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Use of Gemcitabine in Non-Small Cell Lung Cancer Practice Guideline Report # 7-8 (Version 2.2002)

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ORIGINAL GUIDELINE: September 24 2002

This practice guideline report was published in 2003 as:

Ellis P, Mackay JA, Evans WK, and the Lung Cancer Disease Site Group. Use of gemcitabine in non-small-cell lung cancer. *Current Oncology* 2003;10:3-26.

It replaces an earlier version of the report that was completed in 1998 and published as: Evans WK, Kocha W, Gagliardi, A, Eady A, Newman T and the Provincial Lung Cancer Disease Site Group in conjunction with the Provincial Systemic Treatment Disease Site Group. The Use of Gemcitabine in Non-Small-Cell Lung Cancer. *Cancer Prevention & Control*, 1999; 3(1): 84-94.

SUMMARY

Guideline Question

What is the role of gemcitabine (Gemzar®), alone or in combination, in the treatment of patients with locally advanced or metastatic non-small cell lung cancer?

Target Population

These recommendations apply to adult patients with locally advanced or metastatic non-small cell lung cancer who are considered candidates for first-line or second-line chemotherapy.

Recommendations

- Cisplatin-gemcitabine can be recommended as one of several first-line chemotherapy regimen options for patients with locally advanced or metastatic non-small cell lung cancer.
- There is insufficient evidence to recommend adding a third drug to a gemcitabine-platinum combination.
- There is insufficient evidence to recommend routinely substituting carboplatin for cisplatin when combined with gemcitabine.
- At present there is insufficient evidence to recommend gemcitabine combined with a taxane as first-line therapy for non-small cell lung cancer.
- There is currently no evidence from randomized clinical trials that second-line chemotherapy with gemcitabine is associated with any improvement in survival. The routine use of gemcitabine as second-line chemotherapy cannot be recommended.

Qualifying Statements

- Other first-line chemotherapeutic options that have shown response rates and survival outcomes equivalent to the combination of cisplatin-gemcitabine include (i) cisplatin-vinorelbine, (ii) carboplatin-paclitaxel, (iii) cisplatin-paclitaxel, and (iv) cisplatin-docetaxel.
- Differences in scheduling and toxicity of these regimens should be the criteria used to choose between the different therapies.
- Preliminary evaluations of two different dose schedules of cisplatin-gemcitabine have been conducted in large randomized clinical trials: gemcitabine 1000 mg/m² on days 1, 8, and 15 and cisplatin 80 to 100 mg/m² every four weeks; gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 to 80 mg/m² every three weeks. There is insufficient evidence to recommend a specific schedule at this time.

Methods

Entries to MEDLINE (1966 through June 2002), CANCERLIT (1975 through June 2002), and Cochrane Library (2002, Issue 2) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1998 through 2001) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative Lung Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Lung Cancer Disease Site Group, which comprises medical and radiation oncologists, surgeons, a medical sociologist, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- There were ten randomized clinical trials of first-line chemotherapy comparing cisplatin-gemcitabine to other chemotherapy regimens, most commonly cisplatin-vinorelbine or a platinum-taxane combination. Response rates for the cisplatin-gemcitabine regimen varied from 22% to 67%, with a range in median survival from 8.1 to 9.8 months. Three large randomized trials, two of which were reported in abstract form only, detected similar response rates and survival for cisplatin-gemcitabine compared with cisplatin-vinorelbine, cisplatin-paclitaxel, carboplatin-paclitaxel, and cisplatin-docetaxel. The cisplatin-gemcitabine combination had a longer time to progression compared with cisplatin-paclitaxel in one study (4.2 versus 3.4 months, $p=0.001$), but this was not associated with any improvement in median survival (8.1 versus 7.8 months) or one-year survival (36% versus 31%).
- There were differences in the toxicity of cisplatin-gemcitabine in comparison with other regimens. Grade 3/4 thrombocytopenia and anemia generally occurred more often with cisplatin-gemcitabine. The difference was reported as significant for thrombocytopenia when compared with cisplatin-etoposide (55% versus 13%, $p=0.0457$), mitomycin-ifosfamide-cisplatin (38% versus 12%, $p<0.001$), cisplatin-vinorelbine (16% versus <1%, $p<0.05$), and cisplatin-paclitaxel (50% versus 6%, $p<0.05$) and for anemia when compared with cisplatin-paclitaxel (28% versus 13%, $p<0.05$). The frequency of neutropenia was more variable although it was more common with cisplatin-etoposide (76% versus 64%),

p=0.0009) and cisplatin-vinorelbine (44% versus 16%, p<0.05) than with cisplatin-gemcitabine.

- There were seven randomized trials of three drug regimens containing gemcitabine as first-line chemotherapy. Three trials by the Southern Italy Cooperative Oncology Group, which may include some of the same data, detected improved response rates and survival for cisplatin with gemcitabine and either vinorelbine or paclitaxel compared with two drug combinations. Three additional large randomized trials published in abstract form showed no benefit from three drug combinations compared to two drug combinations. One small randomized trial, also published in abstract form, detected a higher response rate for a triplet regimen of gemcitabine-carboplatin-paclitaxel compared to a doublet regimen of carboplatin-paclitaxel (61% versus 28%, p=0.017).
- Thirteen phase II trials of gemcitabine alone or in combination as second-line chemotherapy showed response rates of 3% to 33% and a median survival of 3.9 to 11 months.

Related Guidelines

Cancer Care Ontario Practice Guidelines Initiative's Practice Guideline Reports:

- 7-2: *Chemotherapy in stage IV (metastatic) non-small cell lung cancer*
- 7-5: *Use of vinorelbine in non-small cell lung cancer*
- 7-7-1: *The role of taxanes in first-line therapy of advanced non-small cell lung cancer* (currently under development)
- 7-7-2: *The role of single-agent docetaxel (Taxotere®) as a second-line treatment for advanced non-small cell lung cancer*
- 7-10: *The role of systemic chemotherapy in the treatment of advanced non-small cell lung cancer* (currently under development)

Authors and Acknowledgements

The Lung Cancer Disease Site Group would like to thank Dr. Peter Ellis for taking the lead in drafting and revising this practice guideline report. For a complete list of the members of the Lung Cancer Disease Site Group and the Practice Guidelines Coordinating Committee, please visit our web site at <http://www.cancercare.on.ca/ccopgi/>.

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*The Practice Guidelines Initiative is sponsored by:
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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FULL REPORT

I. QUESTION

What is the role of gemcitabine (Gemzar®), alone or in combination, in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)?

II. CHOICE OF TOPIC AND RATIONALE

Gemcitabine (2',2'-difluorodeoxycytidine) is a nucleotide analogue that is transported into the cell and phosphorylated. It is incorporated into DNA and appears to prevent the addition of other nucleotides to DNA by DNA polymerase (masked chain termination). Gemcitabine inhibits DNA repair because proofreading enzymes are unable to remove the gemcitabine nucleotide from DNA. Gemcitabine incorporation into DNA also results in depletion of the deoxycytidine triphosphate (dCTP) pools required for DNA synthesis. Pre-clinical tests have shown that cachexia can be prevented during treatment with gemcitabine. Based on a number of phase II trials demonstrating anti-tumour activity and minimal toxicity, gemcitabine was approved in Canada for use in the treatment of advanced stage NSCLC.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC) using methods of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by one member of the PGI Lung Cancer Disease Site Group (Lung DSG) and methodologists. Members of the Lung DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of gemcitabine in non-small cell lung cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

A practice guideline report on the use of gemcitabine in non-small cell lung cancer was originally completed in 1998 and published in *Cancer Prevention & Control* 1999; 3(1):84-94 (2). At that time, the Lung DSG recommended the use of single agent gemcitabine as first-line therapy only in situations where cisplatin-based chemotherapy or therapy with vinorelbine alone was not recommended. For patients who experienced serious adverse side effects with vinorelbine, which would preclude its continued use, gemcitabine was considered a reasonable alternative. No recommendations were made regarding the role of gemcitabine as adjuvant or induction chemotherapy in patients with stage I, II, or III disease or in combination with radiation therapy. Given the large amount of new data from phase III randomized clinical trials, the Lung DSG decided to completely revise and update its 1998 report. This document replaces the 1998 report.

Literature Search Strategy

MEDLINE (1966 through June 2002), CANCERLIT (1975 through June 2002), and the Cochrane Library (2002, Issue 2) databases were searched for evidence relevant to this practice guideline report. "Carcinoma, non-small cell lung" (Medical subject heading (MeSH)) was combined with each of the following phrases used as text words: "non small cell lung", "gemcitabine" and "gemzar". These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, and randomized controlled trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and conference proceedings of the American Society of Clinical Oncology (ASCO, 1998 through 2001) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>) were searched for existing evidence-based practice guidelines.

Inclusion criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Study conducted in patients with advanced stage non-small cell lung cancer;
2. Randomized clinical trial of gemcitabine as first-line chemotherapy, alone or in combination with other chemotherapy agents, compared to best supportive care (BSC) or another chemotherapy regimen;
3. Randomized or phase II clinical trials of gemcitabine, alone or in combination, as second-line chemotherapy;
4. The trial was fully published or presented in abstract form at ASCO. Abstracts from the ASCO meetings were included in the guideline because most key research findings are first presented at ASCO, which is the largest clinical oncology meeting in the world.
5. Response rate and/or survival data were reported.

Exclusion criteria

1. Letters and editorials;
2. Papers published in a language other than English;
3. Phase II clinical trials published in abstract form only.

Synthesizing the Evidence

It was decided not to pool the results of the randomized trials since the combination of chemotherapy regimens used was heterogeneous. As no two studies had the same treatment arms, a meaningful comparison of aggregate data could not be done.

IV. RESULTS

Literature Search Results

Table 1 summarizes the trials selected for inclusion in the systematic review of the evidence. In view of the large number of randomized controlled trials evaluating the role of gemcitabine as a first-line therapy for advanced NSCLC, phase II trials of these regimens were excluded. However, phase II trials have been included in this guideline if they addressed the role of gemcitabine as second-line chemotherapy for NSCLC. No relevant clinical practice guidelines were identified.

Table 1. Summary of trials included in this practice guideline report.

Gemcitabine regimens	Trial design	Published trials	Abstracts of trials	Reference numbers	Tables containing detailed information
First-line					
Single-agent	RCT	3	1	(3-6)	2a and 2b
Cisplatin containing doublet regimens	RCT	5	5	(7-16)	3a, 3b and 3c
Carboplatin containing doublet regimens	RCT	0	3	(17-19)	4a and 4b
Regimens comparing different doses or schedules	RCT	2	0	(20,21)	5a and 5b
Platinum-based triplet regimens	RCT	3	4	(22-28)	6a and 6b
Non-platinum containing regimens	RCT	3	1	(29-32)	7a and 7b
Second-line					
Single-agent	Non-randomized Phase II	4	0	(33-36)	8a and 8b
Combination regimens	Non-randomized Phase II	9	0	(37-45)	8c and 8d

Notes: RCT – randomized controlled trial

Of the 30 randomized trials included in the guideline, 14 were reported in abstract format only. For two of these, information reported in the guideline was obtained from both the abstract and the presentation provided on the web site of the American Society of Clinical Oncology (http://www.asco.org/asco/ascoMainConstructor/1,47468,_12|002328,00.asp) (15,16).

Two trials identified in the literature search (Frasci et al (46) and Georgoulas et al (47)) were not included in the guideline since they appeared to have been updated in later publications by Comella et al (22) and Androulakis et al (42), respectively.

