Editorial

Chemotherapy in non-small cell bronchial carcinoma

Each year about 40 000 people in the United Kingdom develop squamous or large cell carcinoma or adenocarcinoma of the lung (non-small cell lung cancer), and very few of them are cured by surgery or radiotherapy. About 60% of patients have metastases at presentation and most of the others will develop local or systemic recurrence after surgery or radiotherapy. Many of those with advanced non-small cell lung cancer are elderly and in poor health and in such cases symptomatic treatment is all that can and should be offered. There remains, however, a substantial number of patients with advanced local disease or metastases who are reasonably young and active. Patients and clinicians are then often anxious that some form of treatment should be given and the question of whether there is anything to be gained by using chemotherapy then arises. In the last few years several drugs have shown antitumour activity when given as single agents and there are now many reports of improved survival in patients with responsive tumours. Is there a place for chemotherapy in selected patients?

A critical examination of the reports of the results of chemotherapy shows that there are many problems in study design, which have led to confusing and unreliable data. When tumours are growing slowly, as are some squamous cell lung cancers, early treatment will be associated with relatively long survival even if the "treatment" is totally ineffective or indeed harmful. Tumours at an early stage in their natural history are less widely metastatic and patients with these tumours will be more likely to have a good performance score, limited intrathoracic disease, and single rather than multiple metastases. All of these features have been shown to be indicators of a good prognosis.[1] The problem is that not only will such patients live longer untreated than those with more advanced disease but they may be more likely to respond to chemotherapy. Response to chemotherapy may then be taken to be the reason why they survive longer than those who do not respond, rather than an associated or parallel feature. For this reason the comparison of survival between responders and non-responders is not a reliable indication of the value of chemotherapy.[2] Common sense suggests, however, that a response to chemotherapy will contribute to improved survival even if it is not the sole cause. The only means of resolving this dilemma is to undertake randomised comparisons between groups of treated and untreated patients in whom a careful assessment of known prognostic determinants has been made.

Satisfactory studies of this sort have not been undertaken. A recent report by Lad *et al*[3] illustrates some of the difficulties. In this study a low dose nitrosourea was used as a control in a study of combination chemotherapy. Although there was a 44% response rate in the combination chemotherapy arm and no responders in the so called controls, there was no survival advantage for the drug combination, making the point that a higher response rate is not always associated with improved survival. The study was small and data about prognostic factors were not included. The size of a study is especially important since small scale trials of chemotherapy are quite likely to be misleading. In non-small cell lung cancer the survival advantage associated with chemotherapy at, say, one or two years is likely to be small and will be demonstrated with a reasonable degree of confidence only if large numbers of patients are entered into a study. When early trials of chemotherapy based on small numbers of patients have encouraging results, it is generally found that results are less impressive when the trials are repeated with larger numbers. Small studies may also miss a useful therapeutic effect.

There are other deficiencies in the design of many studies. In early reports the importance of distinguishing between histological types of tumour was not recognised and some studies failed to exclude cases of small cell carcinoma. It is clear that response to chemotherapy depends on histological type. Small cell lung cancer is now known to be much more sensitive than other types, but whether histological subtype is an important determinant of response to cytotoxic drugs among non-small cell cancers is still not clear. Careful histological review is essential because mixed histological appearances (for example, small cell and large cell) are not infrequent and may make comparison of response rates between different regimens unreliable.

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In recent studies the criteria for response have usually been well defined. This is an essential component of chemotherapy trials but in practice some of the criteria are often unrealistic—for example, a 50% reduction in the sum of two perpendicular diameters is a widely adopted criterion for partial response even though the measurement may prove to be little more than guesswork on many chest radiographs. The difference between "regression," defined more subjectively, and "response" is probably only one of degree.[4] Most responses to chemotherapy have been partial and short lived—usually a matter of two to four months—so that benefit to the patient is marginal, especially if toxic combinations are used.

Differing criteria for inclusion in studies, variable mixtures of cases with different prognosis, and varying histological types and response criteria have therefore all contributed to widely divergent views on which drugs or combinations of drugs are effective. Nevertheless, we can discern some trends and be fairly confident about which drugs are associated with response rates of 15–20% or more and which combinations of drugs might prove to be useful. Equally, we can be reasonably certain which regimens are toxic and useless.

Several drugs have been shown to produce responses in non-small cell lung cancer. In early studies[5] the reported response rates were probably too optimistic. Nowadays the results in trials of new drugs are just as likely to be underestimates since many studies, especially in the United States, are restricted to patients resistant to other agents—a factor known to be associated with a diminished response rate in lung cancer and other tumours.[6]

Among the traditional alkylating agents, more recent re-evaluation has shown that nitrogen mustard is associated with a response rate (based on the criteria mentioned above) of 10% in squamous carcinoma[7] and cyclophosphamide with a response rate of 12% in adenocarcinoma.[8] There has been considerable recent interest in the reports of Costanzi[9] and Harrison[10] on the efficacy of ifosfamide. The response rate to this drug appears to be up to 30% in squamous carcinoma and 25% in adenocarcinoma. It is less myelosuppressive than cyclophosphamide but more likely to cause haemorrhagic cystitis, which can be largely avoided by the use of 2-mercaptoethane sulphonate. Two other new alkylating agents, dianhydrogalacticol and dibromodulcitol, do not have any important activity.

