Difficult Decisions

Chemotherapy in lung cancer

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Introduction

Lung cancer remains the single most common cause of death from malignant disease in the West, and although this may be improved if preventive measures, particularly directed against smoking, are successfully adopted, the incidence is unlikely to fall for the remainder of this century. Improved control of the disease with surgery (currently possible in < 5% of all cases) or radiotherapy (in some localized inoperable tumours) might be achieved if effective screening led to more cases being detected at an early stage, but no suitably effective programme has yet been developed. New approaches to the treatment of cancer based on increased understanding of tumour cell biology are on the horizon, but it is clear that no major breakthrough in the management of lung tumours is at hand. Thus there is a huge demand for effective chemotherapy in this disease, and appropriately there has been an intensive research effort directed at the development of useful drug regimens over the past 10–15 years. Initially there were encouraging advances, particularly in relation to small cell lung cancer (SCLC), which led to the hope that chemotherapy might have a major impact on the natural history of the disease, but now in the mid/late 1980s a plateau has seemingly been reached with a significant but unspectacular improvement in the outlook of patients with SCLC, but no definite benefit for the 70–75% with squamous, large-cell or adenocarcinoma (in this context bracketed together as non small-cell lung cancer, NSCLC).

This somewhat disappointing position is at variance with the optimistic tenor of some reporting of trials of chemotherapy in both SCLC and NSCLC, in which a minor response in terms of shrinkage of tumour or short survival benefit has been regarded favourably, even though relatively intensive or toxic treatments may have been used, after extensive and invasive staging investigations. The complications of therapy and the net change in the quality of life as a result of it have been given little attention. Trials reported from

1971–77 were reviewed¹ and criticised for, among other aspects, a failure to record toxicity and changes in symptoms and performance status during treatment.

These factors, hard to measure,² though now more widely acknowledged to be important³ still do not always receive appropriate consideration. The effect has been to increase scepticism regarding the potential value of these treatments within the medical profession, and to hinder appropriate referral of the patient with lung cancer to the cancer specialist. The result is potentially unsatisfactory, with in some instances useful treatment not applied, and from the other point of view, important investigations delayed as a result of slow recruitment of patients to trials.

Here we will review the current position of chemotherapy in lung cancer, with emphasis on how patients might be selected for those treatments which are of established benefit, as well as discussing areas of greater uncertainty from where future advances might come.

Small-cell lung cancer

The small-cell subtype accounts for approximately 25% of all cases, and without treatment has the worst prognosis, with median survival 10 weeks from diagnosis, and < 5% of patients alive at one year. Local measures such as surgery or radiotherapy alone are inadequate, even in apparently localized disease, because distant metastases develop early such that it may be assumed that there is occult dissemination at the time of presentation. Small-cell tumours are highly chemosensitive, a large number of agents having activity, and since a small improvement in survival was seen in patients treated with cyclophosphamide by Green,⁴ chemotherapy has become established as the primary treatment. Response to treatment correlates with the extent of disease at presentation. In SCLC a simplified staging system⁵ is commonly employed in view of its propensity to early metastasis. Limited disease (LD) is that confined to one hemithorax including ipsilateral hilar and supraclavicular nodes. Extensive disease (ED) indicates distant spread, in-

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cluding pleural involvement. Comprehensive staging of patients prior to treatment with X-ray, bronchoscopy, bone marrow biopsy, bone scan and liver scan is common practice,⁶ so that response to treatment can be monitored. Responses are recorded as partial (PR), i.e. at least a 50% reduction in two perpendicular measurements of tumour size, or complete (CR), i.e. resolution of all evaluable tumour.