Outcomes

First-line Chemotherapy

Single-agent Gemcitabine

The results of four randomized trials of gemcitabine as a single-agent are summarized in Tables 2a and 2b (3-6). Anderson et al (3) randomized 300 patients to gemcitabine plus BSC or BSC alone. There was no difference in either median survival (5.7 months vs 5.9 months) or one-year survival rates (25% vs 22%). The response rate to gemcitabine as a single-agent was 18.5% (95% confidence interval [CI], 13% to 26%). The toxicity of single-agent gemcitabine was low. Quality of life (QOL) was assessed utilizing the European Organization for Research and Treatment of Cancer (EORTC) quality of life assessment instruments – the Quality of Life Questionnaire and the Lung Cancer Module (QLQC30 and LC13, respectively). A significantly greater proportion of patients randomized to gemcitabine compared with BSC alone had sustained improvements in QOL after four weeks (22% vs 9%, $p=0.0014$) and, for patients treated with gemcitabine, QOL was better at two, four, and six months, although this difference was only statistically significant at four months (44% vs 25%, $p=0.015$).

Two additional studies randomized patients to single-agent gemcitabine or to cisplatin-etoposide (5,6). The response rates of gemcitabine in these two studies were similar to the response rate reported by Anderson et al (3). In addition, there was no evidence of any differences in response rates, time to disease progression, median survival, or one-year survival of single-agent gemcitabine compared with cisplatin-etoposide. Cisplatin-etoposide caused significantly more neutropenia and thrombocytopenia (5) as well as more nausea/vomiting and neurotoxicity (5,6). In the study by ten Bokkel Huinink et al (5), no differences in QOL were observed between the groups, although patients receiving cisplatin-etoposide experienced

significantly worse fatigue ($p < 0.05$), appetite loss ($p < 0.05$), nausea and vomiting ($p < 0.001$), and hair loss ($p < 0.001$) between baseline and two-month follow-up. In the same period, there was also a significant worsening of nausea and vomiting for patients receiving gemcitabine ($p < 0.05$). In one study reported in abstract format, Vansteenkiste et al (4) found gemcitabine to be comparable to cisplatin-vindesine with respect to response rate and median survival but superior with respect to toxicity and symptom control.

Table 2a. RCTs of single-agent gemcitabine: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Anderson 2000 (3)	G: G 1000mg/m ² d1,8,15 q4w + BSC	150/135*	0/59/41	PS: Karnofsky 60-90. No CNS metastases.
	BSC: any palliative treatment	150/NA*	0/61/39	
Vansteenkiste 2000 (4) (abstract)	G: G 1000mg/m ² d1,8,15 q4w	84/NR	NR	NA
	PVn: P 100mg/m ² d1 + Vn 3mg/m ² d1-g27 15 q4w	85/NR		
ten Bokkel Huinink 1999 (5) randomized phase II	G: G 1000mg/m ² d1,8,15 q4w	72/59 †	6/18/76	PS: Zubrod 0-2. No CNS metastases.
	PE: P 100mg/m ² d1 + E 100mg/m ² d1-3 q4w	75/62	8/17/75	
Perng 1997 (6) randomized phase II	G: G 1250mg/m ² d1,8,15 q4w	27/26	4/30/67	PS: Zubrod 0-2.
	PE: P 80mg/m ² d1 + E 80mg/m ² d1-3 q4w	26/24	4/15/81	

Notes: BSC – best supportive care, CNS – central nervous system, d – day, E – etoposide, G – gemcitabine, NA – not applicable, No. – number, NR – not reported, P – cisplatin, PS – performance status, pts – patients, q – every, RCT – randomized controlled trial, Vn – vindesine, w – week(s).

* Patients evaluable for quality of life = 99 G+BSC versus 102 BSC alone, response rate = 135 G+BSC, survival = 300 (intent-to-treat analysis).

† In the G and PE arms, 67 and 72 patients, respectively, qualified for the efficacy analysis.

Table 2b. RCTs of single-agent gemcitabine: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% (95% CI) *	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Anderson 2000 (3)	<u>G:</u> 25 total <u>BSC:</u> NR	18.5 (13-26) ITT: 16.7 NA	NR NR	5.7 (4.6-7.6) 5.9 (5.0-7.9) p=0.84 logrank	25 22	<u>Toxicity (G only)</u> Neutropenia 13%, thrombocytopenia 2%, N/V 9%. <u>QOL: EORTC QLQC30-LC13</u> Sustained improvements for G vs BSC.
Vansteenkiste 2000 (4) (abstract)	<u>G:</u> NR <u>PVn:</u> NR	21.8 (12.4-31.2) 24.3 (14.3-34.3)	<u>TTP</u> 2.1 3.0 p=0.59	7.9 6.1 p=0.13	NR	<u>Toxicity</u> PVn significantly higher than G for leukopenia (p=0.0004), neutropenia, N/V and alopecia (p<0.0001), neurotoxicity (p=0.02) and constipation (p=0.03). For G, thrombocytopenia, 2 pts. <u>QOL: Not assessed.</u> Symptom control improved for G vs PVn (p=0.03).
ten Bokkel Huinink 1999 (5) randomized phase II	<u>G:</u> 0/12 <u>PE:</u> 0/11	17.9 (9.6-29.2) ITT: 16.7 15.3 (7.9-25.7) ITT: 14.7 p=0.82	<u>TTP</u> 3.0 (2.2-3.9) 3.2 (2.1-4.8) p=ns	6.6 (4.9-7.3) 7.6 (5.4-9.3) p=ns	26 24	<u>Toxicity G vs PE</u> Neutropenia 8% vs 45% (p=0.0000003), anemia 7% vs 10% (p=ns), thrombocytopenia 1% vs 20% (p=0.003), N/V 11% vs 30%, grade 1/2 neurotoxicity 4% vs 10%. PRBCT 14% vs 23%, PIT 0% vs 4%. <u>QOL: EORTC QLQC30-LC13</u> No significant group differences.
Perng 1997 (6) randomized phase II	<u>G:</u> 0/5 <u>PE:</u> 0/5	19.2 (8.3-30.1) ITT: 18.5 20.8 (9.5-32.1) ITT: 19.2	<u>TTP</u> 8.1 7.8	8.5 11.1 p=0.65 logrank	NR	<u>Toxicity G vs PE</u> Leukopenia 4% vs 31%, thrombocytopenia 7% vs 8%, anemia 7% vs 15%, N/V 4% vs 35%, neurologic toxicity 0% vs 4%. FN 0% vs 15%. Blood transfusion 4pts vs 6pts. <u>QOL: Not assessed.</u>

Notes: BSC – best supportive care, CI – confidence interval, CR – complete response, E – etoposide, EORTC - European Organization for Research and Treatment of Cancer, FN – febrile neutropenia, G – gemcitabine, ITT – intention to treat, mos – months, NA – not applicable, NR – not reported, ns – not significant, N/V – nausea and vomiting, P – cisplatin, PFS – progression-free survival, PIT – platelet transfusion, PR – partial response, PRBCT – packed red blood cell transfusion, pts – patients, QLQC30-LC13 – Quality of life questionnaire - lung cancer subscale, QOL – quality of life, RCT – randomized controlled trial, RR – response rate, TTP – time to disease progression, Vn – vindesine, vs – versus.

* Response rate as reported by the authors. ITT values calculated by reviewer from published data.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with World Health Organization (WHO) grade 3/4 effects unless stated otherwise, and significance levels are reported where provided by the authors.

Gemcitabine-Platinum Doublets

The 13 randomized trials (five fully published, eight abstracts) comparing gemcitabine in combination with a platinum agent to another chemotherapy regimen are shown in Tables 3a through 3c and Tables 4a and 4b (7-19). The performance status (PS) of patients included in these studies has varied. None of the studies included patients with an Eastern Cooperative

Oncology Group (ECOG) PS >2, and some only included patients with an ECOG PS of 0 or 1. The dose of gemcitabine in these studies ranged from 1000 mg/m² to 1250 mg/m². Older studies administered gemcitabine on days 1, 8, and 15 every four weeks, whereas more recent studies have administered gemcitabine on days 1 and 8 every three weeks. In the 10 studies combining gemcitabine with cisplatin, the dose of cisplatin ranged from 70 mg/m² to 100 mg/m² with the lower doses generally administered in studies using gemcitabine in a three-week schedule. The response rates of gemcitabine-platinum across the 13 studies ranged from 22% to 67%. Only three of the 13 studies listed (9-11) were included in the previous Cancer Care Ontario gemcitabine practice guideline (2).

Gemcitabine-cisplatin doublets

Sandler et al (9) randomized 262 patients with NSCLC to cisplatin alone and 260 patients to cisplatin-gemcitabine given every four weeks. The combination of cisplatin-gemcitabine produced significantly higher response rates (30.4% vs 11.1%, p<0.0001), longer progression-free survival (median, 5.6 months vs 3.7 months, p=0.0013 logrank), longer median survival (9.1 months vs 7.6 months, p=0.004 logrank), and higher one-year survival (39% vs 28%). No difference in QOL was detected between the treatment groups using the Functional Assessment of Cancer Treatment – Lung (FACT-L) questionnaire.

Two studies compared cisplatin-gemcitabine with the older combination chemotherapy regimens of cisplatin-etoposide (PE) (10) and cisplatin-ifosfamide-mitomycin C (MIP) (11). Cisplatin-gemcitabine produced higher response rates than either PE (41% vs 22%, p=0.02), or MIP (38% vs 26%, p=0.029). However, no differences in survival or QOL were detected in either of these studies. More grade 3/4 neutropenia and febrile neutropenia was caused by PE, and both PE and MIP resulted in significantly more grade 3/4 alopecia, whereas cisplatin-gemcitabine caused significantly more thrombocytopenia than either PE or MIP.

Three large studies, two of which were reported in abstract form, compared cisplatin-gemcitabine to combinations including newer chemotherapy agents (7,15,16). Schiller et al (7) randomized 1207 patients to one of four regimen—cisplatin with paclitaxel as a 24-hour infusion, cisplatin-gemcitabine (four-week schedule), cisplatin-docetaxel, or carboplatin with paclitaxel as a three-hour infusion. The study was designed to compare each regimen independently to cisplatin-paclitaxel, and 1155 patients were eligible for analysis. There were no differences in objective response rates, with a range of 17% to 22% across the four treatment groups. There was a small but statistically significant increase in time to progression favouring cisplatin-gemcitabine compared with cisplatin-paclitaxel (4.2 months vs 3.4 months, p=0.001). There was no difference in either median survival or one-year survival between any of the regimens and cisplatin-paclitaxel. All four regimens had a high rate of grade 3/4 neutropenia (63% to 75%). Both the cisplatin-gemcitabine and carboplatin-paclitaxel regimens were associated with significantly fewer episodes of febrile neutropenia compared with cisplatin-paclitaxel, but cisplatin-gemcitabine resulted in significantly more anemia, thrombocytopenia, and renal toxic effects.

