Median overall survival (OS) and progression-free survival (PFS) for the patients with nonsquamous histology (adenocarcinoma plus large-cell) and patients with squamous-cell histology. HR, hazard ratio.

	Non squamous-cell carcinoma		Squamous-cell carcinoma	
	PFS (months)	OS (months)	PFS (months)	OS (months)
Gemcitabine/CDDP	4.7	10.4	5.5	10.8
Pemetrexed/CDDP	5.3	11.8	4.4	9.4
HR (95% CI)	0.90 (0.79–1.02)	0.81 (0.70–0.94)	1.36 (1.12–1.65)	1.23 (1.00–1.51)



NSCLC and showed a difference on the safety profile of treatment including bevacizumab by the difference of histological subtype. Bevacizumab, a humanized monoclonal anti VEGF, has shown clinical activity against several types of human cancer.

The use of bevacizumab in patients with squamous histology is excluded because of the increased risk of bleeding, which is potentially fatal for patients with squamous lung cancer, as demonstrated in a phase II study.²⁷ Therefore, ECOG conducted a randomized study in which 878 patients with recurrent or advanced non-squamous NSCLC were allocated to the paclitaxel/CBDCA alone group or to the bevacizumab group. Patients with brain metastases, clinically significant hemoptysis, uncontrolled hypertension, a history of thrombotic or hemorrhagic disorders, therapeutic anticoagulation, inadequate organ function or poor PS, were also excluded. The median OS of 12.3 months in the reference arm was significantly longer than the 10.3 months in the control arm. (HR: 0.79; 95% CI: 0.67–0.92; $P = 0.003$). There was also a significant PFS difference favoring patients in the bevacizumab arm compared with the control arm (6.2 months versus 4.5 months, HR: 0.66; 95% CI: 0.57–0.77; $P < 0.001$).

The gemcitabine, randomized, placebo-controlled, phase III study (Avastin in Lung Cancer: AVAiL trial) evaluated the addition of bevacizumab to gemcitabine/CDDP for advanced NSCLC.¹⁵ The primary end point was PFS and the eligibility criteria were almost similar to those of the ECOG4599 trial. Between February 2005 and August 2006, 1043 patients were randomized to receive gemcitabine/CDDP alone every 3 weeks for six cycles with placebo or with bevacizumab either 7.5 or 15 mg/kg every 3 weeks until disease progression. Although OS was not significantly increased with bevacizumab, the difference in PFS was statistically significant. The median PFS were 6.1, 6.7 and 6.5 months for chemotherapy alone, plus bevacizumab 7.5 mg/kg and 15 mg/kg, respectively

(HR: 0.75; 95% CI: 0.62–0.91; $P = 0.003$, HR: 0.82; 95% CI: 0.68–0.98; $P = 0.03$), while the median OS were 13.7, 14.1, and 14.5 months, respectively (HR: 0.94; 95% CI: 0.78–1.14; $P = 0.553$, HR: 0.97; 95% CI: 0.80–1.18; $P = 0.75$, respectively). The response rate to gemcitabine/CDDP with bevacizumab was significantly higher than chemotherapy alone (Table 3).

As of 2011, in advanced NSCLC, bevacizumab has been approved only in combination with carboplatin and paclitaxel by the U.S. Food and Drug Administration (FDA), whereas the European Medicines Agency has approved it for administration in combination with any platinum-based chemotherapy. A bevacizumab treatment observational cohort study (Avastin Registry: Investigation of Treatment Effects and Safety: ARIES) which was conducted in the U.S demonstrated that the most used regimen with bevacizumab was paclitaxel/CBDCA in 61.7% patients and only about 10% patients received gemcitabine based chemotherapy combined with bevacizumab.

Squamous cell carcinoma whose development is strongly associated with smoking habit is the second most common histological type of NSCLC in the current era. As previously explained, pemetrexed has shown lower efficacy against squamous cell carcinoma and the increased bleeding risk prevents treatment with bevacizumab. In metastatic NSCLC, standard chemotherapy regimens, including gemcitabine/CDDP, still remain the standard treatment for patients with squamous-cell carcinoma.