The responses to a variety of single agents are reported in the range 20–50%. A consequence of a number of early trials, which have recently been critically reviewed,⁷ has been widespread acceptance of the tenet that, as in Hodgkin's lymphoma and acute leukaemia, there is synergy between non-cross-resistant drugs so that response rates are higher for multiple agent regimens. This has resulted in the development of more complex and more broadly toxic treatments, and has prevented newer agents with high activity such as VP16 (etoposide) and cisplatin being assessed in optimal circumstances, i.e. alone and in previously untreated patients. The frequently quoted figures for activity of VP16 in SCLC (35–50% combined CR + PR⁸) have been substantially improved upon in a recent study⁹ in which response rates of > 80% have been achieved with single agent VP16 administered optimally over 5 days.

Of the combinations of drugs which have been used, no one regimen has achieved general acceptance as that against which new treatments should be compared; cyclophosphamide, adriamycin and vincristine (CAV) were most commonly employed up to the early 1980s, since when VP16, cisplatin and ifosfamide have been widely included. Importantly, it is now clear that the results obtained from these treatments are broadly similar, and although different centres report differences in response rates or survival figures, these differences appear to owe more to variation in assessment of response and interpretation rather than real diversity of achievement. Response rates of 85% (LD) and 70% (ED) are representative, with median survival in the range 10–15 months and 7–10 months respectively.

Attainment of complete response is an important prerequisite for long survival, and whereas this may be achieved in up to 50% of LD patients, considerably less than half that proportion of ED patients enter CR.¹⁰ 'Long survivors' are usually defined as those surviving for > 2 years, and here the figures achieved at the Royal Marsden Hospital with 333 patients between 1978–85¹¹ of 15% of LD and 5% of ED do not differ greatly from those reported from other centres. These long survivors are by no means necessarily cured, including as they do patients who have an evaluable tumour burden when assessed at two years, and the increasingly recognized number who will go on to develop late relapse of their disease, occasionally even as far out from diagnosis as 6¹² or 8¹³ years.

Whether indeed any of them are cured is unknown, but in this respect the more important 5 year survival figures are from time to time being published. An example is the striking 10.7% LD and 4.7% overall 5 year survival reported by the South Western Oncology Group,¹⁴ and although these figures have not been reproduced elsewhere – an under 2% 5 year survival was recorded in a large Finnish series¹⁵ – some hope appears to exist for a small proportion of patients.

The cost of such 'conventional dose' chemotherapy is predictable toxicity, depending upon the particular drugs used. Alopecia and some nausea, with or without vomiting, are usual. All regimens include at least one agent which is severely myelotoxic, and the typical three-drug combinations result in transient, usually mild, neutropenia, with a small risk of septicæmia, during each cycle. The incidence of granulocytopenic infection lies within the range 10–30% for a patient during a course of treatment, and the mortality from treatment related infections is 1–3%. A recent study¹⁶ has suggested that treatment with recombinant granulocyte colony-stimulating factor (G-CSF) can reduce the period of neutropenia, and hence the incidence of severe infections, in patients with SCLC receiving combination chemotherapy. This is potentially an important advance, and may reduce both mortality and morbidity as well as permitting increases in the dose intensity of treatment, but clinical experience in this area is at an early stage.

Specific drugs are associated with particular toxicities which can be troublesome in a few patients, such as neuropathy with vinca alkaloids, cardiotoxicity with adriamycin and nephrotoxicity with cisplatin. There is also a cumulative toxicity manifest by non-specific symptoms such as lethargy and anorexia which can lead to early abandonment of treatment in patients receiving prolonged courses.

Overall, combination chemotherapy appears to offer the possibility of moderate benefit for the majority of treated patients, but to have severe limitations in terms of providing for prolonged survival in all but a few. Whether that benefit is realized depends upon the quality of life which treatment permits. The majority of patients with SCLC have unpleasant symptoms at the time of diagnosis, such as dyspnoea, haemoptysis and bone pain; relief of symptoms is closely correlated with response to treatment¹⁷ and so toxicity of treatment should not be considered a price paid for survival advantage alone. As stated above, this is an area where evaluation is difficult and not often performed, but by and large effective treatment in this condition seems tolerable and useful; the difficulty arises in determining to what extent it is worthwhile pursuing small probabilities of extra benefit with more toxic or prolonged therapies. Moving towards an answer to this question has been the

major thrust of research activity in SCLC over the past 5–10 years, a time during which there has been a relative plateau in actual improvements to therapy. The possibility of an increased number of complete remissions and long survivors has led to investigation of more intensive therapy, while conversely realization of the limits of treatment for the majority of patients, who currently will relapse after a relatively short time, has led to attempts to define minimal therapy which will give increased survival and relief of disease-related symptoms not offset by inconvenience or side effects.