Table 3a. RCTs of gemcitabine combined with cisplatin: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Fully published				
Schiller 2002 (7)	PT: P 75mg/m ² d2 + T 135mg/m ² (24hr) d1 q3w	288/275	0/11/89	PS: ECOG 0-2 (amended to ECOG 0-1, October 1997). Stable CNS metastases allowed.
	PG: P 100mg/m ² d1 + G 1000mg/m ² d1,8,15 q4w	288/268	0/14/86	
	PD: P 75mg/m ² d1 + D 75mg/m ² d1 q3w	289/273	0/14/86	
	CbT: Cb AUC 6 d1 + T 225mg/m ² (3hr) d1 q3w	290/279 *	0/14/86	
Vokes 2001 (8) randomized phase II †	PG: P 80mg/m ² d1,22,43,64 + G 1250mg/m ² d1,8,22,29	187/180 total	IIIa/IIIb only	PS: 0-1 (scale not reported).
	PV: P 80mg/m ² d1,22,43,64 + V 25mg/m ² d1,8,15,22,29			
	PT: P 80mg/m ² d1,22,43,64 + T 225mg/m ² d1,22			
Sandler 2000 (9)	P: P 100mg/m ² d1 q4w	262/226	6/23/70	PS: Karnofsky 70-100.
	PG: P 100mg/m ² d1 + G 1000mg/m ² d1,8,15 q4w	260/214	7/26/67	
Cardenal 1999 (10)	PG: P 100mg/m ² d1 + G 1250mg/m ² d1,8 q3w	69/NR	0/48/52	PS: Karnofsky 60-100. No CNS metastases.
	PE: P 100mg/m ² d1 + E 100mg/m ² d1-3 q3w	66/NR	0/52/48	
Crino 1999 (11)	PG: P 100mg/m ² d2 + G 1000mg/m ² d1,8,15 q4w	155/155	0/21/79	PS: Zubrod 0-2. CNS metastases allowed if emergency treatment not required.
	MIP: P 100mg/m ² d2 + M 6mg/m ² d1 + I 3000mg/m ² d1 q4w	152/152	0/21/79	
Abstracts				
Berardi 2001 (12)	PG: P 80mg/m ² d15 + G 1000mg/m ² d1,8,15 q4w	37/NR ‡	IV only	PS: ECOG 0-2.
	G: G 1000mg/m ² d1,8,15 q4w	35/NR		
Chang 2001 (13) randomized phase II	PV: P 80mg/m ² d15 + V 20mg/m ² d1,8,15 q4w	40/34	IIIb/IV only	PS: ECOG 0-2.
	PG: P 80mg/m ² d15 + G 1000mg/m ² d1,8,15 q4w	36/29		
Cicenas 2001 (14) randomized phase II	PG: P 70mg/m ² d1 + G 1250mg/m ² d1,8 q3w x2	NR/15	IIIa/IIIb only	PS: WHO 0-2.
	PE: P 70mg/m ² d1 + E 120mg/m ² d1,2 q3w x 2	NR/13		
Scagliotti 2001 (15) §	PG: P 75mg/m ² d2 + G 1250mg/m ² d1,8 q3w	205/179	0/19/81	PS: ECOG 0-2. CNS metastases allowed.
	PV: P 100mg/m ² d1 + V 25mg/m ² q1w x 12 then biweekly q4w	201/157	0/19/81	
	CbT: Cb AUC 6 d1+ T 225mg/m ² d1 q3w	201/176	0/18/82	
Van Meerbeeck 2001 (16) §	PT: P 80mg/m ² d1 + T 175mg/m ² (3hr) d1 q3w	159/133	0/18/82	PS: 0-2 (scale not reported).
	PG: P 80mg/m ² d1 + G 1250mg/m ² d1,8 q3w	160/137	0/21/79	
	TG: T 175mg/m ² (3hr) d1 + G 1250mg/m ² d1,8 q3w	161/134	0/19/81	

Notes: AUC – area under curve, Cb – carboplatin, CNS – central nervous system, d – day, D – docetaxel, E – etoposide, ECOG – Eastern Cooperative Oncology Group, G – gemcitabine, hr – hour, I – ifosfamide, M – mitomycin, No. – number, NR – not reported, P – cisplatin, PS – performance status, pts – patients, q – every, RCT – randomized controlled trial, T – paclitaxel, V – vinorelbine, w – week(s), WHO – World Health Organization.

* Total number of patients randomized = 1207; results reported only for 1155 randomized and eligible patients.

† Study involved 2 cycles of induction chemotherapy at the doses reported in this table, followed by chemoradiation with radiation therapy to a total dose of 66 Gy and 2 cycles of attenuated doses of the induction chemotherapy.

‡ Overall, 70 patients were evaluable for survival and 59 for response.

§ Updated data obtained from ASCO 2001 Abstract Presentations (<http://www.asco.org/2001posters/#Lung>).

Table 3b. Fully published RCTs of gemcitabine combined with cisplatin: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR%* (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate % (95% CI)	Comments †
Schiller 2002 (7)	<u>PT</u> : <1%/21% <u>PG</u> : 1%/21% <u>PD</u> : <1%/17% <u>CbT</u> : <1%/16%	ITT: 21 ITT: 22 ITT: 17 ITT: 17 p=ns	<u>TTP</u> 3.4 (2.8-3.9) 4.2 (3.7-4.8) 3.7 (2.9-4.2) 3.1 (2.8-3.9) PT vs PG, p=0.001 logrank	7.8 (7.0-8.9) 8.1 (7.2-9.4) 7.4 (6.6-8.8) 8.1 (7.0-9.5)	31 (26-36) 36 (31-42) 31 (26-36) 34 (29-40) p=ns	<u>Toxicity PT vs PG vs PD vs CbT ‡</u> Neutropenia 75% vs 63% vs 69% vs 63%, anemia 13% vs 28%§ vs 15% vs 10%, thrombocytopenia 6% vs 50%§ vs 3% vs 10%, nausea 25% vs 37% vs 24% vs 9%§, vomiting 24% vs 35% vs 21% vs 8%§, hypersensitivity reactions 3% vs 0% vs 7%§ vs 2%, grade 3-5 renal toxic effects 3% vs 9%§ vs 3% vs 1%, grade 3 neuropathy 5% vs 9% vs 5% vs 10%. FN 16% vs 4%§ vs 11% vs 4%§. <u>QOL</u> : Not assessed.
Vokes 2001 (8) randomized phase II	NR	Reported no difference in RR	NR	17 (all 3 groups)	66 (all 3 groups)	<u>Toxicity PG vs PV vs PT (induction phase)</u> Neutropenia 48% vs 55% vs 48%. No other toxicity or QOL data reported.
Sandler 2000 (9)	<u>P</u> : 1/28 <u>PG</u> : 3/76	ITT: 11.1 ITT: 30.4 p<0.0001	<u>TTP</u> 3.7 (3.3-4.2) 5.6 (4.6-6.1) p=0.0013 logrank	7.6 (6.5-8.2) 9.1 (8.3-10.6)	28 39	<u>Toxicity P vs PG</u> Neutropenia 5% vs 57%, anemia 7% vs 25%, thrombocytopenia 4% vs 50%, nausea 21% vs 27%, vomiting 19% vs 23%, grade 3 neuromotor 3% vs 12%. FN 1% vs 5%. PRBCT 13% vs 38%, PIT <1% vs 20%. <u>QOL</u> : <u>FACT-L</u> No significant difference between P and PG.
Cardenal 1999 (10)	<u>PG</u> : 0/28 <u>PE</u> : 0/14	40.6 (29-53) ITT: 40.6 21.9 (13-34) ITT: 21.2 p=0.02	<u>TTP</u> 6.9 (5.0-8.1) 4.3 (3.5-4.7) p=0.01 logrank	8.7 (7.7-10.2) 7.2 (6.1-9.8)	32 26 p=0.19 logrank	<u>Toxicity PG vs PE ‡</u> Neutropenia 64% vs 76% (p=0.0009), thrombocytopenia 55% vs 13% (p=0.0457), anemia 22% vs 15%, N/V 39% vs 26%, alopecia 13% vs 51% (p<0.0001), neurotoxicity 0% vs 2%, grade 4 hemorrhage 3% vs 3%. FN 7% vs 12%. PRBCT 29% vs 21%, PIT 3% vs 8%. <u>QOL</u> : <u>EORTC QLQC30-LC13</u> No significant group differences.
Crino 1999 (11)	<u>PG</u> : 2/57 <u>MIP</u> : 1/39	ITT: 38 (31-46) ITT: 26 (19-33) p=0.029	<u>TTP</u> 5.0 4.8 p=ns	8.6 9.6 p=0.877 logrank	33 34	<u>Toxicity PG vs MIP</u> Neutropenia 40% vs 34%, anemia 31% vs 25%, thrombocytopenia 38% vs 12% (p<0.001), N/V 18% vs 22%, grade 3 alopecia 12% vs 39% (p<0.001) and neuropathy 0.7% vs 1.4%. FN 1% vs 0%. PRBCT 23% vs 19%, PIT 15% vs 3%. <u>QOL</u> : <u>EORTC QLQ-LC13</u> No significant difference between PG and MIP.

Notes: Cb – carboplatin, CI – confidence interval, CR – complete response, D – docetaxel, E – etoposide, EORTC – European Organization for Research and Treatment of Cancer, FACT-L – Functional Assessment of Cancer Treatment – Lung, FN – febrile neutropenia, G – gemcitabine, I – ifosfamide, ITT – intention to treat, mos – months, M – mitomycin, NR – not reported, ns – not significant, N/V – nausea and vomiting, P – cisplatin, PFS – progression-free survival, PIT – platelet transfusion, PR – partial response, PRBCT – packed red blood cell transfusion, QLQC30-LC13 – Quality of life questionnaire - lung cancer subscale, QOL – quality of life, RCT – randomized controlled trial, RR – response rate, T – paclitaxel, TTP – time to progression, vs – versus.

* Response rate provided as reported by authors. ITT data indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise, and significance levels are reported where provided by the authors.

‡ Toxicity reported as not significant unless otherwise stated.

§ p<0.05 vs PT arm of trial.

|| ITT values calculated by reviewer from published data.

Table 3c. Abstracts of RCTs of gemcitabine combined with cisplatin: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR%* (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Berardi 2001 (12)	PG: 0/9	ITT: 24	TTP 6.7	9.7	NR	Toxicity NR QOL: EORTC QLQ-LC13 Results not reported.
	G: 0/2	ITT: 6	3.5	9.7		
Chang 2001 (13) randomized phase II	PV: 0/9	26 ITT: 22 ‡	TTP 8	NR	NR	Toxicity PV vs PG Neutropenia 26% vs 9%, thrombocytopenia 0% vs 13%. QOL: Not assessed.
	PG: 0/10	34 ITT: 28 ‡ p=ns	8 p=ns			
Cicenas 2001 (14) randomized phase II	PG: 2/8	67	NR	NR	NR	Toxicity Reported as mild in both arms. QOL: Not assessed.
	PE: 0/6	46				
Scagliotti 2001 (15) §	PG: 0/62	ITT: 30	PFS 5.3	9.8	37	Toxicity PG vs PV vs CbT ¶ Neutropenia 16%# vs 44% vs 33%#, anemia 6% vs 7% vs 2%#, thrombocytopenia 16%# vs <1% vs 3%#, N/V 7%# vs 13% vs 1%#, alopecia 10% vs 11% vs 52%#, constipation 1%# vs 3% vs 0%#, grade 2/3 neuropathy 4% vs 7% vs 30%#. FN 1 vs 6 vs 2 cases. PRBCT 16% vs 21% vs 6%, PIT 8% vs 8% vs 2%. QOL: Not assessed.
	PV: 1/60	ITT: 30	4.6	9.5	37	
	CbT: 1/63	ITT: 32	5.5	9.9	43 p=ns	
Van Meerbeeck 2001 (16) §	PT: 0%/31%	ITT: 31 (24-38)	PFS 4.4	8.1	36	Toxicity PT vs PG vs TG Neutropenia 33% vs 43% vs 30%, anemia 3% vs 11% vs 4%, thrombocytopenia 1% vs 36% vs 6%, nausea 8% vs 13% vs 6%, vomiting 8% vs 13% vs 5%, motor neuro 3% vs 1% vs 3%, sensory 3% vs 2% vs 1%, grade 3/4 bleeding 1% vs 0% vs 1%. NF 1% vs 3% vs 2%. QOL: Not reported.
	PG: 1%/36%	ITT: 36 (29-44)	5.6	8.8	33	
	TG: 0%/27%	ITT: 27 (20-34) p=ns **	3.9 p=ns	6.9 PS 0-1 vs 2, 8.6 vs 3.3, p<0.0001	26 p=ns	

Notes: Cb – carboplatin, CI – confidence interval, CR – complete response, E – etoposide, EORTC – European Organization for Research and Treatment of Cancer, FN – febrile neutropenia, G – gemcitabine, ITT – intention to treat, mos – months, NF – neutropenic fever, NR – not reported, ns – not significant, N/V – nausea and vomiting, P – cisplatin, PFS – progression-free survival, PIT – platelet transfusion, PR – partial response, PRBCT – packed red blood cell transfusion, PS – performance status, QLQ-LC13 – Quality of life questionnaire - lung cancer subscale, QOL – quality of life, RCT – randomized controlled trial, RR – response rate, T – paclitaxel, TTP – time to progression, V – vinorelbine, vs – versus.