More recently, the TORCH trial was conducted in patients with unselected NSCLC. This was a phase III trial to investigate the efficacy of erlotinib as first-line therapy administered until progression followed by gemcitabine/CDDP, which compared gemcitabine/CDDP for 6 cycles followed at progression by erlotinib.²⁸ The first planned interim analysis was performed with blinded data after 340 deaths and a median follow-up of 8.3 months. An independent Data Monitoring Committee recommended

Table 3. Results of AVAiL trial.

	OS (months)	PFS (months)	Response rate (%)
Gemcitabine/CDDP/ bevacizumab (7.5 mg/kg) HR (95% CI)	13.6 0.92 (0.77–1.10)	6.7 0.75 (0.62–0.91)	34.1
Gemcitabine/CDDP/ bevacizumab (15 mg/kg) HR (95% CI)	13.4 1.02 (0.85–1.22)	6.5 0.82 (0.68–0.98)	30.4
Gemcitabine/CDDP	13.1	6.1	20.1



early termination, because the boundary of study interruption for inferiority was crossed. The OS (8.5 versus 12.0 months, HR: 1.40; 95% CI: 1.13–1.73) and PFS (2.2 versus 5.7 months) in the arm with erlotinib as first-line therapy were inferior compared with those in the standard arm. Analysis of subgroups also showed that the HR of deaths for non-adenocarcinoma (squamous, large-cell carcinoma or NOS) in 44.5% patients was 1.09 (95% CI: 0.82–1.45). In a previous phase III trial, erlotinib prolonged survival after first-line treatment and survival benefit was also observed in squamous-cell carcinoma.²⁹ However, the result of the TORCH trial indicated that EGFR-TKIs was not recommended for first-line chemotherapy for unselected histology of NSCLC, including squamous-cell carcinoma.

Monotherapy of Gemcitabine for Elderly or Unfit Patients

More than half of patients with NSCLC were 65 years old or older and approximately 30% to 40% of the cases were older than 70 years.³⁰ Increasing age is closely associated with deterioration of organ function and drug pharmacokinetics. Furthermore, advanced NSCLC patients older than 70 years often present co-morbidities, which affect functional status, general health and tumor symptoms, and have a poor PS. Therefore, single-agent chemotherapy used to be the first approach to be tested. The Elderly Lung Cancer Vinorelbine Italian study (ELVIS study), which was the first phase III randomized trial done in elderly patients with advanced NSCLC, demonstrated that mono-chemotherapy with vinorelbine improved survival and quality of life compared to best supportive care (median OS; 6.5 months versus 4.8 months, $P = 0.03$).³¹ Several phase II trials specifically have been designed for elderly patients to confirm the role of gemcitabine, because of its low toxicity profile. In patients over 70 years old, gemcitabine yielded overall response rates of 18%–38% and median OS of 6.8–9 months with acceptable toxicity.³²

The activity of gemcitabine in combination with other agents has also been investigated. Above all, the combination of gemcitabine and vinorelbine has been one of the most extensively studied non-platinum based combinations. However, a large randomized phase III trial which accrued about 700 elderly patients showed that the gemcitabine/vinorelbine combination was not more effective than single-agent chemotherapy

with vinorelbine or gemcitabine.³³ No statistically significant difference was observed among treatment arms from the viewpoints of response rate, PFS, OS and quality of life. Median OS was 36, 28 and 30 weeks for vinorelbine, gemcitabine and their combination, respectively (HR: 1.17; 95% CI: 0.95–1.44 comparing with vinorelbine, HR: 1.06; 95% CI: 0.86–1.29 versus treatment with gemcitabine).

