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Feature Articles

Chemotherapy in Advanced Non-small Cell Lung Cancer

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Chemotherapy in advanced non-small cell lung cancer (NSCLC) has been evaluated with response rate, survival and quality of life as criteria. The data were collected from 142 phase II and III trials. The three main conclusions are: (1) multivariate landmark analyses show that a response to chemotherapy has an independent significant value for prognosis, and all studies of chemotherapy vs. best supportive care show some survival benefit in favour of chemotherapy; (2) NSCLC patients are a heterogeneous group with a large variation of known and unknown prognostic factors, such as the treatment centre, for both response and survival; and (3) retrospective analysis of the data show that response rate and survival are significantly correlated at response rate over 30% and in limited disease patients. The following recommendations are made: (1) new drugs should be compared in randomised phase II trials with a standard active drug; (2) randomised phase III trials of single agents or best supportive care vs. combination chemotherapy should be repeated in a well-defined subgroup of patients with a high performance score and limited tumour load; and (3) the palliative effect of chemotherapy in randomised trials in patients with symptoms should be investigated with relief of symptoms and quality of life as endpoints.
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INTRODUCTION

THE ROLE of chemotherapy in disseminated non-small cell lung cancer (NSCLC) (stage IIIB and IV) is controversial. In 1981 Aisner and Hansen [1] stated that chemotherapy for NSCLC should remain investigative and in 1986 Mulshine *et al.* [2] concluded that there is modest but discernible antitumour activity with combination chemotherapy which can justify delivery of chemotherapy to patients with good performance status in a non-study setting, but improvement is still required and NSCLC patients should be referred for participation in clinical trial protocols. I have reviewed 142 papers, including more than 12 000 patients, for response rate, survival and quality of life to evaluate chemotherapy in NSCLC. Tables with details of all studies will be published in *Lung Cancer* as part of the proceedings of the International Association for the Study of Lung Cancer (IASLC) workshop on locally advanced NSCLC held in Bruges, Belgium, in June 1990.

TRIALS

Phase II trials of single agents since 1986

In 1985 Kris *et al.* [3] reviewed 134 phase II trials of single agents and concluded that out of 42 different drugs the following showed an activity greater than 15%: cisplatin 16% (305 patients), mitomycin-C 17% (88), ifosfamide 27% (130), vindesine 18% (370) and vinblastine 18% (22). In 1987 Sorenson *et al.* [4] reviewed phase II studies of vinca alkaloids: vinblastine 28% (38), vincristine 12% (65) and vindesine 15% (384). Since 1986 at least 39 phase II studies on 34 different drugs tested in 1494 patients (14–109 per study) have been reported [5–42]. 3 new agents showed a response rate higher than 15%: 10-ethyl-10 deaza aminopterin (10-Edam) 32% (20), Navelbine 33% (82) and teniposide 16% (48). However, it is difficult to conclude that these drugs are active and the other 31 are not, since both positive and negative findings for the same drug can occur. One example is ifosfamide [17, 18, 35, 43–46]. This drug has been tested in essentially two schedules: high dose for 1 or 2 days (4 studies, 189 patients, response rates 10–33%) or low dose for 5 days (4 studies, 215 patients, response rates 7–57%). 2 of the 7 studies were negative (Table 1). It is worrying that looking at performance status as the major prognostic factor for response, no differences can be found between the studies. Since performance status is a subjective measure and difficult to compare between different investigators/centres, it may be advisable to test a new drug in a randomised phase II trial against an "active" drug to compare response rates and toxicities. Moreover, it is also important to increase the homogeneity of the study population by strict entry criteria for performance status, weight loss, previous treatment and extent of disease, which are all prognostic factors for response [47–50].

Phase II trials of combination chemotherapy

In 63 studies [47, 51–111], 3580 patients were entered and response rates ranged from 0% to 85%. For obvious reasons these studies are not comparable. In all studies response rates and survival are reported for the whole group of patients and in some by extent of disease. General agreement is found for the prognostic value of performance status but not for extent of disease. Almost all reports state that responders live significantly longer than non-responders. In most studies patients with complete remission (CR) have the longest survival; there is no

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Table 1. Phase II studies of ifosfamide in NSCLC

No. of patients	Dose	Response rate	Previous chemotherapy	Ref.
21	4.0 g/m²	33%	4	43
14	1.2 gm² per day × 5	57%		
31	1.2 g/m² per day × 5 then weekly	32%	16	44
90	4.0 g/m²	24%	20	46
104	1.2 g/m² per day × 5	32%	0	45
41	1.2 g/m² per day × 5	5%	0	17
25	1.2 g/m² per day × 5	12%	Yes	
48	5 g/m²	29%	0	18
30	4 g/m² per day × 2	10%	0	35

difference in survival between partial remissions (PR), minor remissions (MR) or stable disease (SD) and a significantly worse survival for patients with progressive disease (CR > PR = MR = SD > PD). In many reports with rather small numbers of patients, univariate analyses of prognostic significance of subgroups, such as different histologies, often gave rise to so-called non-significant differences. Such analyses seem confusing and misleading when the statistical power to detect a significant different between small subgroups is not indicated.