* Response rate provided as reported by authors. ITT data indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise, and significance levels are reported where provided by the authors.

‡ ITT values calculated by reviewer from published data.

§ Data also obtained from ASCO 2001 Abstract Presentations (<http://www.asco.org/2001posters/#Lung>).

|| Hematological toxicity reported as percentage of cycles, and non-hematological toxicity reported as percentage of patients.

¶ Toxicity reported as not significant unless otherwise stated.

p<0.001 vs PV arm of trial.

** Based on 470 eligible patients.

Scagliotti et al (15) randomized 607 patients to cisplatin-gemcitabine (three weekly), cisplatin-vinorelbine (four weekly), or carboplatin-paclitaxel (three weekly) and reported on 512 patients evaluable for analysis. There were no differences between treatment regimens in response rates (30%, 30%, 32%), progression-free survival (5.3 months, 4.6 months, 5.5 months), median survival (9.8 months, 9.5 months, 9.9 months), or one-year survival (37%, 37%, 43%). Cisplatin-vinorelbine was associated with significantly more neutropenia and nausea/vomiting than the other two regimens and more anemia than carboplatin-paclitaxel. The latter group experienced significantly more neuropathy and alopecia compared with cisplatin-vinorelbine. Significantly more thrombocytopenia was seen with cisplatin-gemcitabine than with cisplatin-vinorelbine, although bleeding complications were not reported, and the incidence of platelet transfusions was the same for both the cisplatin-gemcitabine and cisplatin-vinorelbine treatment arms (8%) compared to the carboplatin-paclitaxel arm (2%). This suggests that the difference in rate of thrombocytopenia between groups is not of great clinical significance.

Van Meerbeek et al (16) randomized 480 patients to cisplatin-paclitaxel (three hour), cisplatin-gemcitabine, or paclitaxel-gemcitabine. The dose of paclitaxel used in this study (175 mg/m²) was less than in most other studies, although a lower dose was used in one arm of the Schiller et al study (7). There were no statistically significant differences in any of the outcome parameters measured by Van Meerbeek et al (16). However, the paclitaxel-gemcitabine treatment arm had the lowest response rate, median survival, and one-year survival, and the cisplatin-gemcitabine treatment arm had the highest hematological toxicities. None of the last three studies reported any data on QOL (7,15,16).

In three small studies published in abstract form (12-14), response rates tended to be higher for gemcitabine-cisplatin combinations compared with gemcitabine alone (12), cisplatin-vinorelbine (13), or cisplatin-etoposide (14), although the levels of statistical significance of the results were not reported. Berardi et al (12) found that median survival was comparable for gemcitabine-cisplatin compared with gemcitabine alone. The two other studies did not report survival data, and toxicities were only provided by Chang et al (13), who detected a higher frequency of neutropenia with cisplatin-vinorelbine compared to cisplatin-gemcitabine (26% vs 9%), while thrombocytopenia occurred more frequently in the latter group (13% vs 0%).

Finally, Vokes et al (8) reported preliminary data on a Cancer and Leukemia Group B (CALGB) study of chemoradiation for stage III NSCLC. Patients were randomized to two cycles of induction chemotherapy with cisplatin-gemcitabine, cisplatin-vinorelbine, or cisplatin-paclitaxel. They then received concurrent chemoradiation with the same agents at reduced doses. In another report of this trial, Curran and Choy (48) indicated that the efficacy of the three treatment arms was similar; however, the sample size of the study suggested it was not powered for treatment comparisons during the chemotherapy induction phase.

Gemcitabine-carboplatin doublets

Three small randomized trials reported on gemcitabine-carboplatin combination chemotherapy (Tables 4a and 4b). Two of the trials compared gemcitabine-cisplatin to gemcitabine-carboplatin. Zatloukal et al (18) detected similar response rates for the two combinations, and Mazzanti et al (19) reported response rates of 45% and 29% and median survival of 13 months and 11 months for gemcitabine-cisplatin and gemcitabine-carboplatin, respectively. However, neither of these studies appeared to be adequately powered to make comparisons between the two chemotherapy combinations. Danson et al (17) reported preliminary findings of a trial comparing carboplatin-gemcitabine with either the MIC or MVP combinations. There were no differences in response rates; however, survival data were not reported.

Table 4a. RCTs of gemcitabine in combination with carboplatin: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Danson 2001 (17) (abstract)	CbG: Cb AUC 5 d1 + G 1000mg/m ² d1,8,15 q4w MVP or MIC, dose not defined	>300 entered in total 108 eligible/NR 124 eligible/NR	NR	PS: not reported.
Zatloukal 2001 (18) (abstract)	PG: P 80mg/m ² d1 + G 1200mg/m ² d1,8 q3w CbG: Cb AUC 5 d1 + G 1200mg/m ² d1,8 q3w	70 total NR/29 NR/34	0/26/74	PS: Karnofsky 70-100.
Mazzanti 2000 (19) randomized phase II (abstract)	PG: P 80mg/m ² + G 1200mg/m ² d1,8 q3w CbG: Cb AUC 5 d2 + G 1200mg/m ² d1,8 q3w	40/NR 34/NR Total of 63 evaluable for response	0/47/53	PS: ECOG 0-2.

Notes: AUC – area under curve, Cb – carboplatin, d – day, ECOG – Eastern Cooperative Oncology Group, G – gemcitabine, MIC – mitomycin, ifosfamide and cisplatin combination, MVP – mitomycin, vinblastine and cisplatin combination, No. – number, NR – not reported, P – cisplatin, PS – performance status, pts – patients, q – every, RCT – randomized controlled trial, w – week(s).

Table 4b. RCTs of gemcitabine in combination with carboplatin: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% * (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Danson 2001 (17) (abstract)	<u>CbG:</u> 1/32 <u>MVP/MIC:</u> 1/37	32.4 33	NR	NR	NR	<u>Toxicity</u> Significantly more hematological toxicity in CbG arm (p=0.006). <u>QOL:</u> Assessed but not reported.
Zatloukal 2001 (18) (abstract)	<u>PG:</u> 2/12 <u>CbG:</u> 2/14	48 47	NR	NR	NR	<u>Toxicity</u> Not reported according to treatment allocation. <u>QOL:</u> Not assessed.
Mazzanti 2000 (19) randomized phase II (abstract)	<u>PG:</u> 1/17 <u>CbG:</u> 0/10	ITT: 45 ITT: 29	NR	13 11	NR	<u>Toxicity PG vs CbG ‡</u> Neutropenia 8% vs 12%, anemia 3% vs 6%, thrombocytopenia 10% vs 18%, N/V 23% vs 3% (significant difference). <u>QOL:</u> Not reported.

Notes: Cb – carboplatin, CI – confidence interval, CR – complete response, G – gemcitabine, ITT – intention to treat, MIC – mitomycin, ifosfamide and cisplatin combination, mos – months, MVP – mitomycin, vinblastine and cisplatin combination, NR – not reported, N/V – nausea and vomiting, P – cisplatin, PFS – progression-free survival, PR – partial response, QOL – quality of life, RCT – randomized controlled trial, RR – response rate, TTP – time to progression, vs – versus.

* Response rate provided as reported by authors. ITT data indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise and significance levels are reported where provided by the authors.

‡ Toxicity reported as not significant unless otherwise stated.

Gemcitabine-Cisplatin Doses and Schedules

Two small studies addressed questions concerning the scheduling and dose of cisplatin-gemcitabine (Tables 5a and 5b). Ricci et al (20) randomized 82 patients to receive gemcitabine on day 1, 8, and 15 and cisplatin on either day 2 or day 15. There was significantly more anemia (8% vs 2%, p<0.05) and thrombocytopenia (15% vs 2%, p<0.01) when cisplatin was given on day 2. The progression-free, median, and one-year survival were greater in the group receiving cisplatin on day 15. This could be partly accounted for by the greater proportion of

stage IIIb patients in this group and the lower dose intensity of gemcitabine in the day 2 cisplatin group. The latter was due to dose reductions and omissions resulting from increased toxicity in this treatment arm.

Table 5a. RCTs comparing different schedules and doses of cisplatin combined with gemcitabine: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Ricci 2000 (20)	P ₂ G: P 80mg/m ² d2 + G 1000mg/m ² d1,8,15 q4w	42/NR	0/19/81	PS: ECOG 0-2. No CNS metastases.
	P ₁₅ G: P 80mg/m ² d15 + G 1000mg/m ² d1,8,15 q4w	40/NR	0/35/65	
Rinaldi 2000 (21) randomized phase II	P100G: P 100mg/m ² d2 + G 1000mg/m ² d1,8 q3w	47/45	0/24/76	PS: ECOG 0-2. CNS metastases allowed if RT not required.
	P70G: P 70mg/m ² d2 + G 1000mg/m ² d1,8 q3w	45/43	5/35/60	

Notes: CNS – central nervous system, d – day, ECOG – Eastern Cooperative Oncology Group, G – gemcitabine, No. – number, NR – not reported, P – cisplatin, PS – performance status, pts – patients, q – every, RCT – randomized controlled trial, RT – radiotherapy, w – week(s).

Table 5b. RCTs comparing different schedules and doses of cisplatin combined with gemcitabine: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% * (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Ricci 2000 (20)	<u>P₂G:</u> NR	ITT: 40.4 (25.5-55.3)	<u>PFS</u> 6 (3-9)	10 (7.0-12.5)	34	<u>Toxicity P₂G vs P₁₅G ‡ §</u> Leukopenia 6% vs 7%, anemia 8% vs 2% (p<0.05), thrombocytopenia 15% vs 2% (p<0.01), grade 1/2 renal toxicity 7% vs 2%. PRBCT 3%. <u>QOL: Not assessed.</u>
	<u>P₁₅G:</u> NR	ITT: 45 (29.5-60.5)	9 (4-14) p<0.02 logrank	17 (13.0-21.6) p<0.01 logrank	63	
Rinaldi 2000 (21) randomized phase II	<u>P100G:</u> 2/17	42 (27.8-56.7) ITT: 40.4	NR	15.4	53	<u>Toxicity P100G vs P70G ‡</u> Leukopenia 15% vs 4% (p=0.0019), anemia 7% vs 6%, thrombocytopenia 23% vs 17%, N/V 20% vs 7%, grade 1/2 nephrotoxicity 20% vs 7%. PRBCT 27% vs 12%, PIT 13% vs 2%. <u>QOL: Not assessed.</u>
	<u>P70G:</u> 0/20	47 (31.6-61.5) ITT: 44.4	NR	11.5 p=0.14 logrank	46	

Notes: CI – confidence interval, CR – complete response, G – gemcitabine, ITT – intention to treat, mos – months, NR – not reported, N/V – nausea and vomiting, P₂ – cisplatin day 2, P₁₅ – cisplatin day 15, P70 – cisplatin 70mg/m², P100 – cisplatin 100mg/m², PFS – progression-free survival, PIT – platelet transfusion, PR – partial response, PRBCT – packed red blood cell transfusion, QOL – quality of life, RCT – randomized controlled trial, RR – response rate, TTP – time to progression, vs – versus.

* Response rate provided as reported by authors. ITT data indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise, and significance levels are reported where provided by the authors.

‡ Toxicity reported as percentage of cycles.

§ Toxicity reported as not significant unless otherwise stated.

|| ITT values calculated by reviewer from published data.

Rinaldi et al (21) randomized 92 patients to gemcitabine (1000 mg/m²) on day 1 and day 8 every three weeks with either cisplatin 100 mg/m² or cisplatin 70 mg/m² on day 2. The detected response rates were similar (42% vs 47%), and there was no difference in survival; however the study appeared to be underpowered for this assessment. The higher dose of

cisplatin was associated with greater grade 3/4 leukopenia (15% vs 4%, $p=0.0019$), thrombocytopenia (23% vs 17%), and nausea/vomiting (20% vs 7%).