Cisplatin has been evaluated in several studies.[11 12] The response rate in squamous cancer is about 17%, and in adenocarcinoma 15%, but very few responses have been seen in large cell tumours (less than 5%). Results with the newer platinum analogues are awaited with interest. Nitrosoureas (lomustine, BCNU, ACNU) have been fairly extensively tested in non-small cell lung cancer but the results have been uniformly disappointing, with no evidence of significant activity.

Of the antimetabolites, methotrexate has been most widely tested, but except in the study of Selawry *et al*[13] no activity has been shown and recent attempts to use the drug in high dose with folinic acid rescue have been disappointing.[14] Many new antimetabolites have been tested recently but none has shown any efficacy.

The vinca alkaloids show an interesting disparity in their effect. Vincristine is without effect but vindesine is associated with a response rate of about 16%.[15] As with other cytotoxic agents, the response rate is about equal in squamous carcinoma and adenocarcinoma but lower in large cell types. The neurotoxicity of vindesine is a disadvantage but its relatively mild myelosuppressive effect makes it a suitable drug for use in combination treatment. Little is known of the efficacy of vinblastine, although Schulman *et al*[16] have reported responses in six of 22 patients using a divided dose schedule—a result that requires confirmation.

Perhaps the most interesting new drug to emerge in recent years is etoposide (VP16-213). Phase II studies (in which the therapeutic effect of a new drug is tested in many tumour types) have shown a response rate of nearly 20% in squamous carcinoma but only 10% in adenocarcinoma.[17] There are few data on patients with large cell tumours on which to judge its effect. Teniposide (VM26), a closely related epipodophyllotoxin, has not shown significant activity. Anthracycline antibiotics, doxorubicin (adriamycin), 4-epiadriamycin, and 4-deoxydoxorubicin have not been shown to have significant activity in any of the three main histological types of tumour, with response rates of 10% or less.[18] The other antitumour antibiotics show a similar lack of promise and low response rates have been reported with bleomycin and actinomycin.

The most promising new single agents are therefore ifosfamide, etoposide, cisplatin, and vindesine; several treatment trials of combinations of these drugs have been carried out and others are in progress. Before the development of these drugs many treatment trials of combination chemotherapy had been carried out with long established drugs. Combinations contained two to five agents and the usual acronyms were used to describe regimens. Typical examples of widely used combinations are CAMP (cyclophosphamide, adriamycin, methotrexate, and procarbazine[19]), MACC (methotrexate, adriamycin, cyclophosphamide, and lomustine[20]), and BACON (bleomycin, adriamycin, lomustine, onocovin, and

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nitrogen mustard[21]). It is difficult to be sure whether any benefit has been derived from these combinations, even on the basis of response rate as an admittedly doubtful indication of benefit. The methodological shortcomings described earlier sometimes make interpretation of the data a matter of guesswork. Examples of this are the response rate of 35% with CAMP in the original report,[19] falling to 22% in the larger Eastern Cooperative Oncology Group (ECOG) study[22]; and the 36–58% response rate with MACC reported by Chahinian *et al*,[20] who found it easy to administer the regimen—which, however, produced only a 12% response rate in the hands of Vogl *et al*[23] (the latter reported treatment related deaths and expressed the view that MACC is "neither safe nor effective").

If a compilation of response rates is made from those studies that have 10 or more patients, there is a tendency for reported response rates to be somewhat higher when three of more drugs are used. The average response rate is about 25% for squamous carcinoma and adenocarcinoma and 15% for large cell carcinoma. There is, however, a very wide range of response (0–60%), and in these earlier studies combination chemotherapy cannot with confidence be said to have produced a higher response rate than is found with single agents. Few of these responses are complete (defined as disappearance of the tumour on the chest radiograph) and most are short lived.