Other confusing items are the still rare reports about quality of life during treatment. As indices for quality of life, performance status, weight, general well-being, subjective improvement and decrease of disease-related symptoms, such as cough, pain and haemoptysis, were used. In most studies response to chemotherapy correlates with subjective improvement. In some, even patients with stable disease seem to improve; in some quality of life does not change; and in a few, quality of life deteriorates significantly during therapy even in responders and returns to pretreatment level after cessation of therapy. Difficulties in interpreting such studies are mainly the lack of uniform criteria to measure quality of life in NSCLC patients and the lack of a good description and evaluation of pretreatment symptoms. Moreover, at least 2 studies reported attention to the deteriorating effects of chemotherapy on quality of life [98, 112].

It seems unlikely that more phase II studies of combination chemotherapy with standard objectives of response rate, survival and toxicity will provide useful information. Instead they may lead to confusion and more widespread improper use of a chemotherapy regime, based on response rates in a selected group patients. Large phase II studies may still be warranted to investigate new prognostic factors or quality of life, if those objectives can be well-defined before the start of the trial.

Randomised phase III studies of single vs. combination agents

7 studies [113–119] of 1753 patients had response rates of 0 to 44%. In 5 studies there was no difference in response rate and no difference in survival between the two arms. In 1 study [117] a significant difference in response rate (7% vs. 26%) did not correlate with a difference in survival. In another study [115] a significant difference in response rate (7% vs. 33%) was reflected in a significant difference in survival. Finally, the study by Bonomi *et al.* [118], which perplexed some [120], since it showed a significantly better response rate (20%) for the combination of mitomycin C, vinblastine and cisplatin (MVP) with a tendency for the worst survival, whereas the combination of carboplatin followed by MVP at progression had a response rate of 90% and a significant survival benefit.

From these studies it is difficult to conclude that active single agents are better or worse than combination chemotherapy in terms of response rate and survival. Furthermore, they do not suggest a strong relation between response and survival.

Randomised phase III trials of combination chemotherapy

In 27 studies [48–50, 112, 121–143] of 3937 patients the response rates varied from 0% to 53%. The following conclusions could be drawn. No difference in survival was observed between the different regimens except one [142], whatever the response rate. Toxicities were always compared, but quality of life measurements were rarely compared. In a few studies the suggestion was made that significant differences between chemotherapy regimens were observed in subgroups of patients with limited disease (LD) and excellent performance status.

2 studies seem more relevant than the others in providing information for future trial designs. Lad *et al.* [126] randomised patients with minimal symptoms to immediate cyclophosphamide, doxorubicin, methotrexate and procarbazine (CAMP) or lomustine, followed by CAMP at the start of symptoms. Although a significant difference in response rate (44% vs. 0%) was observed, survival was not different. Similarly measures of quality of life (time to decrease of performance score or loss of 12% body weight or progression of tumour or death) showed no differences. The other study [142], which showed a significant median survival benefit of 4 months in NSCLC patients with LD, was a comparison of a rather ineffective chemotherapy regimen plus placebo vs. chemotherapy plus mopidamol, a phosphodiesterase inhibitor. Whatever the mechanism of action of mopidamol, it is not cytotoxic and therefore lacks serious side-effects. Unfortunately response rates were not reported. Interestingly, the prognostic factors for survival differed from those observed in chemotherapy trials.