Triplet Regimens Containing Gemcitabine

Seven randomized trials of triplet regimens were identified (three fully published and four abstracts), and these are shown in Tables 6a and 6b (22-28). Three studies have been published by the Southern Italy Cooperative Oncology Group (22-24) and include a common treatment arm of cisplatin 50 mg/m², gemcitabine 1000 mg/m², and vinorelbine 25 mg/m² (PGV) on days 1 and 8 every three weeks. The response rates to this regimen range from 44% to 57%, with a median survival of approximately 12 months in all three studies. In one study (24), PGV was found to be superior to a non-standard regimen of cisplatin-epirubicin-vindesine-lonidamine (p -value not reported). However, randomization was halted after an interim analysis, and subsequent patients were enrolled only into the PGV arm of the trial, which could have led to a bias in patient selection. This study also reported greater improvement in QOL for patients receiving PGV (24), although only 57% and 41% of patients completed the QOL assessments for the PGV and comparison groups, respectively. In addition, better PS (0 vs 1) resulted in a higher response rate in the PGV treatment arm (67% vs 54%) and longer median survival in both the PGV (14.3 months vs 10.6 months) and non-standard (8.3 months vs 5.1 months) treatment arms. However, it is not clear that the three Italian trials were conducted separately, raising questions about the validity of the study findings.

Three additional studies were reported in abstract form at ASCO 2001 (25-27) and one at ASCO 2000 (28). Alberola et al (25) randomized 562 patients to receive cisplatin-gemcitabine with or without vinorelbine every three weeks, or gemcitabine-vinorelbine followed by vinorelbine-ifosfamide. The response rates to cisplatin-gemcitabine (PG) were almost identical to PGV (41% vs 40%) and both were greater than the regimen including ifosfamide (24%) with similar median survival (9.4 months vs 7.8 months vs 10.3 months, respectively) for all three groups. The rate of febrile neutropenia was greater for PGV compared to PG or the ifosfamide combination (22% vs 6% vs 7%, respectively), and the ifosfamide regimen had the lowest rates of both neutropenia and thrombocytopenia.

Edelman et al (26) randomized 204 patients to one of two sequential regimens, either carboplatin-gemcitabine for three cycles followed by paclitaxel for three cycles, or cisplatin-vinorelbine for three cycles followed by docetaxel for three cycles. Response rates (21% vs 28%), median survival (8.5 months vs 8.6 months), and one-year survival (32% vs 31%) were similar in both treatment groups. More grade 3/4 thrombocytopenia was seen with the regimen containing gemcitabine compared to the other regimen (38% vs 3%).

In a four-arm study, Thompson et al (27) detected no significant differences in response rate, progression-free survival, or overall survival in a comparison of triplet regimens of carboplatin-paclitaxel with either gemcitabine or vinorelbine and doublet regimens of gemcitabine with either paclitaxel or vinorelbine. Toxicity was similar for all treatments with the exception of febrile neutropenia, which was more common for patients receiving either carboplatin-paclitaxel-vinorelbine, or gemcitabine-paclitaxel. In a smaller study of 71 patients, Hussein et al (28) detected a significantly higher response rate and a longer median survival with the combination of carboplatin-paclitaxel when gemcitabine was included. Thrombocytopenia and neutropenia were both higher for the gemcitabine regimen.

Table 6a. RCTs of platinum-based triplet regimens containing gemcitabine: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Comella 2001 (22)	PG: P 100mg/m ² d1 + G 1000mg/m ² d1,8,15 q4w	NR/112	0/40/60	PS: ECOG 0-1. CNS metastases allowed.
	PGV: P 50mg/m ² + G 1000mg/m ² + V 25mg/m ² d1,8 q3w	NR/117	0/46/54	
	PGT: P 50mg/m ² + G 1000mg/m ² + T 125mg/m ² (24hr) d1,8 q3w	NR/114	0/42/58	
		360 total/343		
Comella 2000 (23) randomized phase II	PGV: P 50mg/m ² + G 1000mg/m ² + V 25mg/m ² d1,8 q3w	NR/60	0/43/57	PS: ECOG 0-1. Asymptomatic CNS metastases allowed.
	PG: P 100mg/m ² d1 + G 1000mg/m ² d1,8,15 q4w	NR/60	0/43/57	
	PV: P 120mg/m ² d1,29 q6w + V 30mg/m ² q1w x 10	NR/60	0/40/60	
Comella 1999 (24) randomized phase II	PGV: P 50mg/m ² + G 1000mg/m ² + V 25mg/m ² d1,8 q3w	89/87	0/47/53	PS: WHO 0-1 or Karnofsky 70-100. No CNS metastases.
	PEpiVnL: P 80mg/m ² + Epi 80mg/m ² + Vn 3mg/m ² d1 q4w + L 150mg po tid	56/54	0/41/59	
Alberola 2001 (25) (abstract)	PG: P 100mg/m ² d1+ G 1250mg/m ² d1,8 q3w	Total: 562/410	Total: 0/21/79	PS: 0-2. Asymptomatic CNS metastases allowed.
	PGV: P 100mg/m ² d1 + G 1000mg/m ² d1,8 + V 25mg/m ² d1,8 q3w			
	GV-IV: G 1000mg/m ² + V 30mg/m ² d1,8 q3w followed by I 3gm/m ² d1 + V 30mg/m ² d1,8			
Edelman 2001 (26) randomized phase II (abstract)	CbG-T: Cb AUC 5.5 d1 + G 1000mg/m ² d1,8 q3w x 3 then T 225mg/m ² q3w x 3	Total: 204/126	0/20/80	PS: SWOG 0-1.
	PV-D: P 100mg/m ² d1 + V 25mg/m ² d1,8 q3w x 3 then D 75-100mg/m ² q3w x 3	148 evaluable for toxicity		
Thompson 2001 (27) randomized phase II (abstract)	CbTG: Cb AUC 5 d1 + T 200mg/m ² d1 + G 1000mg/m ² d1,8 q3w	Total: 243/205	IIIb/IV only	PS: 0-2.
	CbTV: Cb AUC 6 d1 + T 200mg/m ² d1 + V 20mg/m ² d1,8 or 15 q3w			
	TG: T 200mg/m ² q3w + G 1000mg/m ² d1,8,15			
	GV: G 1000mg/m ² + V 20mg/m ² d1,8,15 q4w			
Hussein 2000 (28) (abstract)	CbT: Cb AUC 6 + T 225mg/m ² d1 q3w	71 total NR/25	NR	PS: ECOG 0-1. No CNS metastases.
	CbTG: Cb AUC 5 + T 200mg/m ² d1 q3w + G 1000mg/m ² d1,8 q3w	NR/28		

Notes: AUC – area under curve, Cb – carboplatin, CNS – central nervous system, D – docetaxel, d – day, ECOG – Eastern Cooperative Oncology Group, Epi – epirubicin, G – gemcitabine, hr – hour, I – ifosfamide, L – lisdamine, No. – number, NR – not reported, P – cisplatin, po – by mouth, PS – performance status, pts – patients, q – every, RCT – randomized controlled trial, SWOG – Southwest Oncology Group, T – paclitaxel, tid – three times daily, V – vinorelbine, Vn – vindesine, w – week(s), WHO – World Health Organization.

Table 6b. RCTs of platinum-based triplet regimens containing gemcitabine: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% * (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate % (95% CI)	Comments †
Comella 2001 (22)	PG: 0/31 PGV: 4/48 PGT: 5/50	28 44 48 p<0.02, PG vs PGV/T	TTP 4.4 5.5 6.7 p<0.002, PG vs PGT	8.8 11.8 11.8 p<0.05	NR	Toxicity PG vs PGV vs PGT ‡ Neutropenia 40% vs 43% vs 48%, anemia 12% vs 14% vs 21%, thrombocytopenia 35% (p<0.05 §) vs 25% vs 20%, N/V 28% (p<0.05 §) vs 14% (p<0.01) vs 15%, grade 3 fatigue 14% (p<0.01 §) vs 13% vs 32%, grade 1/2 neuropathy 5% (p<0.01 §) vs 17% (p<0.05) vs 38%. FN 3% vs 5% vs 7%. QOL: Not reported.
Comella 2000 (23) randomized phase II	PGV: 2/26 PG: 0/18 PV: 0/15	ITT: 47 (34-60) ITT: 30 (19-43) ITT: 25 (15-38)	NR	11.8 9.7 8.1	45 40 34	Toxicity PGV vs PG vs PV ‡ Neutropenia 45% (p<0.001#) vs 40% vs 75%, anemia 15% vs 13% vs 25%, thrombocytopenia 17% vs 30% vs 20%, N/V 15% (p<0.0001#) vs 30% vs 50%, grade 1/2 neuropathy 18% vs 3% vs 20%. QOL: Modified LCSS - not reported.
Comella 1999 (24) randomized phase II	PGV: 4/46 PEpiVnL: 2/18	57 (46-68) ITT: 56 37 (24-51) ITT: 36 ¶	PFS 7.4 4.2	11.5 7.6	48 2-yr, 19 29 2-yr, 0	Toxicity PGV vs PEpiVnL Neutropenia 46% vs 22%, thrombocytopenia 14% vs 11%, anemia 10% vs 13%, N/V 5% vs 13%, grade 1/2 neuropathy 13% vs 11%. NF 9 vs 2 cases. PRBCT & PIT - same both arms. QOL: Modified LCSS. Assessed in 74% of pts - improvement for 59% PGV vs 39% PepiVnL.
Alberola 2001 (25) (abstract)	PG: NR PGV: NR GV-IV: NR	41 40 24.1	NR	9.4 7.8 10.3 ††	NR	Toxicity PG vs PGV vs GV-IV ** Neutropenia 26% vs 30% vs 19%, thrombocytopenia 18% vs 23% vs 7%. N/V, neuropathy, and renal toxicity similar in all arms. NF 6% vs 22% vs 7%. QOL: Not assessed.
Edelman 2001 (26) randomized phase II (abstract)	CbG-T: NR PV-D: NR	21 (12-32) 28 (16-42)	PFS 4.3 4.5	8.5 8.6	32 (21-43) 31 (18-44) p=ns	Toxicity CbG-T vs PV-D ** Neutropenia 48% vs 68%, anemia 15% vs 15%, thrombocytopenia 38% vs 3%, grade 2/4 N/V 10% vs 42%. Bleeding (no grade given) 2% vs 0%. PRBCT 26% vs 15%, PIT 11% vs 0%. QOL: Not reported.
Thompson 2001 (27) randomized phase II (abstract)	CbTG: NR CbTV: NR TG: NR GV: NR	34 42 29 29	PFS 4 4.6 5.2 5.8	10.3 5 7.8 11.3	38 32 40 49 p=ns	Toxicity Similar in all arms except more febrile neutropenia in CbTV (11pts) and TG (8pts) than CbTG (2pts) and GV (4pts). QOL: Not assessed.
Hussein 2000 (28) (abstract)	CbT: 0/7 CbTG: 2/15	28 61 p=0.017	NR	Actuarial: 7.8 10.5 p=ns	NR	Toxicity CbT vs CbTG ‡ Neutropenia 42% vs 58%, thrombocytopenia 4% vs 42% (p=0.001), grade 3 neuropathy 15% vs 3%. PIT 1 pt vs 6 pts. QOL: Not assessed.

Notes: Cb – carboplatin, CI – confidence interval, CR – complete response, D – docetaxel, Epi – epirubicin, FN – febrile neutropenia, G – gemcitabine, I – ifosfamide, ITT- intention to treat, L – lonidamine, LCSS – Lung Cancer Symptom Scale, mos – months, NF – neutropenic fever, NR – not reported, ns – not significant, N/V – nausea and vomiting, P – cisplatin, PFS – progression-free survival, PIT – platelet transfusion, PR – partial response, PRBCT – packed red blood cell transfusion, pt(s) – patient(s), QOL – quality of life, RCT – randomized controlled trial, RR – response rate, T – paclitaxel, TTP – time to progression, V – vinorelbine, Vn – vindesine, vs – versus, yr - year.