Intensification of treatment

Alternating non cross-resistant regimens

The hypothesis has been advanced by Goldie & Coldman¹⁸ that when immediate additive toxicity precludes simultaneous administration of all active drugs in the treatment of a particular tumour, the greatest possibility of cure occurs when two equivalent non cross-resistant regimens are alternated. In their model, this situation is associated with the least risk of treatment failing as a result of acquired multiple drug resistance.

This has been tested in a variety of studies in SCLC with equivocal results. Two large controlled trials have been published within the last 12 months.^{19,20} Both groups used CAV as the control arm, and also as one of the pair of alternating therapies. VP16 was included in the second combination on both occasions. All results, in terms of response, survival and other measures, favoured the alternating treatment arm, but the improvements were modest, in particular for overall survival (median survival differences 1.6 months and 1.0 months for ED patients in the two studies, and 2.3 months for LD, with 3% improvement in 2 year survival). This might be considered insufficient to justify the increased complexity and toxicity, reported by the German group,¹⁹ of the alternating regimen. It is important to note that any advantage may have been due to the use of more effective drugs in the latter option, particularly VP16, rather than as a result of the different scheduling.

High dose chemotherapy

The use of chemotherapy in higher than conventional dosage in the treatment of malignancy is based on the assumption of a dose–response relationship for cytotoxic effect. There is laboratory evidence that such a relationship exists in a number of systems including SCLC xenografts.²¹ High dose regimens have been used in the treatment of a number of tumours such as ovarian carcinoma²² and melanoma²³ with an improved response rate, as well as commonly in leuk-

aemia and lymphoma. Souhami *et al.*²⁴ have obtained a better response rate in SCLC with cyclophosphamide given as a single agent in high dosage to previously untreated patients than can be obtained with this drug in conventional doses. Several units have adopted programmes designed to test the feasibility and efficacy of high dose chemotherapy in SCLC, most frequently in the context of minimal residual disease in patients who have already achieved a good or complete response to conventional chemotherapy.^{25,26} The dose limiting toxicity of the regimens employed is usually myelosuppression, and this can be reduced in duration by the use of autologous bone marrow rescue. Unfortunately, unlike ovarian carcinoma, SCLC frequently involves bone marrow at presentation, and there is a significant risk of returning tumour cells to the patient if this technique is performed. In contrast to the haematological malignancies where similar treatments have an established role, SCLC afflicts predominantly older patients whose general health has been compromised by smoking. Toxicity of such treatments restricts their application to a highly selected group who will be able to tolerate the side effects despite recently completing several months of conventional chemotherapy. The early results to date have not shown a significant improvement over conventional chemotherapy to enable prediction of a major role for high dose treatment. Haemopoietic colony stimulating factors may facilitate future administration of such regimens, but drug resistance is likely to remain as the major problem to be surmounted.

Combined modality therapy

Although chemotherapy is established as the treatment of choice in SCLC, it is a highly radiosensitive tumour, and there is an important role for radiotherapy in relief of symptoms at all stages of the disease, but particularly at relapse after chemotherapy and in specific instances such as localized bone destruction, spinal cord compression and brain metastases.

Two instances where radiotherapy is often employed prophylactically in association with chemotherapy are (i) mediastinal irradiation and (ii) prophylactic cranial irradiation (PCI).