More recently, weekly paclitaxel/CBDCA was compared with single agent chemotherapy in the context of a randomized phase III trial that involved elderly NSCLC patients.³⁴ Patients aged 70 to 89 years old, PS 0–2 and previously untreated Stage III or IV were randomized to receive either paclitaxel/CBDCA (paclitaxel: 90 mg/m² on days 1, 8 and 15, CBDCA : AUC 6 on day 1, every 4 weeks) or single-agent chemotherapy (either gemcitabine: 1150 mg/m², or vinorelbine: 30 mg/m² on days 1 and 8, every three weeks). Patients of both arms were treated with erlotinib after failure of the initial treatment. The planned sample size was 522 patients, however, the trial was prematurely closed after randomization of 451 patients when the second planned analysis showed that the reference arm was beneficial. A median OS of 10.3 for paclitaxel/CBDCA was significantly longer than that of 6.2 months for single-agent chemotherapy (HR: 0.64, 95% CI: 0.52–0.79, $P < 0.0001$). Median PFS was 6.1 and 3.0 months for patients in the doublet arm and single chemotherapy arm, respectively (HR: 0.55, 95% CI: 0.44–0.70, $P < 0.0001$). Early death was defined as death occurring less than three months from the start of treatment and occurred significantly less frequent with the combination therapy as compared to the single-agent chemotherapy group (17% versus 26%, $P = 0.025$), however, more treatment related deaths occurred in combination with the chemotherapy arm than with the control arm (6.6% versus 1.8%, $P = 0.035$).

Platinum-based chemotherapy is currently recommended as the standard approach for patients with advanced NSCLC if they can tolerate it. This was the first prospective phase III trial to investigate the reproducibility of this benefit even in elderly patients. The advantage of platinum-based chemotherapy in terms of OS was demonstrated; however, it must be noted that paclitaxel/CBDCA was associated with significantly increased toxicity of chemotherapy. Therefore, single-agent chemotherapy, such as gemcitabine or vinorelbine, should still be considered as a reasonable treatment choice for unfit elderly. As a problem to be



solved in the future, many efforts will be necessary to identify the elderly patients who can and those who cannot tolerate platinum-based doublet chemotherapy.

It is unclear whether the outcome will be different according to histological subtype, because so far no examinations have been performed in elderly or unfit patients with advanced NSCLC.

Conclusion

At present, most clinicians may consider pemetrexed/CDDP and bevacizumab containing regimens (with either paclitaxel/CBDCA or gemcitabine/CDDP) that seem to be excellent for patients with non-squamous-cell histology of NSCLC. The evaluation of treatment selection for patients with non-squamous histology must consider both the efficacy and safety profiles of these regimens. However, the information on gemcitabine regarding treatment of non-squamous-cell histology of NSCLC is limited. On the other hand, as for squamous cell carcinoma, gemcitabine-CDDP still remains one of the most effective regimens for first-line therapy. In elderly patients, although survival after platinum-based chemotherapy (paclitaxel/CBDCA) was demonstrated in a recent phase III trial, mono-agent chemotherapy, such as gemcitabine or vinorelbine, remains the treatment option for unfit elderly. To our knowledge, with respect to ethics and sex of patients, no precise data for differences of efficacy and toxicity has been demonstrated.

This review showed the current status of NSCLC treatment and the impact of histology on the clinical outcome of advanced NSCLC. Although, in late years, treatment response depending on the histological type is gaining attention due to the appearance of pemetrexed and bevacizumab, there have been very few studies on the response to gemcitabine by difference histological types of NSCLC. Is the difference of the histological type really as important as expected? When clinicians choose appropriate treatment according to the histological type, some problems will arise. At first it is not easy to accurately distinguish non-squamous from squamous type by pathological examination. It is more difficult for poorly differentiated carcinoma in particular, and it is often difficult for experienced pathologists to achieve consensus regarding a definite diagnosis. Therefore, a diagnostic tool that can allow a definite distinction of squamous carcinoma from non-squamous carcinoma is required.

Moreover, the only agent that showed a different effect on non-squamous carcinoma and squamous carcinoma was pemetrexed, but, pemetrexed is not invalidity in squamous cases at all. It is imagined that biomarker that provides for the effect of pemetrexed may exist surely.