* Response rate provided as reported by authors. ITT data indicated where available.
† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise and significance levels are reported where provided by the authors.
‡ Toxicity reported as not significant unless otherwise stated.
§ PG vs PGT
|| PG vs PGV
PV vs PGV
¶ ITT values calculated by reviewer from published data.
†† Median survival reported for 210 patients with at least 12 months from inclusion date.
** Abstract does not state if toxicity is reported by cycle or by patient.

Non-platinum-containing Regimens

One randomized trial compared gemcitabine-vinorelbine (GV) with vinorelbine alone (Tables 7a and 7b). Frasci et al (31) randomized a total of 120 patients and obtained a non-significant increase in response rate (22% vs 15%) in the GV regimen over the single-agent treatment arm. Median survival for the combination was significantly prolonged compared with vinorelbine alone (6.7 months vs 4.2 months, $p < 0.01$). More patients randomized to GV showed improvements in QOL (25% vs 17%) at approximately two months or temporary improvements in symptoms during treatment (26% vs 15%).

Three studies have compared gemcitabine-taxane combinations with platinum-taxane regimens (Tables 7a and 7b). Kosmidis et al (32) and Chen et al (29) randomized 329 and 90 patients, respectively, to paclitaxel with either carboplatin or gemcitabine, while Georgoulis et al (30) randomized 441 patients to docetaxel with either cisplatin or gemcitabine. The gemcitabine-taxane combinations had similar response rates and survival in all three studies, and no significant differences between the treatment groups were reported within studies.

Table 7a. RCTs of non-platinum regimens containing gemcitabine: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Fully published				
Chen 2002 (29) randomized phase II	TCb: T 175mg/m ² d1 + Cb AUC 7 d1 q3w	45/45	0/38/62	PS: WHO 0-2. No CNS metastases.
	TG: T 175mg/m ² d1 + G 1000mg/m ² d1,8 q3w	45/45	0/40/60	
Georgoulis 2001 (30)	PD: P 80mg/m ² d2 + D 100mg/m ² d1 q3w + G-CSF	219/205	0/37/63	PS: WHO 0-2. CNS metastases allowed.
	GD: G 1100mg/m ² d1,8 + D 100mg/m ² d8 q3w + G-CSF	222/201	0/35/65	
Frasci 2000 (31)	GV: G 1200mg/m ² + V 30mg/m ² d1,8 q3w	60/42	0/40/60	PS: ECOG 0-2. Asymptomatic CNS metastases allowed.
	V: V 30mg/m ² d1,8 q3w	60/31*	0/42/58	
Abstracts				
Kosmidis 2000 (32)	TCb: T 200mg/m ² d1 + Cb AUC 6 d1 q3w	165/123	NR	PS: WHO 0-2.
	TG: T 200mg/m ² d1 + G 1000mg/m ² d1,8 q3w	164/130		

Notes: AUC – area under curve, Cb – carboplatin, CNS – central nervous system, D – docetaxel, d – day, ECOG – Eastern Cooperative Oncology Group, G – gemcitabine, G-CSF – granulocyte colony stimulating factor, No. – number, NR – not reported, P – cisplatin, PS – performance status, pts – patients, q – every, RCT – randomized controlled trial, T – paclitaxel, V – vinorelbine, w – week(s), WHO – World Health Organization.

* Of 152 enrolled patients, 32 were excluded from the reported analysis—21 had less than follow-up, 6 were ineligible, and there were insufficient data for 5 patients.

Table 7b. RCTs of non-platinum regimens containing gemcitabine: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% * (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Fully published						
Chen 2002 (29) randomized phase II	<u>TCb:</u> 3/15	40 (25.7-54.3)	<u>TTP</u> 5.7	14.1 (6.3-21.8)	51	<u>Toxicity TCb vs TG</u> Leukopenia 13% vs 9%, anemia 16% vs 13%, thrombocytopenia 11% vs 0% (p=0.021), N/V 2% vs 0%, grade 3 neuropathy 4% vs 4%. <u>QOL:</u> Not formally assessed. Symptom improvement reported for pain control 32% vs 45%, dyspnea 67% vs 48%, cough 62% vs 60%, hemoptysis 80% vs 67%.
	<u>TG:</u> 0/18	40 (25.7-54.3)	6.2	12.6 (7.6-17.5)	53	
Georgoulas 2001 (30)	<u>PD:</u> 3/68	34.6 (26.2-38.6) ITT: 32.4	<u>TTP</u> 8	10	42 2-yr, 8	<u>Toxicity PD vs GD §</u> Neutropenia 34% vs 22% (p=0.01), anemia 5% vs 2%, thrombocytopenia 2% vs 4%, N/V 10% vs 2% (p=0.001), diarrhea 10% vs 3% (p=0.001), grade 2/4 neuropathy 7% vs 5%. FN 14% vs 11%. <u>QOL:</u> Not assessed.
	<u>GD:</u> 2/65	33.3 (24.1-36.2) ITT: 30.2 ‡ p=ns	9 p=ns	9.5	39 2-yr, 8 p=0.98	
Fraci 2000 (31)	<u>GV:</u> 0/13	ITT: 22 (12-34)	NR	6.7	Projected 30	<u>Toxicity GV vs V</u> Neutropenia 38% vs 28%, anemia 7% vs 2%, thrombocytopenia 13% vs 8%, N/V 15% vs 8%, grade 1/2 neuropathy 13% vs 10%. PRBCT overall 5. <u>QOL:</u> Modified LCSS, improved at 2 mos, 25% vs 17%. Temporary symptom improvement during treatment 26% vs 15%.
	<u>V:</u> 0/9	ITT: 15 (7-27)		4.2	13 p<0.01	
Abstracts						
Kosmidis 2000 (32)	<u>TCb:</u> 2.8%/25.9%	28.7 (21-36)	<u>TTP</u> 6.9 (5.6-8.1)	10.7 (7.7-13.6)	41	<u>Toxicity TCb vs TG </u> Neutropenia 10% vs 11%, anemia 4% vs 2%, thrombocytopenia 1% vs 1%, grade 3 neuropathy 5% vs 6%. <u>QOL:</u> not assessed. PS 0-1 prognostic factor for response (p=0.004) and 1-yr survival (p=0.003).
	<u>TG:</u> 4.7%/31.8%	36.5 (29-44) p=0.17	7.2 (5.7-8.7) p=0.47	12.3 (10.3-14) p=0.47	51	

Notes: Cb – carboplatin, CI – confidence interval, CR – complete response, D – docetaxel, FN – febrile neutropenia, G – gemcitabine, ITT – intention to treat, LCSS – Lung Cancer Symptom Scale, mos – months, NR – not reported, ns – not significant, N/V – nausea and vomiting, P – cisplatin, PFS – progression-free survival, PR – partial response, PRBCT – packed red blood cell transfusion, PS – performance status, QOL – quality of life, RCT – randomized controlled trial, RR – response rate, T – paclitaxel, TTP – time to progression, V – vinorelbine, vs – versus, yr – year.

* Response rate provided as reported by authors. ITT indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise and significance levels are reported where provided by the authors.

‡ ITT values calculated by reviewer from published data.

§ Toxicity reported as not significant unless otherwise stated.

|| Abstract does not state if toxicity is reported by cycle or by patient.

Second-line Chemotherapy

There were thirteen fully published phase II studies of gemcitabine as second-line chemotherapy for NSCLC (33-45). This situation is likely to change over the next 12 months, as several studies were reported in abstract form at ASCO 2001. Four studies reported the results of treatment with single-agent gemcitabine as second-line chemotherapy and are shown in Tables 8a and 8b (33-36). Response rates ranged from 5% to 20%, with median survivals of 3.9 to 7.8 months. These differences may be explained by differences in the disease characteristics of the study populations. Quality of life was assessed in two studies. Gridelli et al used the EORTC QLQC30 and LC13 questionnaires and obtained significant improvement in cough with second-line therapy (36). Gillenwater et al reported improvement of ≥ 4 points in the trial outcome index of the FACT-L for eight of 21 patients completing questionnaires after two cycles of treatment (33).

Table 8a. Phase II trials of single-agent gemcitabine as second-line chemotherapy: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Gillenwater 2000 (33)	G 1250mg/m ² d1,8,15 q4w	31/23	0/0/100	PS: ECOG 0-2. First-line CT: CbT (24 pts), EP (4 pts), CbV (1pt), CbVM (1 pts), T (1 pt). Median time for first-line to second-line treatment: 14w.
Sculier 2000 (34)	G 1000mg/m ² d1,8,15 q4w	77/65	0/4/96	PS: Karnofsky ≥ 60 . First-line CT: platinum based.
Crino 1999 (35)	G 1000mg/m ² d1,8,15 q4w	83/83	1/40/59	PS: ECOG 0-2. Stable CNS metastases. First-line CT: At least 1 platinum-based. Median time for first-line to second-line treatment: 22w.
Gridelli 1999 (36)	G 1000mg/m ² d1,8,15 q4w	30/12	0/10/90	PS: ECOG 0-2. First-line CT: platinum-based. Median time for first-line to second-line treatment: 21w.

Notes: Cb – carboplatin, CNS – central nervous system, CT – chemotherapy, d – day, E- etoposide, ECOG – Eastern Cooperative Oncology Group, G – gemcitabine, M – mitomycin, No. – number, P – cisplatin, PS – performance status, pt(s) – patients, q – every, T – paclitaxel, V – vinorelbine, w – week(s).

Nine small studies involved second-line treatment with gemcitabine in combination with docetaxel (four studies), paclitaxel (two studies), or vinorelbine (three studies) (Tables 8c and 8d). Response rates ranged from 3% to 33% with median survival times ranging from 5.5 to 11 months. Comparisons between different combinations have not been made, given the nature of phase II studies. Quality of life was not formally assessed in any of these studies, but Kakolyris et al (38) indicated that chemotherapy did not result in significant symptomatic improvement.

Table 8b. Phase II trials of single-agent gemcitabine as second-line chemotherapy: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% * (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Single-agent						
Gillenwater 2000 (33)	0/2	ITT: 6.5	NR	5.1 (4.2-7.4)	16	<u>Toxicity</u> (% of 212 doses delivered) Neutropenia 8%, thrombocytopenia 3%, anemia 3%. <u>QOL</u> : FACT-L Improvement at 2m in 8 of 21 evaluated pts (38%).
Sculier 2000 (34)	0/4	ITT: 5.2 (0-10.8)	NR	3.9	NR	<u>Toxicity ‡</u> Leukopenia 5%, thrombopenia 16%. <u>QOL</u> : Not assessed.
Crino 1999 (35)	0/16	ITT: 19.28 (10.79-27.77)	NR	7.8	45	<u>Toxicity</u> Leukopenia 7%, grade 3 thrombocytopenia 7% and N/V 1%. <u>QOL</u> : Not assessed.
Gridelli 1999 (36)	0/6	ITT: 20 (8-39)	<u>TTP</u> 2.3 (1.6-2.8)	5.1 (3.9-6.7)	NR	<u>Toxicity</u> Anemia 7%, grade 2 neutropenia 13%, grade 2/3 thrombocytopenia 10%. <u>QOL</u> : EORTC QLQ-LC13 Cough significantly improved.

Notes: CI – confidence interval, CR – complete response, EORTC – European Organization for Research and Treatment of Cancer, FACT-L – Functional Assessment of Cancer Treatment – Lung, ITT – intention to treat, mos – months, NR – not reported, N/V – nausea and vomiting, PFS – progression-free survival, PR – partial response, PS – performance status, pt(s) – patient(s), QLQ-LC13 – Quality of life questionnaire - lung cancer subscale, QOL – quality of life, RR – response rate, TTP – time to progression, vs – versus.

* Response rate provided as reported by authors. ITT data indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise, and significance levels are reported where provided by the authors.

‡ For the 56 patients that received at least two courses of gemcitabine.