Mediastinal irradiation Despite its tendency to early widespread metastases, SCLC most frequently relapses at the primary site within the chest after chemotherapy, with an overall local recurrence rate of > 60%²⁷ and local recurrence as site of first relapse in 30%.²⁸ Radiation to the primary site and mediastinum has been combined with chemotherapy by many groups. In one recent study²⁹ an improved CR rate and reduced frequency of local relapse was demonstrated,

in agreement with previous reports. This group also noted a modest survival advantage for the combined modality therapy over chemotherapy alone; several previous trials^{28,30} have not shown this, and further confirmation and follow-up is awaited. Toxicity is significant, with standard acute complications of anorexia, tiredness and oesophagitis. Pulmonary toxicity is the most important late complication, occurring to a mild degree in up to 25% of patients.³¹ The place of mediastinal radiotherapy is not clearly defined, but it may be that this measure will in future turn out to be of value in good prognosis patients with limited disease who have had a complete response to chemotherapy, in the hope of improving long survival in this group.

Prophylactic cranial irradiation Intracranial metastases are a major source of morbidity in patients responding to systemic chemotherapy in SCLC, with increasing incidence with lengthening survival.³² Although these are radiosensitive, treatment at the time of clinical detection risks persisting disabling symptoms, and thus prophylactic cranial irradiation (PCI) at an earlier stage has been advocated and widely employed. With PCI, the incidence of symptomatic cerebral metastases can be reduced to <10%,³³ although once again there is no significant associated survival advantage. Most units using PCI confine it to patients achieving CR, in whom survival may be sufficiently long to make cerebral metastases a significant risk and threat to the quality of life.¹⁷ The decision is not entirely straightforward, however, in that late sequelae of PCI itself, such as memory impairment and confusion,³⁴ are increasingly reported among the long survivors it is designed to benefit.

Less toxic chemotherapy

Simplified regimens

With the increasing realization that greater treatment intensification has had little impact on the central problem in SCLC, namely early relapse despite initial chemosensitivity, there has been a move towards use of simplified drug regimens aimed at improved patient acceptability. In particular, the proportion of patients with ED who survive 2 years from diagnosis is very small whatever the treatment, and it is difficult to justify treatment which will result in prolonged hospital stay or unpleasant side effects in this group.

Satisfactory response and survival rates in both ED and LD patients have been obtained using VP16 as a single agent, with toxicity being largely confined to alopecia and mild cytopenia.⁹ Morgan *et al.*³⁵ have used oral VP16 together with vincristine in predominantly ED patients, and achieved 70% response and 11% 2 year survival despite the unpredict-

table absorption of VP16. This treatment had the advantage of outpatient administration. There is an increasing experience with carboplatin (JM8), which has activity as a single agent;³⁶ this is a platinum derivative with similar activity to cisplatin but with less gastrointestinal and renal toxicity, thus enabling outpatient treatment without prehydration and vigorous intravenous anti-emetic cover.

Short duration therapy

The optimum duration for which chemotherapy should be continued in SCLC is unclear. Frequently treatment has been given at regular intervals (e.g. in 3–4 weekly courses) up to the time of relapse, or for one year for those surviving disease free to that point. It now seems that such 'maintenance' chemotherapy is of no benefit,³⁷ and it is common practice to limit treatment to, say, 6 courses and to discontinue therapy if disease has ceased to respond. Smith *et al.*³⁸ gave only 4 courses of carboplatin and VP16, and considered that this may have been insufficient, but Dorward *et al.*³⁹ gave only three courses of a 4 drug combination with satisfactory results.

Treatment at relapse

The prognosis of patients at relapse receiving chemotherapy for SCLC is poor. Treatment is usually palliative, and so asymptomatic disease progression does not necessarily require treatment. Local measures such as radiotherapy may be more appropriate than further systemic chemotherapy in many instances. Further responses to chemotherapy are obtained, but are generally short, lasting a few months. Alternative drugs, putatively non-cross-resistant with those used to obtain first remission have usually been employed, although it has recently been shown that rechallenging with the original drugs can produce comparable results.⁴⁰ Minimal toxicity is the most important criterion at this stage.

