It is interesting to speculate on the possible applications of noninvasive ventilatory devices to a broader group of pulmonary problems. Recently, two groups have reported successfully utilizing nasal intermittent positive pressure ventilation to stabilize patients with cystic fibrosis awaiting lung transplants.\(^{10,11}\) What future role might NIV play in organ transplantation?\(^9\) Maybe Conwell is right: the jewels lie before us, if we’d only see them.

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Chemotherapy and Survival of Patients with Non-Small Cell Lung Cancer

A Contrary View

Dr. Buccheri (see page 1325) has concluded that all new patients with unresectable non-small cell lung cancer should be offered chemotherapy. Although I agree that all studies of cisplatin-based chemotherapy compared with best supportive care alone have shown a higher median survival for those patients treated with chemotherapy, I disagree that this fact alone proves the value of this costly and toxic modality. My reasons for disagreeing with this conclusion can be summarized as follows:

First, all of the available clinical trials for this disease demonstrate survival curves that are approximately exponential, with no sign of a "plateau" or "tail on the curve." This fact is strong evidence against a curative potential for currently available forms of chemotherapy for patients with advanced disease.

Second, even if one accepts that chemotherapy confers a survival advantage, the quantitative impact of chemotherapy on survival is minuscule. There have been six prospectively randomized clinical trials comparing chemotherapy to best supportive care alone as initial treatment.\(^1,6\) This group does not include the trials conducted by Buccheri and colleagues because they used historical controls, rather than concurrently randomized patients. If one combines all of these prospectively randomized trials, the aggregate median survival for patients receiving chemotherapy is 5.7 months, compared with 4.6 months for patients treated with best supportive care alone (a difference of 1.1 months). If one excludes the two earlier trials performed before the availability of cisplatin, the respective aggregate survival results are 6.3 months for chemotherapy and 4.0 months for best supportive care (a difference of 2.3 months).

Cisplatin-based chemotherapy is expensive, most patients must be hospitalized for treatment, and these regimens are very toxic (with such side effects as deafness, loss of taste, renal dysfunction, neuropathy, nausea, vomiting, bone marrow suppression, and the risk of toxic death). Given these risks and costs, I consider chemotherapy to be an investigational modality for the treatment of advanced, unresectable non-small cell lung cancer. I therefore limit its use to highly motivated patients with a good performance status who choose to participate in well-designed clinical trials. In my view, supportive care alone without chemotherapy is still the best available treatment for most other patients with advanced non-small cell lung cancer.

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Chemotherapy for Non-Small Cell Lung Cancer
The Continuing Challenge

Few malignancies have been as frustrating to medical oncologists as has non-small cell lung cancer (NSCLC); this is compounded by the high incidence of the disease, its frequently disseminated stage at presentation, and a median survival that is best measured in weeks or months for all but the few patients presenting with highly localized and surgically accessible disease. Since local treatment modalities such as surgery or radiotherapy provide little hope for effectively palliating or, ultimately, curing this systemic disease, the use of chemotherapy has been under intensive investigation in NSCLC for the last three decades.

As summarized by Buccheri in this issue (see page 1328), the emotional pendulum toward the role of chemotherapy has swung widely over the years, reflecting increasing disappointment with chemotherapy that results in reproducible toxicity and provides questionable activity.

We agree with Buccheri that randomized trials comparing chemotherapy to supportive care in patients with unresectable (stage IIIB or IV) disease can be used to justify the use of chemotherapy. To date, five such trials have been peer-reviewed and published; of these, the trial by Rapp et al. showed a statistically significantly improved survival for patients treated with chemotherapy compared to “best supportive care.” Cost-benefit analysis also supported the use of chemotherapy in this trial. Because of its good scientific study design and the use of active drugs (cisplatin, vindesine), this trial is the most widely accepted evidence supporting the use of chemotherapy. The study by Cormier et al. also showed a survival advantage; however, the number of patients enrolled was small, thus depriving the study of statistical power; in addition, the survival on the control arm was exceptionally poor. Three additional trials have been reported and, while suggesting a trend toward improved survival in chemotherapy-treated patients, statistical significance was not reached.

We disagree with two statements by Buccheri regarding these randomized trials. When several trials show a trend toward improved survival but lack statistical significance, it is tempting but inappropriate to conclude that a real benefit must exist; however, a statistical method, meta-analysis, has been developed that combines the analysis of several randomized trials addressing the same clinical issue. This technique is useful when lack of significance may be due predominantly to low patient accrual numbers, as is the case in some of these trials. Using meta-analysis, it might be possible to consolidate the evidence that the benefit from chemotherapy in NSCLC is real rather than state that it must be real. Similarly, it is speculative to imply that investigators of randomized trials had a negative bias towards the role of chemotherapy and the outcome of their trials. Unless such bias had led to improper trial design or faulty analysis of data, it is irrelevant to the outcome.

Despite these reservations, we agree that at least the Canadian trial can be interpreted as supporting an eventual role for chemotherapy in NSCLC, particularly as part of clinical trials. However, we caution against its routine use outside clinical trials for two reasons. First, while improved survival in NSCLC may result from the use of chemotherapy, all evidence suggests that this benefit is very modest at best and must be balanced against frequently severe toxicities. Prognostic factors have been established for patients with NSCLC, and toxicity seems particularly pronounced in patients with a poor performance status at the time of diagnosis. Second, an optimal chemotherapy regimen has not been established; aggressive combinations have yielded higher response rates, but have resulted in inferior survival compared to single agent chemotherapy in randomized trials; therefore, at present, a “standard” chemotherapy combination does not exist.

In view of these facts, we would recommend restricting the use of chemotherapy for NSCLC strictly to patients with a good initial performance status who, despite best efforts, cannot be enrolled on a clinical trial, rather than indiscriminately treating all patients with chemotherapy at the community hospital level. Given the modest impact of all known regimens to date, this emphasis on clinical research is highly indicated.

We advocate a strategy focusing on the discovery of new drugs with single agent activity in NSCLC, the incorporation of such drugs into existing regimens with known activity, and the biochemical modulation of established regimens. It is clear that carefully conducted phase I and phase II trials are best suited