Table 8c. Phase II trials of gemcitabine combination regimens as second-line chemotherapy: trial descriptions.

First author, Year (Reference)	Treatment	No. of pts entered/evaluable for response	% of pts, stage IIIa/IIIb/IV	Comments
Gemcitabine-taxane combinations				
Hainsworth 2001 (37)	G 800mg/m ² + D 30mg/m ² d1,8,15 q4w	40/31	NR Locally progressive/metastatic	PS: ECOG 0-2. No CNS metastases. First-line CT: platinum/T +/- V or G (32 pts), CbE (2 pts), other (6 pts). Time since first-line treatment: <6m, 53% pts, ≥ 6m, 47%.
Kakolyris 2001 (38)	G 900mg/m ² d1,8 + D 100mg/m ² d8 + G-CSF q3w	32/32	0/28/72	PS: WHO 0-2. Stable CNS metastases. First-line CT: MIP (10 pts), PE (13 pts), DP (9 pts). Median time for first-line to second-line treatment: 2m.
Kosmas 2001 (39)	G 1000mg/m ² d1,8 + D 100mg/m ² d8 + G-CSF q3w	43/43	9/40/51	PS: WHO 0-2. Asymptomatic CNS metastases. First-line CT: paclitaxel + platinum.
Spiridonidis 2001 (40)	G 800mg/m ² d1,8,15 + D 100mg/m ² d1 q4w	40/NR	0/20/80	PS: SWOG 0-2. Asymptomatic CNS metastases. First-line CT: platinum/V (26 pts), platinum/E (10 pts), single-agent (4 pts).
Rosati 2000 (41)	T 125mg/m ² + P 50mg/m ² + G 1000mg/m ² d1,8 + G-CSF q3w	26/26	0/38/62	PS: ECOG 0-2. Stable CNS metastases. First-line CT: PV (14 pts), PMVn (12 pts). Median time for first-line to second-line treatment: 24w.
Androulakis 1998 (42)	G 900mg/m ² d1,8 + T 175mg/m ² d8 + G-CSF q3w	49/NR	0/16/84	PS: WHO 0-2. Stable CNS metastases. First-line CT: P-based (22 pts), DP (20 pts), DV (7 pts).
Gemcitabine-vinorelbine combinations				
Kosmas 2001 (43)	G 1000mg/m ² + V 25mg/m ² d1,8 q3w	40/39	5/35/60	PS: WHO 0-2. Stable CNS metastases. First-line CT: taxane + platinum (+/- ifosfamide).
Pectasides 2001 (44)	G 800mg/m ² + V 25mg/m ² d1,8 q3w	39/35	NR Advanced	PS: ECOG 0-2. First-line CT: platinum/taxane (30 pts), platinum/E (6 pts), platinum/I (2 pts), platinum (1 pt). Median time for first-line to second-line treatment: 5.6m.
Hainsworth 2000 (45)	G 1000mg/m ² + V 20mg/m ² d1,8,15 q4w	55/46	NR Locally progressive/metastatic	PS: ECOG 0-2. No CNS metastases. First-line CT: platinum-based (53 pts), D (1 pt), T (1 pt).

Notes: Cb – carboplatin, CNS – central nervous system, CT – chemotherapy, D – docetaxel, d – day, E- etoposide, ECOG – Eastern Cooperative Oncology Group, G – gemcitabine, G-CSF – granulocyte colony stimulating factor, I – ifosfamide, M – mitomycin, m – month(s), No. – number, NR – not reported, P – cisplatin, PS – performance status, pt(s) – patient(s), q – every, SWOG – Southwest Oncology Group, T – paclitaxel, V – vinorelbine, Vn – vindesine, w – week(s), WHO – World Health Organization.

Table 8d. Phase II trials of gemcitabine combination regimens as second-line chemotherapy: trial results.

First author, Year (Reference)	Response CR/PR	Reported RR% * (95% CI)	Median PFS or TTP, mos (95% CI)	Median survival, mos (95% CI)	1-year survival rate %	Comments †
Gemcitabine-taxane combinations						
Hainsworth 2001 (37)	0/3	10 ITT: 7.5 ‡	NR	6	20	<u>Toxicity</u> § Leukopenia 15%, thrombocytopenia 13%, peripheral neuropathy 3%. NF 8%. PRBCT 13%. <u>QOL</u> : Not assessed.
Kakolyris 2001 (38)	0/5	ITT: 15.6 (3.0-28.2)	<u>TTP</u> 7	6.5	28	<u>Toxicity</u> Neutropenia 16%, anemia 9%, thrombocytopenia 6%. FN 2 pts. <u>QOL</u> : Not assessed. Symptomatic improvement not seen on chemotherapy.
Kosmas 2001 (39)	0/14	ITT: 33 (18.5-46.6)	<u>TTP</u> 6	8.5	30	<u>Toxicity (NCI grade 3 or 4)</u> Leukopenia 56%, neutropenia 53%, thrombocytopenia 7%, anemia 12%, febrile neutropenia 14%. <u>QOL</u> : Not assessed.
Spiridonidis 2001 (40)	1/12	ITT: 32.5 (19-49)	<u>PFS</u> 4.4	8.1 <u>PS <2 vs 2</u> 10.5 vs 2.5 (p=0.0015)	32 actuarial	<u>Toxicity (NCI grade 3 or 4)</u> Neutropenia 68%, anemia 22%, thrombocytopenia 22%, N/V 8%, grade 2/3 neuropathy 5%. FN 4 pts. PRBCT 22%, PIT 10%. <u>QOL</u> : Not assessed.
Rosati 2000 (41)	0/7	ITT: 27 (11.6-47.8)	NR	5.5	NR	<u>Toxicity</u> Neutropenia 34%, thrombocytopenia 15%, anemia 7%, grade 2/3 neuropathy 38%. FN 3 pts. <u>QOL</u> : Not assessed.
Androulakis 1998 (42)	1/8	ITT: 18 (4-24)	NR	11	NR	<u>Toxicity</u> Neutropenia 12%, thrombocytopenia 2%, grade 2/3 neurotoxicity 32%. NF 1 pt. <u>QOL</u> : Not assessed.
Gemcitabine-vinorelbine combinations						
Kosmas 2001 (43)	9/40	ITT: 22.5 (10.8-38.5)	<u>TTP</u> 4.5	7	17	<u>Toxicity (NCI grade 3 or 4)</u> Neutropenia 33%, leukopenia 35%. Rh-Epo allowed (given to 14 pts). <u>QOL</u> : Not assessed.
Pectasides 2001 (44)	0/1	ITT: 2.6 (0.09-17.6)	<u>TTP</u> 4.7	7.3	35	<u>Toxicity</u> Neutropenia 5%, N/V 13%, neurotoxicity 3%. FN 13%. <u>QOL</u> : Not assessed. Reported symptomatic clinical benefit for pain (23%), cough (50%), hemoptysis (25%), dyspnea (20%), anorexia and fatigue (25%), fever (40%).
Hainsworth 2000 (45)	1/8	18 ITT: 16 ‡	NR	6.5	20 actuarial	<u>Toxicity</u> Leukopenia 46%, neutropenia 36%, anemia 20%, thrombocytopenia 22%, N/V 3%. NF 7%. PRBCT 22%, PIT 3%. <u>QOL</u> : Not assessed.

Notes: CI – confidence interval, CR – complete response, FN – febrile neutropenia, ITT – intention to treat, mos – months, NCI – National Cancer Institute, NF – neutropenic fever, NR – not reported, N/V – nausea and vomiting, PFS – progression-free survival, PIT – platelet transfusion, PR – partial response, PRBCT – packed red blood cell transfusion, PS – performance status, pt(s) – patient(s), QOL – quality of life, RR – response rate, TTP – time to progression, vs – versus.

* Response rate provided as reported by authors. ITT data indicated where available.

† Only statistically significant toxicities or the following major grade 3/4 toxicities are reported: hematological, renal, nausea or vomiting, grade 2-4 neuropathy. Toxicity is reported as percentage of patients with WHO grade 3/4 effects unless stated otherwise and significance levels are reported where provided by the authors.

‡ ITT calculated by reviewer from published data.

§ Criteria for assessing toxicity were not reported.

|| Reported response rate calculated on 46 evaluable patients and 4 patients with rapid disease progression, classified as non-responders.

V. INTERPRETIVE SUMMARY

In the original guideline for gemcitabine in NSCLC (2), the Lung DSG recommended the use of single agent gemcitabine in first-line therapy only in situations where cisplatin-based chemotherapy or therapy with vinorelbine alone was not recommended. For patients who experienced serious adverse side effects with vinorelbine, which would preclude its continued use, gemcitabine was considered a reasonable alternative. No recommendations were made regarding the role of gemcitabine as adjuvant or induction chemotherapy in patients with stage I, II, or III disease or in combination with radiation therapy. There are considerably more data available in 2002 on which to make recommendations about the use of gemcitabine. Several trials directly compare cisplatin-gemcitabine to the regimen of cisplatin-vinorelbine as first-line chemotherapy. The latter regimen is currently funded by Cancer Care Ontario as the chemotherapy of first choice in Ontario for patients with locally advanced or metastatic NSCLC.

Gemcitabine-cisplatin has also been compared with platinum-taxane combinations as first-line treatment for advanced NSCLC. The response rates, progression-free survival, median survival, and one-year survival of patients treated with cisplatin-gemcitabine were similar to that of any of the newer combination chemotherapy regimens including cisplatin-vinorelbine, cisplatin-docetaxel, cisplatin-paclitaxel, and carboplatin-paclitaxel. The principal differences are in the toxicity profile, administration schedule, and cost of these regimens.

Several randomized trials have established the efficacy of cisplatin-gemcitabine when given on a three weekly schedule with lower doses of cisplatin (70 to 80 mg/m²), although the evidence is currently only available in abstract format. Given in this manner, cisplatin-gemcitabine causes less neutropenia and nausea and vomiting but more thrombocytopenia than cisplatin-vinorelbine, at least in the doses and schedules reported in the randomized trials. Despite the higher frequency of thrombocytopenia with cisplatin-gemcitabine, this is infrequently associated with bleeding or the need for platelet transfusions.

At present, there are inadequate data to recommend substituting carboplatin for cisplatin when combined with gemcitabine. However, for patients in whom cisplatin is contraindicated, it may be appropriate to consider substituting carboplatin for cisplatin.

There is conflicting evidence regarding the use of triplet regimens as first-line chemotherapy. At present, inadequate data exist to support the addition of other drugs to cisplatin-gemcitabine. There is emerging data concerning the combination of gemcitabine and taxanes; however, there are insufficient data to recommend a taxane-gemcitabine combination. For patients in whom platinum combination chemotherapy is not considered appropriate, there is no evidence to support the combination of gemcitabine-vinorelbine. It is reasonable to consider chemotherapy with either gemcitabine or vinorelbine as single agents.

Data from one study in elderly patients presented at ASCO 2001 by Gridelli et al (49), and recorded by one of the DSG members but not reported in the published abstract, indicated that gemcitabine or vinorelbine used as single agents in first-line therapy have similar response rates and survival in this patient population, with no additional benefit from the two drugs in combination. However, until the results of this study are published, these data should be considered preliminary.

Gemcitabine has shown some activity in phase II trials as second-line chemotherapy. At present, there are no randomized data to support the use of gemcitabine as second-line chemotherapy for NSCLC.