At present, when the most appropriate chemotherapeutic regimen for an individual is being sought, not only the use of molecular markers but also histological types will play key roles when seeking personalized treatment for patients with advanced NSCLC. In the old days, morphology was regarded as the most important factor, but it seems that a therapy based on molecular biology will become more important in the near future. Therefore, specially designed prospective randomized trials and translational studies are warranted to find useful predictors of the efficacy of every chemotherapeutic agent.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ*. 1995;311:899-909.
2. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. *J Clin Oncol*. 2004;22:254-61.
3. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92-8.
4. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol*. 2001;19:3210-8.
5. Hertel LW, Boder GB, Kroin JS, et al. Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). *Cancer Res*. 1990;50:4417-2.
6. Mini E, Nobili S, Caciagli B, et al. Cellular pharmacology of gemcitabine. *Ann Oncol*. 2006;17 Suppl 5:v7-12.
7. Abbruzzese JL, Grunewald R, Weeks EA, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol*. 1991;9:491-8.
8. Csoka K, Liliemark J, Larsson R, et al. Evaluation of the cytotoxic activity of gemcitabine in primary cultures of tumor cells from patients with hematologic or solid tumors. *Semin Oncol*. 1995;22:47-53.
9. Von Hoff DD. Activity of gemcitabine in a human tumor cloning assay as a basis for clinical trials with gemcitabine. San Antonio Drug Development Team. *Invest New Drugs*. 1996;14:265-70.



10. Pollera CF, Ceribelli A, Crecco M, et al. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m²) and high-dose (875 mg/m²) levels. *Invest New Drugs*. 1997;15:115–21.
11. Abratt RP, Sandler A, Crino L, et al. Combined cisplatin and gemcitabine for non-small cell lung cancer: influence of scheduling on toxicity and drug delivery. *Semin Oncol*. 1998;25:35–43.
12. Rinaldi M, Crino L, Scagliotti GV, et al. A three-week schedule of gemcitabine-cisplatin in advanced non-small-cell lung cancer with two different cisplatin dose levels: a phase II randomized trial. *Ann Oncol*. 2000;11:1295–300.
13. Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 1999;17:12–8.
14. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2000;18:122–30.
15. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol*. 2009;27:1227–34.
16. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542–50.
17. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2009;362:2380–8.
18. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2009;11:121–8.
19. Hirsch FR, Varella J, Gerstl M, et al. The prognostic and predictive role of histology in advanced non-small cell lung cancer: a literature review. *J Thorac Oncol*. 2008;3:1468–81.
20. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543–51.
21. Le Chevalier T, Scagliotti G, Natale R, et al. Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. *Lung Cancer*. 2005;47:69–80.
22. Hoang T, Dahlberg S, Johnson JSD. Does Histology Predict Survival of Advanced Non-Small Cell Lung Cancer (NSCLC) Treated with Standard Platin-Based Chemotherapy? S493, abstr PD6.4.1. *J Thorac Oncol*. 2009.
23. Scagliotti GV, De Marinis F, Rinaldi M, et al. The role of histology with common first-line regimens for advanced non-small cell lung cancer: a brief report of the retrospective analysis of a three-arm randomized trial. *J Thorac Oncol*. 2009;4:1568–71.
24. Ohe Y, Ichinose Y, Nakagawa K, et al. Efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B12 in previously treated patients with non-small cell lung cancer. *Clin Cancer Res*. 2008;14:4206–12.
25. Peterson P, Park K, Fossella F, et al. Is pemetrexed more effective in patients with non-squamous histology? A retrospective analysis of a phase III trial of pemetrexed vs. docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). Abstract P#6521, The European Cancer Conference 2007 (ECCO 14). *Eur J Cancer*. 2007;5:363.
26. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009;374:1432–40.
27. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22:2184–91.
28. Gridelli C, Ciardiello R, Feld R, et al. International multicenter randomized phase III study of first-line erlotinib (E) followed by second-line cisplatin plus gemcitabine (CG) versus first-line CG followed by second-line E in advanced non-small cell lung cancer (aNSCLC): The TORCH trial (abstract #7508). *J Clin Oncol*. 2010;28:540s.
29. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123–32.
30. Gridelli C, Perrone F, Monfardini S. Lung cancer in the elderly. *Eur J Cancer*. 1997;33:2313–4.
31. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. *J Natl Cancer Inst*. 1999;91:66–72.
32. Perrone F, Gallo C, Gridelli C. Re: Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst*. 2002;94:1029–30; author reply 1030–1.
33. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst*. 2003;95:362–72.
34. Quiox EA, Oster J, Westeel V, et al. Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC).(abstract #0002). *J Clin Oncol*. 2010;28:946s.

Publish with Libertas Academica and every scientist working in your field can read your article

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

<http://www.la-press.com>