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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:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*

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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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