VI. ONGOING TRIALS

Protocol IDs	Title and details of trial
NCCTG-N0026	Phase II Randomized Study of Pemetrexed Disodium and Gemcitabine in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer. Comparison of 3 different schedules of pemetrexed and gemcitabine combinations. Outcomes: response duration, time to progression, time to treatment failure, survival, toxicity. Projected accrual: 180 patients over 20 months. Summary last modified: 12/2001. Status: open.
CHNT-GEM, EU-20062	Phase II/III Randomized Study of 2 Schedules of Gemcitabine with Best Supportive Care in Patients with Locally Advanced or Metastatic Poor Prognosis Non-Small Cell Lung Cancer. Outcomes: response rate, survival, toxicity, quality of life. Projected Accrual: 174 patients. Summary Last Modified: 08/2001. Status: open.
MDA-DM- 99015, NCI- 4450	Phase II Study of Cisplatin, Gemcitabine, and Trastuzumab (Herceptin) in Patients with p185-HER2 Overexpressing Stage IIIB or IV Non-Small Cell Lung Cancer. Outcomes: therapeutic efficacy, toxicity, pharmacokinetic interactions. Projected Accrual: 20-48 patients. Summary Last Modified: 02/2002. Status: closed.
CLB-119802	Phase II Study of Fluoxetine with Gemcitabine and Cisplatin in Patients with Advanced or Recurrent Non-Small Cell Lung Cancer. Outcomes: response rate, response duration, overall survival, toxicity, quality of life. Projected accrual: 35 patients over 9 months. Summary Last Modified: 03/2002. Status: open.
NCCTG-982452	Phase II Randomized Study of Docetaxel and Gemcitabine in Patients with Stage IIIB/IV Non-Small Cell Lung Cancer. Comparison of various schedules of docetaxel with gemcitabine. Outcomes: response rate, survival, toxicity, quality of life. Projected accrual: 19-53 patients within 6-18 months. Summary Last Modified: 04/2001. Status: closed.
CLB-39809 (CALGB study)	Phase II Randomized Study of Gemcitabine and Docetaxel versus Gemcitabine and Irinotecan in Chemotherapy Naïve Patients with Stage IIIB or IV Non-Small Cell Lung Cancer. Outcomes: response rate and duration, survival, toxicity. Projected accrual: 72 patients within 12 months. Summary Last Modified: 02/2001. Status: closed.
E-1599	Phase II Randomized Study of Paclitaxel and Carboplatin versus Gemcitabine and Cisplatin in Patients with Non-Small Cell Lung Cancer. Outcomes: response rate, survival, time to disease progression, toxicity. Projected accrual: 40-90 patients within 12 months. Summary Last Modified: 07/2000. Status: closed.
ITA-GEMVIN EU-99016	Phase III Randomized Study of Gemcitabine Plus Vinorelbine vs Standard Chemotherapy Containing Cisplatin in Patients with Stage IIIB or IV Non-Small Cell Lung Cancer. Outcomes: response rate, survival, toxicity, quality of life. Projected accrual: 500 patients. Summary Last Modified: 08/2001. Status: closed.

PD-994-013, ILEX-994-013	Phase III Randomized Study of Gemcitabine with or without CI-994 in Patients with Advanced Non-Small Cell Lung Cancer. Outcomes: detailed outcomes not specified. Projected Accrual: 176 patients. Summary Last Modified: 11/2000. Status: closed.
AG-3340-017	Phase III Randomized Study of Prinomastat (AG3340) or Placebo in Combination with Gemcitabine and Cisplatin in Patients with Metastatic or Recurrent Non-Small Cell Lung Cancer. Outcomes: response rate, survival, safety, quality of life. Projected Accrual: 420 patients. Summary Last Modified: 09/2000. Status: closed.
ZENECA- 1839IL/0014	Phase III Randomized Study of ZD 1839 Combined with Gemcitabine and Cisplatin in Chemotherapy Naive Patients with Stage IIIB or IV Non-Small Cell Lung Cancer. Comparison of gemcitabine and cisplatin, with or without ZD 1839. Outcomes: survival, time to worsening of disease. Projected Accrual: 1029 patients. Summary Last Modified: 07/2001. Status: closed.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

There was consensus among members of the Lung DSG that there is sufficient evidence from randomized clinical trials to recommend cisplatin-gemcitabine as a first-line treatment option for patients with advanced NSCLC. Differences exist in both the toxicity and scheduling of combination regimens, including cisplatin-gemcitabine, and these factors should be considered in deciding which regimens to recommend to an individual patient. An additional consideration of increasing importance in Ontario is timely access to surgical services for the insertion of venous access devices. As this is frequently required in patients receiving vinorelbine, those patients with difficult venous access should be preferentially considered for cisplatin-gemcitabine. In some areas in the province which serve small remote communities, patients may be seen initially at a regional cancer clinic and then have chemotherapy administered under the supervision of their family physician. Gemcitabine may be preferred in these situations because there are fewer concerns regarding extravasation.

There was discussion as to whether the recommendation for the combination of cisplatin-gemcitabine should be restricted to patients in select circumstances or should be available as an option for all patients with advanced NSCLC. The Lung DSG felt that as cisplatin-gemcitabine may have less toxicity than the currently recommended regimen of cisplatin-vinorelbine, and there are factors restricting access to the cisplatin-vinorelbine regimen, cisplatin-gemcitabine should be considered a treatment option for all patients with advanced NSCLC.

Two different schedules of cisplatin-gemcitabine have been evaluated in large randomized clinical trials: gemcitabine 1000 mg/m² on days 1, 8, and 15 and cisplatin 80 to 100 mg/m² every four weeks; gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 to 80 mg/m² every three weeks. Following discussions among group members, the Lung DSG chose not to recommend one dose schedule over another, as there are no trials directly comparing these two combinations. However, there appears to be less toxicity with the three-week schedule of treatment, as this schedule contains a lower dose of cisplatin.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT Draft Recommendations

Based on the evidence described above, the Lung DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with locally advanced or metastatic NSCLC.

Draft Recommendations

Key Recommendations

- Cisplatin and gemcitabine can be recommended as one of several first-line chemotherapy regimen options for patients with locally advanced or metastatic NSCLC.
- There is insufficient evidence to recommend adding a third drug to a gemcitabine-platinum combination.
- There is insufficient evidence to recommend routinely substituting carboplatin for cisplatin when combined with gemcitabine.
- At present there is insufficient evidence to recommend gemcitabine combined with a taxane as first-line therapy for NSCLC.
- There is currently no evidence from randomized clinical trials that second-line chemotherapy with gemcitabine is associated with any improvements in survival. The routine use of gemcitabine as second-line chemotherapy cannot be recommended.

Qualifying Statements

- Other chemotherapeutic options that have shown response rates and survival outcomes equivalent to the combination of cisplatin and gemcitabine include (i) cisplatin and vinorelbine, (ii) carboplatin and paclitaxel, (iii) cisplatin and paclitaxel, and (iv) cisplatin and docetaxel.
- Differences in scheduling, toxicity, and cost of these regimens should be criteria used to choose between the different therapies.
- Preliminary evaluations of two different dose schedules of cisplatin and gemcitabine have been conducted in large randomized clinical trials: gemcitabine 1000 mg/m² on days 1, 8, and 15 and cisplatin 80 to 100 mg/m² every four weeks; gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 to 80 mg/m² every three weeks. There is insufficient evidence to recommend a specific schedule at this time.

Related Guidelines

Cancer Care Ontario Practice Guidelines Initiative's Practice Guideline Reports:

- 7-5: *Use of Vinorelbine in Non-Small Cell Lung Cancer.*
- 7-7-2: *The Role of Single-Agent Docetaxel (Taxotere®) as a Second-Line Treatment for Advanced Non-Small Cell Lung Cancer.*

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 38 practitioners in Ontario (all medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Results

Twenty-four responses were received out of the 38 surveys sent (63% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 21 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 9.

Table 9. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%) *		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	20 (95%)	1 (5%)	0
There is a need for a clinical practice guideline on this topic.	15 (71%)	6 (29%)	0
The literature search is relevant and complete.	21 (100%)	0	0
The results of the trials described in the report are interpreted according to my understanding of the data.	20 (95%)	0	1 (5%)
The draft recommendations in this report are clear.	21 (100%)	0	0
I agree with the draft recommendations as stated.	20 (95%)	0	1 (5%)
This report should be approved as a practice guideline.	16 (76%)	4 (19%)	1 (5%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? †	Very likely or likely	Unsure	Not at all likely or unlikely
	17 (81%)	2 (10%)	1 (5%)

* Percentages do not always total to 100% due to rounding errors.

† One response was missing for this question.

Summary of Written Comments

Seven respondents (33%) provided written comments. The main points contained in the written comments were:

1. Gemcitabine is a reasonable second-line treatment option for those not previously given this drug.
2. This practice guideline provides a thorough expansion of the original guideline and a useful analysis of the current evidence.
3. Gemcitabine could be used as third-line treatment for some patients with a good performance status.
4. The cost differential between administration of vinorelbine and gemcitabine may be important.

Modifications/Actions

1. Although the results of phase II trials indicate that gemcitabine has some activity as second-line chemotherapy, evidence from randomized trials is not currently available, and the Lung DSG felt that a recommendation could not be made in support of the use of gemcitabine as second-line therapy at this time.
2. No action required.
3. There is currently no evidence to support the use of gemcitabine as third-line chemotherapy. Therefore, the Lung DSG did not feel it was appropriate to recommend any treatment as third-line chemotherapy in advanced NSCLC. It would be reasonable to consider participation in a clinical trial for appropriately selected patients progressing after second-line therapy.
4. The use of cisplatin-gemcitabine will lead to an increase in drug costs in comparison to cisplatin-vinorelbine. However, the Lung DSG felt that the modest toxicity profile of the

gemcitabine-cisplatin combination justified the use of this regimen in some clinical situations and counterbalanced the increased cost. This argument was accepted by the Policy Advisory Committee of the New Drug Funding Program when it approved the recommendations contained in the guideline.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Seven PGCC members approved the practice guideline report as written and, four members approved the guideline and provided suggestions for consideration by the Lung DSG. The Lung DSG reviewed the PGCC suggestions and revised the guideline as deemed appropriate.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Lung DSG and the PGCC.

Target Population

These recommendations apply to adult patients with locally advanced or metastatic non-small cell lung cancer who are considered candidates for first-line or second-line chemotherapy.

Recommendations

- Cisplatin-gemcitabine can be recommended as one of several first-line chemotherapy regimen options for patients with locally advanced or metastatic non-small cell lung cancer.
- There is insufficient evidence to recommend adding a third drug to a gemcitabine-platinum combination.
- There is insufficient evidence to recommend routinely substituting carboplatin for cisplatin when combined with gemcitabine.
- At present there is insufficient evidence to recommend gemcitabine combined with a taxane as first-line therapy for non-small cell lung cancer.
- There is currently no evidence from randomized clinical trials that second-line chemotherapy with gemcitabine is associated with any improvement in survival. The routine use of gemcitabine as second-line chemotherapy cannot be recommended.

Qualifying Statements

- Other first-line chemotherapeutic options that have shown response rates and survival outcomes equivalent to the combination of cisplatin-gemcitabine include (i) cisplatin-vinorelbine, (ii) carboplatin-paclitaxel, (iii) cisplatin-paclitaxel, and (iv) cisplatin-docetaxel.
- Differences in scheduling and toxicity of these regimens should be the criteria used to choose between the different therapies.
- Preliminary evaluations of two different dose schedules of cisplatin-gemcitabine have been conducted in large randomized clinical trials: gemcitabine 1000 mg/m² on days 1, 8, and 15 and cisplatin 80 to 100 mg/m² every four weeks; gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 to 80 mg/m² every three weeks. There is insufficient evidence to recommend a specific schedule at this time.

Related Guidelines

Practice Guidelines Initiative Practice Guideline Reports:

- 7-2: *Chemotherapy in stage IV (metastatic) non-small cell lung cancer*

- 7-5: *Use of vinorelbine in non-small cell lung cancer*
- 7-7-1: *The role of taxanes in first-line therapy of advanced non-small cell lung cancer (currently under development)*
- 7-7-2: *The role of single-agent docetaxel (Taxotere®) as a second-line treatment for advanced non-small cell lung cancer*
- 7-10: *The role of systemic chemotherapy in the treatment of advanced non-small cell lung cancer (currently under development)*

X. JOURNAL REFERENCE

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XI. ACKNOWLEDGEMENTS

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