Selection of patients for treatment in SCLC

The approaches to treatment outlined above call for means of identifying patients with good prognosis who have a reasonable chance of attaining CR and thus potentially long survival. Experimental approaches with more intensive programmes are justifiable in this group. Conversely, patients with negligible chance of prolonged benefit should not be exposed to unnecessary toxicity or hospital stay. Currently the best prognosticators are stage and performance status at presentation, and attainment of CR once treatment has begun.⁴¹ These are limited

their usefulness, however, in that the majority of 'good prognosis' patients fare badly and the occasional ED patient will survive > 2 years. Moreover, all patients are put through an intensive staging procedure which is time consuming and expensive of resources.

Recently attempts have been made to simplify staging, and in retrospective analyses Souhami *et al.*⁴² and Vincent *et al.*¹¹ have found that performance status and routine laboratory tests such as serum sodium, albumin and liver enzymes were of greater prognostic value than conventional staging. Newer investigations such as assessment of tumour marker status may introduce useful prognostic information.⁴³

Overall, the efficacy with which chemotherapy can improve symptoms in SCLC suggests that even poor performance or elderly⁴⁴ patients should be given a trial of treatment, preferably of low toxicity and employing a simple regimen of not more than 3 agents. The possibility of using single agent therapy should be considered, and VP16 might be regarded as the drug of first choice, combining efficacy and acceptable toxicity. Combined modality treatments should be reserved for patients with limited disease who achieve CR. Complex staging procedures may not be justified in all cases, provided that adequate information is available from simpler tests to allow planning of treatment and monitoring of response.

Non-small cell lung cancer (NSCLC)

Chemotherapy has been used in three different situations in NSCLC, i.e. (i) as primary therapy in metastatic disease, (ii) as adjuvant treatment, either after surgery or radiotherapy in patients with early stage disease, and (iii) in the 'neoadjuvant' context, i.e. with the intention of reducing the bulk of locally advanced disease before surgery or radiotherapy.

Chemotherapy in advanced NSCLC

As in small cell lung cancer, a variety of drugs have activity, but response rates for single agents in this instance are less impressive, ranging from 10–20%. Combination therapy, particularly when including platinum derivatives, has been reported to produce more consistent responses, with rates in the range 40–50%, and even a few complete responders being seen.⁴⁵ There is considerable variation between studies, and in particular, cooperative studies have tended to fail to reproduce encouraging early results from single centres. The relevance of these responses, however, is called into question by failure to demonstrate consistent prolongation of survival as a consequence of therapy. Frequently observed small survival advantages for responders vs non-responders are at least partly due to disease heterogeneity (good prog-

nosis patients untreated are those most likely to respond), and might also occur because toxic therapy is shortening the lives of non-responders. Randomized trials comparing chemotherapy with conventional supportive treatment are few in number; one such study recently published demonstrated a short prolongation of median survival which was significant in one out of two chemotherapy arms.⁴⁶ Toxicity was severe in at least 40% of treated patients. In a cooperative study between Southampton, UK and Sydney, Australia⁴⁷ there was no improvement in survival obtained with chemotherapy, which was administered to approximately 100 patients. Those with early stage disease were most likely to benefit from treatment, but even in this sub-group the difference was not statistically significant.

