# Chemotherapy for Metastatic Non–Small-Cell Lung Cancer — Can That Dog Hunt?

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Although no longer the most common cancer diagnosed in the United States, a dubious distinction now credited to breast cancer, bronchogenic carcinoma remains by far the principal cause of cancer-related deaths. Little progress has been made in the management of lung cancer during the past 20 years because of the systemic nature of this carcinoma and the lack of effective therapy other than surgical resection. More than 75% of patients with non–small-cell lung cancer present with unresectable disease, and even those with resectable lesions have a high propensity to experience recurrence with extrathoracic metastases. Unfortunately, an effective systemic therapy for non–small-cell lung cancer does not exist. Indeed, chemotherapy has failed to prove curative in even an occasional patient with metastatic disease.

Since chemotherapy regimens used to treat metastatic non–small-cell lung cancer have no curative potential, what can one reasonably expect from them? An improvement in a patient's quality of life or a prolongation in survival would make therapy warranted. Presumably, a prolongation of life would be accompanied by a reduction in tumor-related symptoms, although this is not necessarily the case. Does chemotherapy improve the survival of non–small-cell lung cancer patients with metastatic disease? In this issue of the Journal, Cartei et al. describe the results of a randomized phase III trial in which 102 patients with metastatic non–small-cell lung cancer received either supportive care or a cisplatin-based chemotherapy regimen plus supportive care (*1*). Supportive care consisted of analgesics, an antitussive, antibiotics, steroids, palliative radiotherapy, and the relief of increased intracranial pressure. Patients given combination chemotherapy survived a median of 8.5 months compared with just 4 months for those randomly assigned to receive supportive care alone, a difference that has high statistical significance ($P<.0001$). This observation is encouraging, especially because it is not the first study to demonstrate an improvement in the median survival of patients with stage IV non–small-cell lung cancer treated with chemotherapy. A well-designed Canadian trial of similar size (*2*) also demonstrated a doubling of the median survival for patients receiving chemotherapy. Does this mean that patients with stage IV non–small-cell lung cancer routinely benefit from chemotherapy? Unfortunately, the answer is no. Other investigators (*3-6*) have conducted well-designed randomized studies with negative results.

Why have these randomized trials yielded divergent outcomes? Space constraints do not permit a full discussion of all the potential reasons, but one possible explanation is that chemotherapy is simply *not* effective against non–small-cell lung cancer and that chance alone was responsible for the occasionally positive trial. A second possibility may relate to problems with selection of a study design that is not only appropriate to the purpose of the study but also feasible. A double-blinded trial, for example, is not always feasible. The treating physician may see patients on a chemotherapy arm more frequently and, with a vested interest in their care, treat them with "supportive care" on a more aggressive basis.

A third possibility is that chemotherapy *is* active against non–small-cell lung cancer but that the magnitude of benefit derived from treatment is modest. To demonstrate a small but clinically meaningful improvement in median survival, however, would require a study of many more patients than were entered into any of the published trials; all accrued fewer than 200 patients. Study results support the third possibility for two reasons. First, the median survival of the untreated patients in the randomized trials with negative results (*3-6*) was uniformly poor and remarkably constant (approximately 4 months). Second, patients treated with cisplatin-based chemotherapy regimens typically survived longer than their untreated counterparts, even though differences in median survival were not always statistically significant or clinically meaningful (*1-6*). This evidence of longer survival certainly suggests that existing cisplatin-based chemotherapy regimens possess at least some degree of activity against non–small-cell lung cancer which, if properly exploited, might prove beneficial.

Accepting the fact that there were differences in trial design and patient selection criteria that may have influenced the outcomes of these studies, are there other possible explanations for the divergent results? Perhaps the designers of the above studies simply used the "wrong" cisplatin-based chemotherapy combination or possibly employed the "wrong dose" of cisplatin (a commonly posited argument). The first possibility seems highly unlikely because randomized trials have failed to demonstrate any differences in survival outcome with commonly used cisplatin-based chemotherapies (*7*). The argument that the dose of cisplatin was inadequate also seems to be spurious, given the lack of good data demonstrating a dose–response curve for non–small-cell lung cancer in randomized trials, laboratory data notwithstanding (*8,9*).

Is it possible that the different outcomes in the reported randomized trials have more to do with the biology of the tumors than with the factors discussed above? Recently, Gazdar (*10*) observed that non–small-cell lung cancer cell lines with neuroendocrine features respond more favorably to chemotherapy than do those without these features. Could it be that the trials demonstrating a favorable effect with chemotherapy had a preponderance of neuroendocrine-positive patients in the chemotherapy-treated group and that this led

*See "Notes" section following "References."

to the observed survival differences? Are there other unidentified prognostically important biological parameters that simply were not considered when these trials were being designed? Certain biological features, such as expression of blood group antigens, the presence or absence of epidermal growth factor receptors, or ras oncogene mutations, have been found to influence prognosis in early-stage, resectable non–small-cell lung cancer (*11,12*). Do these factors also play a prognostically important role in more advanced disease? Is it possible that these or other biological changes are important in determining tumor response in vivo to chemotherapy, radiotherapy, or biological therapies? Interestingly, in laboratory studies, missense mutations in the ras oncogene have been shown to influence tumor responsiveness both to irradiation and to chemotherapy (*13*). Although expression of the MDR1 gene (also known as PGY1) does not appear to be a major factor causing drug resistance in lung cancer, alterations in topoisomerase expression have been shown to be present in some lung tumors (*14,15*). Might not these alterations play a role in therapeutic outcome?

What do these laboratory observations mean clinically? If nothing else, they suggest that future chemotherapy trials in stage IV non–small-cell lung cancer should include an attempt to correlate these and other newly described biological features with response and survival outcome. The information obtained could then be used to determine the clinical relevance of these factors and may help refine our treatment of lung cancer. Furthermore, continued investigation into the biology of lung cancers is warranted if we are to understand better why most tumors fail to respond to our meager therapeutic offerings.

Finally, what was the quality of life of the patients entered in the randomized studies (*3-6*)—in both the treated and the untreated groups? Unfortunately, a definitive answer is not available because none of those trials successfully completed a quality-of-life analysis, even when an attempt was made to collect the data (*2,4*). We still do not know if existing chemotherapy regimens favorably influence symptom resolution and quality of life, although the data appear to be encouraging in this regard (*16*). If chemotherapy could regularly alleviate pain, dyspnea, cough, and other tumor-related symptoms without engendering unpleasant and/or life-threatening toxic effects, one could more easily justify its use in the treatment of metastatic disease. Further study is needed.

What have we learned from the studies by Cartei et al. and others? We now know that existing chemotherapy regimens do not have a *major* favorable impact on the survival of patients with stage IV non–small-cell lung cancer. As noted previously, to detect a small but real improvement in median survival would require many more patients than were entered into any of the published trials. Is a large trial worth mounting to prove this point? I personally think not—at least not without quality-of-life measurement. How many physicians would feel compelled to offer treatment to their patients if quality of life remained poor or deteriorated, even if a statistically superior but modest survival was demonstrated? Are the data from Cartei et al. sufficient to mandate the routine administration of chemotherapy to patients with metastatic non–small-cell lung cancer? I'm afraid that dog won't hunt—not yet.

## References


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## Notes


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Manuscript received April 6, 1993; accepted April 8, 1993.