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Medical Management of Non-small Cell Lung Cancer

I.E. Smith

CHEMOTHERAPY is clearly established in the treatment of small cell lung cancer. Its role in non-small cell lung cancer (NSCLC) is much more controversial. A recent survey of chest physicians, surgeons and oncologists in the U.K. showed that this treatment was offered to only 8% of patients and actually given to only 5% (Cancer Research Campaign, 1991). Attitudes are changing, however, and there is increasing evidence of modest but nevertheless clinically relevant benefit with chemotherapy for this disease.

NSCLC is by no means completely resistant to chemotherapy. Response rates of 30–40% are consistently reported with modern cisplatin-containing regimens [1], and more intensive schedules have achieved responses in greater than 50% of patients [2]. Higher response rates of almost 70% have been demonstrated for locally advanced (stage IIIB) disease and for pre-operative (neoadjuvant) chemotherapy [3] with complete histological resolution in 14–19% of patients proceeding to subsequent surgery [3, 4].

The impact of chemotherapy on survival in NSCLC has been better studied than for many other common cancers, and a recent overview analysis of seven randomised trials showed a significant survival benefit of chemotherapy over best supportive care in three and a similar but non-significant survival trend in all the others [5]. These results have recently been confirmed in an MRC overview, soon to be published.

Just as important as survival, if not more so, in this area of palliative medicine is symptom relief. We have recently completed a study of 120 patients with locally advanced or metastatic NSCLC treated with moderate dose palliative chemotherapy using mitomycin C 8 mg/m^2 i.v. day 1 (alternate courses), vinblastine 6 mg/m^2 i.v. day 1 and cisplatin 50 mg/m^2 i.v. day 1 (MVP), repeating every 21 days for a maximum of six courses. Objective response was seen in 32% of patients. Clinically more relevant, however, were our findings of good symptom relief; complete disappearance or good improvement in tumour-related symptoms occurred in 69% of patients including improvement in malaise (53%), pains (60%), cough (66%) and dyspnoea (59%) [6]. Similar findings, showing a high incidence of symptom relief, have also recently been reported for the MIC (mitomycin C, ifosfamide, cisplatin) chemotherapy schedule [7].

In such a common disease, there is unease at the perceived high costs of palliative chemotherapy. Cost effectiveness is of course a central issue here, but anxieties may be based on a false premise. Chemotherapy represents only a small fraction of the total cost of care for a patient with advanced cancer; it has been shown for example in breast cancer that this may be less than 10% [8]. Supportive care, particularly as an inpatient, can be very much more expensive. A Canadian trial has shown that chemotherapy in NSCLC not only prolonged survival compared with best supportive care alone, but actually reduced overall costs of care [9]. It appears from this study that savings were probably achieved because chemotherapy, which is relatively inexpensive, reduced the number of very expensive inpatient days required for control of symptoms. More detailed trials of overall cost-effectiveness are now essential in this field.

The greatest scope for progress in the near future may be with chemotherapy as neoadjuvant/pre-operative treatment in NSCLC. Two recent trials have produced surprisingly encouraging results here. In the first, patients with stage IIIA disease were randomised to immediate surgery or three courses of pre-operative chemotherapy (mitomycin C, ifosfamide and cisplatin)

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and all patients subsequently received mediastinal radiation. Analysis after entry of 60 patients showed a major median survival benefit for patients treated with pre-operative chemotherapy (26 versus 8 months, $P<0.001$) such that the trial was stopped prematurely [10]. In the second trial, of similar design, patients treated with six cycles of pre-operative chemotherapy (cyclophosphamide, etoposide and cisplatin) had an estimated median survival of 64 months compared with 11 for patients treated with surgery alone ($P<0.008$) and again the trial was stopped early following entry of 60 patients [11]. These results require cautious interpretation, principally because of the very small number of patients. Nevertheless, two trials, albeit small, both reporting similar findings carry considerable statistical power, and further data in this important area are urgently required.

In terms of patient numbers, primary/neoadjuvant chemotherapy prior to radiotherapy may have a more important role than before surgery. In the last few years, two large randomised trials in patients with locally advanced NSCLC have reported significant survival improvement. In a CALGB trial, chemotherapy before radiotherapy was associated with a 43% improvement in median survival and a three year survival of 23% versus 11% [12]. Similarly, in a French trial, patients pretreated with three cycles of vindesine, cyclophosphamide, cisplatin and lomustine prior to radiotherapy had a modest but statistically significant survival improvement up to 3 years after treatment ($P = 0.08$) [13]. An MRC overview analysis of all such trials (soon to be published) confirms a small but statistically significant survival benefit. Further large trials addressing this important question are currently under way.

Future trials must attempt to identify predictive factors for response to chemotherapy to enable more selective treatment to be delivered. These could include both clinical and biological parameters, e.g. *K-RAS*. Meanwhile, clinicians must continue to use common sense; palliative chemotherapy is unlikely to be appropriate for frail or chronically ill patients with low performance status, but for selected patients, there is now good evidence of palliative benefit with a small survival prolongation.

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Chemotherapy in Head and Neck Cancer

J.P. Armand and C. Couteau

HEAD AND neck cancers include all squamous cell carcinomas that originate in the anatomical region comprising the oral cavity, pharynx and larynx and are estimated to be one of the most prevalent tumours in the world. The standard treatment is usually surgery alone and/or radiotherapy. Despite the use of optimal therapy, 50% of patients develop local recurrences and 30% metastatic disease. The overall survival rate is 40% for complete resection and only 20% for unresectable disease [1].

Treatment for local recurrence of metastatic disease is often chemotherapy, even if its efficacy is low. Less than 40% of patients achieve a response, generally of short duration (average 6 months) and median survival is 6–10 months [1].

Response rates with single agents are often variable because patient groups are heterogeneous. Six drugs have demonstrated a high level of activity: methotrexate, cisplatin, carboplatin, 5-fluorouracil (5FU), bleomycin and ifosfamide [2–5].

Methotrexate has been used as a single agent with 40–60 mg/m^2. High doses have not demonstrated any advantages (randomised trial of Southeastern Cancer Study Group with 500 mg/m^2) [3]. Cisplatin, with an average response rate of 28%