T cell receptor in the presence of macrophages or cytokines are T cells triggered to secrete IL-2, enter to S phase and temporarily express IL-2R, which can be released into the serum as a soluble IL-2 receptor (sIL-2R) [14].

An increase in serum sIL-2R expression has been reported in patients with various malignant disorders. In some of them, the sIL-2R serum level appears to be closely correlated with progression and response to therapy [15]. In this régard, sIL-2R has been suggested as a "blocking factor" produced by the malignant cells to inhibit the host's immune response to the tumour. Thus, it is tempting to speculate that exogenous application of IL-2 might help overcome this dysregulation of the immune system.

A dilemma is the lack of appropriate preclinical models. New research approaches must therefore be defined, and close cooperation among preclinical and clinical scientists must be promoted.

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Combined Modality Treatment in Small Cell Lung Cancer (SCLC)

A. Gregor

DESPITE THE accepted use of chemotherapy as primary treatment in SCLC, with increasing intensity and sophistication of drug treatment protocols, more than 90% of patients relapse and die from recurrence of chemoresistant tumour. One of the many strategies used to prolong remission and increase long term survival was the introduction of irradiation to bulky sites of primary and metastatic disease and other common sites of failure, including prophylactic cranial irradiation (PCI). Moderate radiation doses can reduce by half the expected lifetime risk of recurrences both at primary site (60 versus 30%) and in the brain (30 versus 10%), but numerous randomised trials have failed to translate this "local control" advantage into survival benefit. There could be a number of reasons for this, related to the population of patients studied, to the technical aspects of radiation delivered or to increased toxicity resulting from the use of combined modality therapy. The most likely, however, is the methodological problem of sample size needed to show small differences. This has been addressed finally by a meta-analysis combining results of 13 randomised trials and 2001 limited stage SCLC patients. In this large group, the relative risk of death for patients receiving combined modality therapy was 0.86 (95% CI

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0.78–0.94, $P<0.001$). This can be expressed as a relative reduction in the mortality rate of 14% with an absolute 3 year survival difference of 5.4% in favour of the combined modality group [1]. This analysis has provided formal evidence of a small but definite benefit of thoracic irradiation for "good prognosis" patients with SCLC which is now accepted in routine clinical practice.

Many important issues (radiation dose, volume, fractionation and integration with chemotherapy) remain unresolved. Trying to "fine tune" combined modality treatment for SCLC is a formidable challenge. The individual benefits attributable to different parameters of this puzzle are likely to be small and manipulation of one may indirectly affect a cascade of events with conflicting effects on overall outcome. These methodological concerns are noticeable in the paucity of large scale randomised trials addressing these questions.

Few existing clinical trials have looked at radiation dose as a sole clinical variable. Retrospective analysis of studies using radiation following cyclophosphamide and doxorubicin containing regimens suggested that high doses (50–60 Gy) may be needed for durable local control. Using concurrent cisplatinum/etoposide and irradiation in the more modern setting, doses in the region of 45 Gy in 25 fractions appear to be adequate. Whether this will be a durable local control with increasingly prolonged survival is uncertain. Heterogeneity of SCLC may demand higher doses, or "sensitisation" with concurrently used chemotherapy may reduce it further.

A further practical question concerns the radiation volume. The tradition of irradiating large volumes of "prechemotherapy involvement" to tumoricidal doses may not be necessary and more modest volumes and margins lead to reduced toxicity.

Several phase II studies of radiation given in multiple daily fractions (MDF), either concurrently with cisplatin and etoposide or in an interdigitated sequence, are being followed by two large randomised trials (EGOC/RTOG and CCTG). Whether these can confirm the promising 35–40% survival figures (2–4 years) reported in these preliminary studies is a subject of intense interest.

The issue of radiotherapy timing has not been convincingly resolved either. An early 3 arm randomised CALGB trial [2] suggested that best survival/toxicity ratio can be obtained by delaying radiation until the fourth cycle of chemotherapy. More recently, a Canadian trial [3] produced a significant but intriguing survival advantage for early (cycle 2) concurrent therapy due to unexplained reduction of brain metastases. Attempts to introduce radiotherapy early into the treatment scheme without increasing toxicity have included alternating schedules. A series of non-randomised sequential studies by the French collaborative groups [4] are being tested in a randomised trial by the EORTC Lung Cancer Co-operative Group. Attempts at increasing dose intensity by shortening the overall treatment time based on the principle of "toxicity independence" has had to be abandoned due to serious haematological toxicity. A large phase III trial nearing completion compares five courses of CDE (cyclophosphamide/doxorubicin/etoposide) chemotherapy and 50 Gy in 20 fractions of thoracic irradiation given sequentially or as 4 weekly courses following the second and subsequent chemotherapy. Whilst high level of effectiveness of this combined modality approach can be seen, both in terms of response and early survival, acute toxicities are more frequent and severe using the alternating approach which is also more demanding for patients and health care resources. Unless a significant survival advantage can be demonstrated for this arm the use of alternating schedules in clinical practice cannot be justified.

The other controversial area of use of radiotherapy in SCLC is prophylactic cranial irradiation (PCI). A number of randomised trials have shown substantial reduction in incidence of brain metastases following PCI, but no demonstrable impact on survival; concerns of late CNS morbidity have held back its use and acceptability outside clinical trials [5]. A host of retrospective studies demonstrated a variety of clinical, psychological and neuro-radiological deficits in approximately half of all long-term survivors of SCLC, the majority of whom have received PCI during their treatment. The cause and effect relationship between these abnormalities and PCI in these often complex treatment regimens is not easy to unravel. The most profound functional deficits were seen in patients treated with concurrent chemotherapy and irradiation, prolonged courses of neuro-toxic chemotherapeutic agents (nitrosourea, methotrexate) and those receiving high doses of cerebral irradiation given in large individual treatment fractions [6]. A much lower incidence of neuropsychometric morbidity and no clear cut relationship with Quality Of Life impairment was seen in other studies [7]. The continuing high incidence of isolated CNS relapse in long term survivors, the significant impact on their quality of life and functional abilities [8], and the failure of alternative management strategies to reduce CNS tumour involvement has led to resurgence of interest in PCI and its evaluation in prospective randomised studies [9]. One of these has recently been reported as showing significant reduction of brain metastases (RR 0.32, $P<0.0001$) and interestingly improved survival (29% 2 years survival versus 21% 2 years survival $P = 0.14$; RR 0.83) in favour of low dose (24 Gy in 8 fractions over 12 days) PCI [10]. No significant neurofunctional deficits were observed, although 11% of PCI and 3% of no PCI patients had CT abnormalities on follow up. A further randomised trial of prophylactic cranial irradiation in complete responders to induction treatment is being conducted by the UKCCCR and EORTC LCCG. A third of the patients recruited for this study are undergoing formal neuropsychometric assessments pre-PCI and at regular intervals during their follow up. Whilst formal analysis of this trial is not yet available, preliminary evaluation of retrospective data and recently reported prospective analysis suggests that PCI can be given without gross and crippling neurological morbidity, and provides an effective 3-fold reduction in the rate of cranial relapse. The challenge remains to identify the optimal timing, dose and fractionation designed to abolish brain metastases with minimal morbidity.

Combined modality treatment in SCLC represents a state of the art care for patients who are candidates for long term survival. A number of issues aimed at improved locoregional control remain unresolved and optimal integration of treatment schedules is yet to be defined. Searches for a more effective systemic approach, addressing the major cause of treatment failure, must continue.

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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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