Relation between response rate and survival

Since several studies suggest a lack of relation between response rates and survival, available data in the reviewed combination chemotherapy trials about major response rate (CR+PR) and median survival were graphed (Fig. 1). 139 groups of patients were found to plot. The mean response rate was 26.5% (S.D. 17.3%, median 24%). Mean survival was 6.8 months (S.D. 2.5, median 6.1). Not surprisingly the majority of the response rates observed in the randomised trials (closed symbols) tended to be in the lower regions (under 35%). Overall, there was a significant correlation between response rate and survival ($r = 0.57, P < 0.0001$). Subgroup analysis showed that in the group with a response rate under 25%, no significant correlation existed ($r = 0.14, P = 0.22$), whereas above 25% a significant correlation was found ($r = 0.48, P < 0.0001$). This analysis suggests that the overall significant relation between response rate and survival is dependent of the existence of such an association above a response rate of 25%. Furthermore, although the numbers of studies with only LD or extensive disease (ED) patients are small, LD patients (squares) show a relation and ED patients (triangles) no relation between response

rate and survival. These data support the habit of reporting both response rate and survival and suggest the need to report survival by stage.

Randomised phase III trials of combination chemotherapy vs. best supportive care

In 6 studies of 747 patients [144–149], the response rate was 12–35%. All studies show a survival difference in favour of the chemotheapy arm (Table 2). The difference is significant in 3 studies, 1 of which contains the highest percentage of LD patients. The smallest difference is observed in the study by Ganz *et al.* [149], who entered only ED patients.

CONCLUSION AND RECOMMENDATIONS

The first obvious conclusion is that patients with advanced NSCLC are a heterogeneous group with a large variation of known and probably also unknown prognostic factors for response to chemotherapy and/or survival. This is important since NSCLC is rather insensitive to chemotherapy. Therefore a possible beneficial effect of chemotherapy will be small and limited to only some of the patients.

Evaluation of new drugs in phase II trials is hampered by the fact that the response rate is not only dependent on known but also on unknown prognostic factors, such as the centre where the study is done [111]. The standard procedure to overcome such a problem is randomisation. I therefore propose that randomised phase II trials, comparing a standard drug with a new compound, are required these days. The same shortcomings, connected with phase II studies of single agents, apply to phase II studies of combination chemotherapy. Since no firm conclusions, except feasibility, can be drawn from the studies of combination regimens, although they form the largest category in this review, it seems unlikely that new phase II studies of combinations will provide useful information.

The randomised phase II studies of single agents vs. combination chemotherapy, and one combination vs. another, do not provide convincing evidence that active single agents are worse than combination chemotherapy or that one combination differs from the other, unless something other than a cytotoxic drug is added [142]. One of the main reasons for this lack of differences may be that in randomised studies less strict selection criteria are used, many or only ED patients are entered and, in most studies, response rates below 30% are obtained. The same argument may be applied to the randomised trials of combination chemotherapy vs. supportive care. In all studies, a difference in survival is observed in favour of the chemotherapy arm, which was significant in 3 out of the 6 studies. The fact that the smallest difference was found in the study by Ganz *et al.* [149], who entered only ED patients, and the tendency towards a significant survival difference between the two groups of LD patients in the Australian study [147] supports this argument.

The analysis of the relation between response rate and survival, based on unselected data for this review, showed a significant correlation between both criteria, which was absent in patients with a response rate below 30% and in ED patients. Such a conclusion requires substantiation in prospective trials. However, it supports the data which show that survival benefit from chemotherapy should be investigated in a well-defined subgroup of patients with a high performance score, possibly limited tumour load and a high response rate.

I support the conclusion of Mulshine *et al.* [2] "that chemotherapy seems to have a modest but discernable antitumour activity", which is probably limited to a subgroup of patients. Therefore, I recommend repeating the randomised studies of active single agents vs. combination chemotherapy and combination chemotherapy vs. best supportive care in patients with a high performance score and limited tumour load. The response rate and survival should be analysed separated for LD and ED patients. Furthermore, randomised trials of chemotherapy vs. supportive care are needed in patients with symptoms and with

Table 2. Randomised phase III trials of combination chemotherapy vs. supportive care in NSCLC

Regimen	No. of patients	Response rate	Survival (mo)	*P*	Percent LD	Ref.
MACCe	39	35%	7.6	<0.0005	50%	144
Placebo		0%	2.1			
CEP/MVpCe	89	21%	8.5	NS	40%	146
BSC		0%	5.0			
VdsP	233	25.3%	8.1			
CAP		15.3%	6.1	0.02	14%	148
BSC		0%	4.2			
VdsP	201	28%	5.7	NS	27%	147
BSC		0%	4			
VdsP	LD 25	36%	10.7	0.13		
BSC	LD 39	0%	6			
VdsP	43	39%	6.4	<0.001	0%	145
BSC		0%	2.2			
PVbl	60	12%	5.1	NS	0%	149
BSC		0%	3.3			

M = methotrexate, A = doxorubicin, C = cyclophosphamide, Ce = CNU, P = cisplatin, Vp = vepesid, Vds = vindesine, Vbl = vinblastine and E = epidoxorubicin.
BSC = best supportive care.
NS = not significant.

