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Symptomatic benefit from gemcitabine and other chemotherapy in advanced non-small cell lung cancer: changes in performance status and tumour-related symptoms

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Results from recent trials challenge the traditional view that chemotherapy offers no survival or quality of life benefits over best supportive care. Meta-analyses of recent trials reveal a modest survival benefit for combination chemotherapy over best supportive care, although there is no strong evidence from randomized trials for superiority of combination over single-agent therapy. In chemotherapy trials where data on performance status change were collected, performance status improved in one-third of patients and remained constant in a further third. Fewer studies have measured changes in specific disease-related symptoms, but there are data from studies with gemcitabine which show improvements in a range of symptoms, including cough, haemoptysis, pain, dyspnoea and anorexia. Thus more patients benefit from chemotherapy than may be suggested by objective response. Surveys have shown that patients are more likely to accept intensive chemotherapy for what are perceived by health care professionals as potentially small benefits. Studies have shown evidence of cost savings associated with chemotherapy over best supportive care.

Introduction

The two major arguments against the use of chemotherapy in advanced non-small cell lung cancer (NSCLC) are (1) marginal, if any, survival improvement, and (2) chemotherapy toxicity which is often considered to be severe and even unacceptable. Recent results of more modern chemotherapy and experience with newer agents challenge these traditional arguments. The reticence over the use of chemotherapy fails to take account of the large number of patients presently dying of advanced NSCLC for whom improvement with chemotherapy is the only real possibility of treatment advance.

It is true however that relatively few active agents have been identified. The most active in terms of overall response rates of 15% or more are shown in Table 1.[1] However, the rate for complete responses is less than 5%. The use of more sophisticated imaging methods for assessing response leads to a fall in response rates of the newer agents compared with those of older agents assessed by less stringent methods.[2] Nevertheless, gemcitabine, a new nucleoside analogue, has a response rate of 20% (95% confidence limits: 15.7–24.7), assessed from a database of over 300 patients with advanced NSCLC.

Table 1. Single-agent response rates in NSCLC (in > 100 patients from > 4 studies)

Drug	No. patients	Overall response rate (%)	Mean objective response rate (PR + CR) (%)
Ifosfamide	237	7–32	26
Cisplatin	140	6–32	20
Mitomycin C	115	9–40	20
Vindesine	288	6–31	17
Doxorubicin	261	6–38	13
Etoposide	195	3–21	11
Methotrexate	247	0–26	10
Cyclophosphamide	369	4–42	8

PR = Partial response, CR = complete response.

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Table 2. Early combination chemotherapy studies for NSCLC (> 40 patients)

Combination	Objective response * (%)	Overall survival * (median months)
CTX + CCNU	9	4
COMB (CTX, VCR, MeCCNU, BLEO)	5 (24)	2.5–3.5 (2–5)
CAMP (CTX, ADRIA, MTX, PCZ)	17 (35)	6 (8.4)
MACC (MTX, ADRIA, CTX, CCNU)	12 (44)	3.5 (8.0)
BACON (BLEO, ADRIA, CCNU, VCR, N_2M)	21 (43)	4 (5)

CTX = Cyclophosphamide; CCNU = lomustine; O = vincristine; MeCCNU = methylCCNU; BLEO = bleomycin; ADRIA = doxorubicin; PCZ = procarbazine; MTX = methotrexate; N_2M = nitrogen mustard. * Numbers in parentheses refer to response rates reported in initial studies.

Table 3. Chemotherapy vs best supportive care in locally advanced and metastatic NSCLC: older trials

Reference	Regimen	No. patients	OR (%)	Median survival (months)		Survival at 1 year (%)	*p* value
				CT vs No CT		CT vs No CT	
Wolf (1960) [29]	N_2M	168	NR	4.3	3.3	NR	NR
Green (1969) [30]	N_2M	1364	NR	2.6	2.2	NR	NS
	Cyclo		NR	2.9			
Durrant (1971) [31]	N_2M	249	NR	8.7 †	8.4 †	NR	NS
Laing (1975) [32]	PCZ	188	NR	6.9	7.9	NR	< 0.05
	MVPP			2.7			

† Mean survival. OR = objective response, CT = chemotherapy. N_2M = Nitrogen mustard; Cyclo = cyclophosphamide; PCZ = procarbazine; MVPP = nitrogen mustard, vinblastine, procarbazine, prednisolone. NR = Not recorded, NS = not significant, $p > 0.05$.