The introduction of cisplatin and vindesine has led to many more recent studies based on these drugs. Gralla *et al*[24] investigated cisplatin and vindesine, comparing two dose schedules of platinum. With the lower dosage there were 19 out of 41 responses (three complete) and with the higher dose 16 out of 40 (five complete), but the median duration of response was greater with the higher dose (12 months compared with 5·5). The high overall response rate of 43% was encouraging. Adenocarcinomas predominated (57/81) in the study. Although responders lived longer than non-responders it is not yet clear what the long term survival of the entire groups, with no exclusions, will be. The combination of cyclophosphamide, adriamycin, and cisplatin (CAP) has been studied by several groups.[25] If we combine the results of several studies, which use varying dose schedules and include patients in different prognostic categories, the response rates are about 31% for squamous carcinoma, 26% for adenocarcinoma, and 25% for large cell carcinoma. Only three out of a total of 332 patients had a complete response and the duration of response was in general short. Cisplatin and etoposide were assessed by the lung cancer working party of the European Organisation for Research and Treatment of Cancer (EORTC).[26] The response rate was 38% overall, rising to 56% in patients who were previously untreated and who had locoregional disease (tumour confined to the chest); in this group the median survival was 50 weeks. When the same group added vindesine to the combination[27] the response rate was similar (34%), and so was the median survival (12 months). The neurotoxicity was greater in the three drug regimen. These findings show that the addition of a third active agent may serve only to increase toxicity. Kelsen *et al*[28] also failed to improve on the results with cisplatin and vindesine when either doxorubicin or cyclophosphamide was added.

The ECOG[29] has recently reported on a randomised comparison of four platinum containing regimens: AFP (doxorubicin, 5-fluorouracil, cisplatin), CAP, CBP (cyclophosphamide, bleomycin, cisplatin), and MVP (mitomycin C, vinblastine, and cisplatin). The dose of platinum was on the low side in each regimen. The study is a model in several respects: the tumour types and all prognostic factors are clearly set out; the response rate, median survival, and toxicity are carefully evaluated; and there are over 100 patients in each treatment category. A control group treated symptomatically would have made the study both unique and of inestimable value. The overall response rate in squamous carcinoma was about 20%, with AFP the worst (15%) and MVP the best (22%); in adenocarcinoma the response rate was about 26% (CBP 17%, MVP 29%) and in large cell 23% (AFP 15%, MVP 26%). MVP was marginally the most active regimen. Of a total of 432 patients, only 10 had a complete response, and the median survival was about 23 weeks. Responses were much more frequent in patients with good performance scores (38·6%), in women (29·6%), and in those with no weight loss before treatment (25·9%). Survival was longer in patients who responded early.

The ECOG authors feel that they are making "some progress in treating this disease" because they now have a discernible complete response rate (pointing out that in all their other trials they have seen only two complete responses). Nevertheless, the toxicity was considerable. Severe, life threatening, or fatal reactions were frequent, with severe vomiting in 25% and haematological toxicity in 29% (42% in those who received the MVP regimen).

Toxicity is, of course, the major problem. If none of these regimens were toxic or expensive clinicians would not be so concerned about whether they should or should not treat. Alopecia, nausea and vomiting, mucositis, peripheral neuropathy, and intravenous infusions are great burdens for the

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patient. Haematological toxicity is a considerable concern for the doctor, but less so for the patient unless infection or bleeding occur. On the other hand, not all patients are made distressingly ill by chemotherapy, and chemotherapy regimens are not equal in this respect. Alopecia is unpleasant but many patients are quite prepared to face this prospect; nausea and vomiting may be mild, or easily controlled in skilled hands; appreciable mucositis is infrequent. The assessment of what will or will not be tolerable in an individual patient is not one which cannot easily be made by the physician before treatment begins. Furthermore, fit patients are both more able to cope with chemotherapy and much more likely to respond.

Clearly most patients with advanced non-small cell lung cancer do not benefit from treatment with cytotoxic chemotherapy. There might be a prolongation of survival in subgroups of patients such as those who have a good performance status, but until a randomised comparison is made between the best available chemotherapy and symptomatic treatment we will not know the answer. Such a study must include many hundreds of patients for the result to be convincing, and it must also categorise them on the basis of the known prognostic factors in the manner of the ECOG study quoted above. This might allow us to detect a subgroup of patients who could benefit even if there is no overall value in drug treatment.

In the meantime the physician being pressed for treatment would not go too far wrong with the following guidelines: (1) patients with poor performance status and weight loss will do badly; (2) ifosfamide, etoposide, platinum, and vindesine are probably the most useful drugs; (3) there may be an advantage in using two or more drugs in combination, but the toxicity will be greater; (4) if patients do not respond after two or three cycles treatment is not worth continuing.

It is easy, and perhaps justifiable, to be gloomily dismissive of attempts to improve the treatment of advanced non-small cell lung cancer. Review of the publications of the last decade shows strikingly that contributions from the United Kingdom are rare and that we now rely almost entirely on our colleagues in the United States and continental Europe to undertake this work. Perhaps this reflects the prevailing pessimism in the UK, but whether this is a desirable attitude is at least open to question. The current results are certainly not encouraging. Nevertheless, now that surgery and radiotherapy have attained their maximum effectiveness progress is unlikely to be made in either localised or advanced disease unless effective drug regimens are found. Perhaps the advent of newer drugs with a little more activity should encourage us to believe that progress will be made.

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