Toxicity is a major problem in all active regimens, and in the context of this disease improved survival alone, if indeed achieved, is not sufficient justification for such therapy. Many enthusiastic trial reports inadequately quantitate toxicity, but when this is done, important insights can be obtained. Bakker, *et al.*⁴⁸ gave vinblastine, bleomycin and cisplatin to a group of high performance status patients with advanced NSCLC, and although a 48% response was documented, including one CR, both responders and non-responders alike experienced weight loss and reduction in performance status, and 25% of the patients found the treatment intolerable. The median survival of 33 weeks was not notably different from that expected in untreated inoperable NSCLC with good performance indicators.⁴⁹ The solitary responding patient who benefited in terms of improved performance status did so through relief of bone pain, which might have been achieved by considerably simpler means, such as single fraction radiotherapy.⁵⁰ A similar drug combination was better tolerated in a study reported by Osoba *et al.*⁵¹ in which chemotherapy was also effective in controlling pre-treatment symptoms, but the importance of measuring and recording such details is well demonstrated. In randomized trials designed to test different drug combinations, once again toxicity as well as response should be compared between treatments. Harvey *et al.*⁵² found no advantage in using a more toxic platinum containing regimen over one in which platinum was substituted by methotrexate.

The justification for use of combination chemotherapy in NSCLC, as argued by Greco,⁵³ is that tumours currently regarded as responsive were at some time unresponsive to the then treatment, and that development of therapies in those conditions led from partial responses with single agents to some durable complete responses with multiple agents, and has eventually brought about an improvement in overall management for a large proportion of patients. At present this pattern seems unlikely to be mirrored

in NSCLC; nevertheless the way forward remains to enter as many patients as possible into clinical trials. The clinical trials using currently available agents which are likely to be of value are easily defined; large numbers of diverse studies carried out at individual centres are unlikely to be of major benefit. The current multicentre study based at Birmingham, UK is of potential importance. In an initial pilot study⁵⁴ the combination of ifosfamide, cisplatin and mitomycin-C were shown to be active, with an overall response rate of > 50%. In the subsequent study, in which this combination is being compared with conventional 'supportive' therapy including radiotherapy, there is no provision for the control group to receive chemotherapy at any stage. This should help to answer the question whether or not optimum 'conventional' combination chemotherapy can influence survival in advanced NSCLC. If the answer to this is negative, then we remain dependent on the development of newer more active agents. In the meantime there is no role for chemotherapy outside such trials.

Adjuvant chemotherapy

Of patients with NSCLC undergoing apparently successful surgical resection, less than 50% are alive at 5 years.⁵⁵ These failures primarily arise as a result of metastatic disease below the limits of clinical detection. Adjuvant chemotherapy has been given to patients undergoing surgery in a number of randomized trials, notable being those conducted by the Veterans Administration Surgical Adjuvant Group, and that by Brunner⁵⁶ in which no benefit for the treated group was demonstrated. In the latter study there was a small increase in recurrences among patients receiving cyclophosphamide. Newer combinations, including agents with greater activity in NSCLC such as cisplatin, are being used in current studies, and the results are awaited.

Similarly there is no established value in combining chemotherapy with radiotherapy in inoperable NSCLC. Representative is a recently reported trial of radiotherapy with or without the active cisplatin-adriamycin-cyclophosphamide regimen CAP.⁵⁷ A non-significant improvement in response rate for the combined modality arm was seen, but identical median survival duration and 1 year and 2 year survival rates. Although in these patients there was no significant exacerbation of radiation toxicity by chemotherapy, this is a potential risk, and overall toxicity will be greater for the more intensive combined approach.

Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy, namely that given prior to surgery or radiotherapy to reduce the tumour bulk and so increase the chance of success with the primary treatment, is a relatively new concept which has only recently been explored in NSCLC. It has greatest relevance in the management of locally advanced disease without evidence of distant metastasis. There are early encouraging indications that a proportion of inoperable tumours can be rendered operable, particularly when chemotherapy and radiotherapy are applied sequentially.^{58,59} At operation, some patients have been found to be histologically free from tumour. In at least one study in which surgery was not attempted, but radiotherapy was given with or without prior chemotherapy, there was a better response rate and an early survival advantage in the chemotherapy arm.⁶⁰

Overall this has the potential to be a valuable application for chemotherapy in NSCLC. It seems likely that chemotherapy will remain most useful in selected groups of patients as part of a multi-modality approach to treatment, as here, until such time as new, more active agents become available.

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