This 20% response rate is comparable to the older active agents and was confirmed by an independent Oncology Review Board procedure which examined scans and other evidence for response documentation.

In the 1970s single drugs with low activity, i.e. overall response rates < 15%, were combined in an attempt to obtain better response rates and increased survival (Table 2).[3,4] The response rates reported with these drug combinations were better than those for the same drugs used as single agents. However, later and larger studies failed to confirm the higher response rates (Table 2).[3,4] There are also data from the older randomized studies before the mid-1970s, reporting that chemotherapy was no better and indeed on occasions resulted in worse survival when compared with best supportive care in advanced NSCLC (Table 3).[5] It is not surprising therefore that chemotherapy for NSCLC was considered to be of no value, and this view is still not uncommon.

Evidence for activity of chemotherapy in advanced non-small cell lung cancer

Survival

One important question is whether chemotherapy offers any advantage over best supportive care in advanced NSCLC. The earlier randomized studies used drugs which would now be considered ineffective (Table 3).[5] There is now evidence from the more recent randomized studies that survival benefit, although modest, can be obtained with chemotherapy over best supportive care, which has included palliative radiotherapy (Table 4).[5–7] The large study from Canada was later assessed in terms of cost effectiveness, and economic advantage was claimed for patients treated with chemotherapy.[8] The use of the CAP regimen vs best supportive care resulted in the saving of Canadian $7625 per year of life gained apparently because of a reduction in the cost of medical resources required by patients

Table 4. Chemotherapy vs supportive care in locally advanced and metastatic NSCLC: recent trials

Reference	Regimen	No. patients	OR (%)	Median survival (months)		Survival at 1 year (%)		*p* value
				CT vs No CT		CT vs No CT		
Cormier (1982) [33]	MACC	39	35	7.6	2.1	35	6	0.005
Rapp *et al.* (1988) [8]	CAP	150	15	6.1	4.2	21	10	0.01
	PV		25	8.1		22		
Ganz *et al.* (1989) [15]	PVb	48	22	5.1	3.3	20	10	NS
Woods *et al.* (1990) [16]	PV	201	28	6.8	4.3	NR	NR	NS
Buccheri (1990) [34]	MACC	175	8	8.0	5.0	27	17	0.01
Kaasa *et al.* (1991) [35]	PE	87	11	5.0	3.8	NR	NR	NS
Cellerino *et al.* (1991) [36]	CEP/MEC	128	21	8.5	5.0	32	23	NS
Quoix (1991) [37]	PV	49	42	7.1	2.6	NR	NR	< 0.001
Leung (1992) [38]	PE	119	21	12.4	8.7	53	30	0.05
Cartei (1993) [39]	PCM	102	25	8.5	4.0	39	12	0.0001

OR = Overall response rate, CT = chemotherapy. MACC = Methotrexate, doxorubicin, cyclophosphamide, CCNU; CAP = cyclophosphamide, doxorubicin, cisplatin; PV = cisplatin, vindesine; PVb = cisplatin, vinblastine; PE = cisplatin, etoposide; CEP = cyclophosphamide, epirubicin, cisplatin *alternating with* MEC = methotrexate, etoposide, CCNU; PCM = cisplatin, cyclophosphamide, mitomycin C. NR = Not recorded, NS = not significant, $p > 0.05$.

Table 5. Multivariate analyses of prognostic variables for survival in patients given chemotherapy for advanced NSCLC

Reference	Stanley (1980) [40]	Lanzotti (1977) [41]	O'Connell (1986) [42]	Miller (1986) [43]	Finkelstein (1986) [44]	Klastersky (1989) [45]	Ferguson (1990) [46]	Luedke (1990) [47]	Albain (1991) [12]
No. patients	5138	428	378	483	893	176	772	435	2531
PS	Y	Y	Y	Y	Y	Y	–	Y	Y
Age	–	Y	N	N	N	Y	–	N	Y
Weight loss	Y	Y	N	–	Y	N	–	–	N
Female	–	–	Y	Y	Y	N	Y	N	Y
Extrathoracic metastases	Y	Y	Y	Y	Y	Y	–	N	(Y)
SCF nodes	Y	Y	–	–	N	–	–	–	–
Bone	–	Y	Y	N	Y	–	–	N	–
Liver	Y	Y	N	N	Y	–	–	Y	–
Brain	–	Y	N	N	–	–	–	Y	–
Histology	N	N	N	–	Y	N	–	N	–
Previous RT	N	N	N	–	N	–	–	N	–
LDH	–	–	Y	–	–	–	–	–	(Y)
Previous surgery	Y	–	N	–	N	–	–	–	–
Survival associated with OR	–	–	Y	–	–	–	–	–	–
Chemotherapy	–	N	–	Y	Y	N	–	N	Y