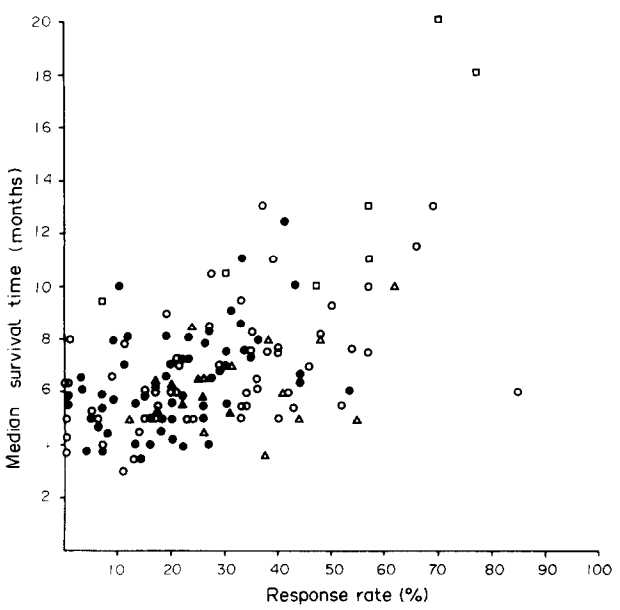

Fig. 1. Relation between response rate, induced by combination chemotherapy, and median survival time of 139 groups of patients. △ = extensive disease, □ = limited disease and ○ = mixture of extensive and limited disease. Open symbols = data from non-randomised phase II trials and closed symbols = data from randomised phase III trials.

a lower performance status to investigate relief of symptoms and quality of life, if both these endpoints can be properly defined.

Data from the trial of Zacharski *et al.* [142] suggest that studies with drugs that interfere with tumour growth in a different way from cytotoxic drugs, are warranted.

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The New Genetics and Non-Hodgkin Lymphoma

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THE IDENTIFICATION of genes and proteins that are important in the pathogenesis and behaviour of lymphomas has proceeded rapidly in the past decade. These advances are of interest to clinicians, firstly because they may provide a new system of classification based on cytogenetic abnormalities, gene rearrangement and gene expression, and secondly because it may eventually be possible to manipulate these genes as targets for tumour-specific therapy. This article reviews some of the recurrent chromosome translocations found in B-cell non-Hodgkin lymphoma (NHL), how these have led to the molecular cloning of previously unrecognised genes and how these translocations influence the *in vivo* behaviour of the tumour.

RECURRENT CHROMOSOMAL TRANSLOCATIONS

Although lymphoma cells often grow well *in vitro*, obtaining and interpreting high resolution chromosome preparations makes heavy demands on time and experience. Despite these difficulties, many recurrent chromosomal translocations have been recognised in B-cell NHL (Table 1 and Fig. 1). In Table 1, three varieties of translocation have been distinguished. Group 1 DNA sequences are known on either side of the translocation breakpoint. Group 2 DNA sequences are known only on one side of the translocation. These translocations usually involve immunoglobulin on T-cell receptor (TCR) loci which allows rapid molecular cloning of the breakpoint. Group 3 DNA sequences are unknown on both sides of the breakpoint.

Some of these translocations may be extremely common within a given histological subgroup of disease—e.g. t(8;14) (q24.1;q32.1) in Burkitt's lymphoma and t(14;18) (q32.1;q21) in follicular lymphomas. This led to the idea that specific translocations were linked to a specific histological disease with a characteristic clinical behaviour; thus, Burkitt's lymphomas follow an aggressive clinical course, while follicular lymphomas are mostly indolent. In the acute myeloid leukaemias this idea still holds true with certain translocations being associated with a given cytological type of leukaemia, for example t(15;17) in acute promyelocytic leukaemia. However, further analyses have revealed that in B-cell NHL this linkage may not be so "tight"; t(14;18) may be found in up to 30% of diffuse B-cell NHL as well as in rare cases of B-cell acute leukaemia.

The presence of the t(14;18) translocation in cytologically diverse B-cell tumours is a paradigm of the multistep model of tumorigenesis [1, 2]. Follicular lymphomas with t(14;18) as the only cytogenetic abnormality generally grow slowly and respond well to therapy; in contrast, rare tumours with both t(14;18) and t(8;14) translocations are almost invariably of leukaemic phenotype, follow an aggressive clinical course and respond

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