PS = Performance score, RT = radiotherapy, LDH = lactate dehydrogenase, OR = objective response, Chemotherapy = chemotherapy with/without radiotherapy. – = Not tested, Y = significant variable, N = not significant variable, (Y) = subset of 362 patients with good PS in recent studies.

Table 6. Single agent vs combination chemotherapy studies for advanced NSCLC (> 100 patients)

Reference	No. patients	Regimen	Objective response (%)	Median survival	*P* value (for survival)
Davis (1980) [48]	124	C	5	5.1 months	NS
		CL	8	4.4 months	
		CLA	6	4.7 months	
Elliott (1984) [49]	105	Vd	7	4 months	0.008
		VdP	33	11 months	
Einhorn (1986) [50]	124	Vd	14	18 weeks	NS
		VdP	27	26 weeks	
		VdPM	20	17 weeks	
Sorenson (1987) [51]	279	Vd	22	29 weeks	NS
		CML	23	29 weeks	
		CMLVd	27	34 weeks	
Kubota (1988) [52]	155	Vd	12	9 months	NS
		VdP	29	10 months	
Klastersky (1989) [53]	176	P	19	26 weeks	NS
		PE	26	22 weeks	
Bonomi *et al.* (1989) [14]	743	VbP	13	25.1 weeks	0.008
		MVbP	20	22.7 weeks	
		MVbP/CAMP	13	25.0 weeks	
		Carboplatin	9	31.7 weeks	
		Iproplatin	6	26.1 weeks	
Rosso (1990) [54]	216	E	7	6 months	NS
		PE	26	8 months	
Crino (1990) [55]	156	P	4	18 weeks	0.001
		PE	30	35 weeks	
		PEM	26	37 weeks	
Luedke (1990) [47]	435	Vd	1	14.8 weeks	NS
		VdM	27	20.4 weeks	
		VdP	19	24.7 weeks	
Vokes (1992) [56]	101	6TG	4	6 months	NR
		PF	29	10 months	
Giaccone (1993) [57]	225	T	6	5.8 months	0.019
		PT	22	7.2 months	
Veeder (1993) [58]	150	M	27	16.3 weeks	NS
		MVP	32	23.3 weeks	
Bang (1993) [59]	127	P	19	8.2 months	NS
		PEVb	43	11.0 months	
Le Chevalier (1994) [60]	612	Vi	14	31 weeks	≤ 0.04
		ViP	30	40 weeks	
		VdP	19	32 weeks	
Depierre (1994) [61]	240	Vi	16	32 weeks	NS
		ViP	43	33 weeks	

C = Cyclophosphamide; A = doxorubicin; L = lomustine; E = etoposide; Vd = vindesine; P = cisplatin; M = mitomycin C; CAMP = cyclophosphamide, doxorubicin, methotrexate, procarbazine; CML = cyclophosphamide, methotrexate, lomustine; CMLVd = as CML + vindesine; Vb = vinblastine; Vi = vinorelbine; T = teniposide; 6TG = 6 thioguanine; F = fluorouracil and leucovorin. NS = Not significant, NR = not recorded.

on CAP compared with the cost incurred by those receiving supportive care.[9] A meta-analysis of seven trials has been published which showed an advantage for combination chemotherapy, at least in terms of a reduction in mortality during the first 6 months of treatment.[10] A more convincing and

complete meta-analysis has recently been reported involving eleven trials and 1190 patients.[11] There was a 10% improvement in the 1 year survival rate (from 16% to 26%) with a 2 month improvement in the median survival from 6 to 8 months when platinum-based regimens were used. Interestingly, with the older long-term alkylating agents, treatment was less satisfactory in terms of 1 year survival (7% less) and median survival (1 month less).[11] Although these differences in survival are small, it is clear that a subset of advanced NSCLC patients do derive survival benefit from chemotherapy. It is no longer correct to assume that there will be absolutely no survival advantage for patients receiving chemotherapy for advanced NSCLC. It is important to identify the characteristics of the patients most likely to benefit from treatment, and a summary of statistically significant independent prognostic factors derived from multivariate analyses is given in Table 5.[5] Age was not a consistent prognostic factor. Surprisingly, in the large SWOG analysis, age 70 years was a favourable prognostic factor.[12] The selection of patients with NSCLC for chemotherapy based on age alone is therefore not a valid criterion.

Interestingly, there is no strong evidence as yet from randomized trials that combination chemotherapy has a significant survival advantage over the use of single agents (Table 6).[5–7,13] Indeed carboplatin as a single agent used as initial therapy had a superior survival compared with combination chemotherapy involving other cisplatin regimens.[14] Of 16 randomized trials comparing single-agent activity, usually with a vinca, platinum combination treatment, only four studies have shown a statistically significant survival advantage for combination chemotherapy (Table 6).[5–7,13] As yet there is no agreed standard chemotherapy for advanced NSCLC, although most oncologists would consider the use of cisplatin-based regimens. These platinum combinations give overall response rates of around 30% with median survival of about 6 months. There is clearly much room for improvement and it is vital to recognize the activity of new agents, especially those with a more satisfactory toxicity profile such as gemcitabine.

Performance status change

It is often assumed that the patients' performance status and quality of life inevitably deteriorate with chemotherapy for advanced NSCLC. In the past this was particularly true for patients who had a low performance status before starting treatment. It would appear that approximately one-third to one-half the patients in the randomized trials experienced some form of severe side effect, particularly with the platinum-based regimens (Table 4).[6] However, these data do not take into account the better control of emesis by the newer 5-HT_3 antagonists. Despite the side effects which were judged to be considerable with chemotherapy, there was no difference in terms of performance status or patient weight between chemotherapy and best supportive care.[8,15,16] Nevertheless in one phase II study, although there was a 48% objective response rate with a platinum combination, the fall in performance status was considered to remove any potential advantage for the majority of patients.[17] It is therefore not always reasonable to suppose that response rate is a surrogate for improvement in patients' symptoms.

Conversely, it is important to recognize a number of chemotherapy studies, mainly from Europe, in which data on performance status change were collected. These data indicate that in about one-third of patients, performance status actually improves and in another third it remains constant (Table 7).[5,18] Indeed, improvement in performance status occurred in a considerably higher proportion of patients than those who were characterized as having tumour response. Information from a recent Medical Research Council study of palliative radiotherapy in advanced NSCLC is provided in Table 7. In this radiotherapy study, steroids and other adjuncts to supportive care were allowed and are likely to have improved the performance status over that obtained with radiotherapy alone.[19] These data can be compared with the chemotherapy studies in which performance status change was carefully described with the newer cisplatin combinations and also with single-agent gemcitabine (Table 7). In the gemcitabine study, steroids as supportive care were not allowed during chemotherapy. In the Copenhagen/Manchester study described by Anderson *et al.*, gemcitabine resulted in 31% of patients improving their performance status over at least four consecutive observations for a period of 28 days.[18] The complete database for gemcitabine indicated that 52% of patients improved from an original WHO performance status of 2 (Table 7). In the radiotherapy study the criterion for improvement was based on just one assessment.[19]

Another important aspect of these studies was that the performance status improvement and symptom relief were similar when obtained with either single-agent gemcitabine or combination platinum chemotherapy. Palliative radiotherapy in the case of patients treated with gemcitabine was no longer

Table 7. Change in performance status

Reference	Regimen	No. patients	Objective response (%)	Median survival (months)	Performance (% of pts)		
					+	s	–
Thatcher (1986) [62]	I	48	29	5	37	35	28
Bakker *et al.* (1986) [17]	PVdB	28	48	8	1 pt	–	–
Thatcher (1988) [63]	IC	45	38	7	40	27	33
Cullen (1988) [64]	MIP	74	56	9	30	61	9
Kris (1990) [65]	EDAM MV	85	59	12.8	44	40	26
Gurney (1991) [66]	IM	42	24	7	24	64	12
von Rohr (1992) [67]	IM Carbo	34	32	11	37	30	33
MRC (1991) [19]	XRT	369	30	6	40 *	–	–
Anderson (1994) [68]	Gemcitabine	82	23	8.1	31	67	2
All studies	Gemcitabine	332	20	8.1–9.2	52 *	–	–

Performance status: + = better, s = stable, – = worse. * Patients improving from PS 2. I = Ifosfamide; PVdB = cisplatin, vindesine and bleomycin; C = cyclophosphamide; M = mitomycin C; P = cisplatin; V = vinblastine; 10 EDAM = edatrexate; Carbo = carboplatin; XRT = radiotherapy.

Table 8. Symptom improvement

Treatment	XRT	MVP	PV + M or I	MIP	Gemcitabine	
Reference	MRC (1991) [19]	Hardy (1989) [22]	Fernandez (1989) [23]	Cullen (1993) [24]	All studies (1994)	
					All	Mod./severe
Cough	60%	71%	45%	70%	44%	73%
Haemoptysis	84%	–	91%	92%	63%	100%
Pain	78%	63%	47%	77%	32%	37%
Dyspnoea	61%	65%	78%	46%	26%	51%
Anorexia	67%	–	50%	58%	29%	38%
Response	30%	21%	42%	56%	20%	
Median survival (months)	6.4	6	NR	9.8	8.1–9.2	

XRT = Radiotherapy; PV = cisplatin, vindesine with either M = mitomycin or I = ifosfamide; MVP = mitomycin, vinblastine, cisplatin; MIP = mitomycin, ifosfamide, cisplatin. NR = Not recorded. For gemcitabine, "All" refers to the percentage of patients with symptoms (mild, moderate and severe) who had relief; "Mod./severe" refers to the percentage of patients with just moderate and severe symptoms who improved.

necessary in about one-third due to improvement in symptoms.[18] Although these data are of interest, formal quality of life studies in NSCLC are almost entirely lacking. Most studies assess "quality of life" during treatment by proxy indices such as performance status change and symptom relief. The one randomized comparative trial in the context of chemotherapy against radiotherapy was from Norway. The results indicated that patients were willing to trade treatment toxicity for the chance of responding to treatment with no detriment in quality of life for those patients treated with cisplatin-based chemotherapy compared with those treated with radiotherapy.[20]

It should now be recognized that the reporting of changes in performance status, disease-related symptoms and hopefully, in the future, formal quality of life measures should be an important aspect of clinical evaluation of patients receiving treatment for advanced NSCLC. Gathering data from properly validated questionnaires on quality of life is costly and labour-intensive, with difficulties still in the analysis of the data. However, there are now instruments to measure quality of life, e.g. the Rotterdam symptom check list, hospital anxiety depression scale and the newer EORTC QLQ-C30 lung cancer module.[21] The routine use of these questionnaires in cancer therapy trials should help to determine

Table 9. Attitudes to three potential benefits of two forms of chemotherapy: intensive and mild (numbers represent percentages of individuals who would accept chemotherapy (intensive and mild, respectively) for a given potential benefit)

Potential benefit	General public	Cancer nurses	General practitioners	Radiation oncologists	Medical oncologists	Patients
Intensive chemotherapy						
Cure (1%)	19	13	12	4	20	53
Survival increased by 3 months	10	6	3	0	10	42
Symptom relief (1%)	10	6	2	0	7	43
Mild chemotherapy						
Cure (1%)	35	39	44	27	52	67
Survival increased by 3 months	25	25	27	13	45	53
Symptom relief (1%)	19	26	21	2	12	59

Slevin *et al.*, 1990.[28]

more effective treatments and also identify those patients with psychosocial problems who could benefit from counselling and other forms of intervention.

Symptom relief

As indicated above, the performance status of patients treated with chemotherapy including single agents does not always deteriorate, and indeed can improve quite markedly. But fewer studies are available which have described changes in disease-related symptoms such as breathlessness etc.[22–24] In the single-agent gemcitabine studies, attempts were made to determine the relief or otherwise of disease-related symptoms.[18] Comparisons with palliative radiotherapy and other forms of combination chemotherapy using platinum which have recorded changes in the symptoms are displayed in Table 8. Symptom relief was obtained in a good proportion of patients treated with palliative radiotherapy and also with combination platinum chemotherapy. Perhaps most interestingly there was marked benefit with single-agent gemcitabine with the potential for use on an out-patient basis. The relief of pain with gemcitabine in 32% of the patient group was reflected also by a 23% decrease in the use of analgesics. Symptom improvement was even more marked with gemcitabine for those patients who were classed as having moderate or severe symptoms before treatment. These data suggest that patients with significant and even severe symptoms should not on this basis alone be excluded from chemotherapy trials. The duration of symptom relief was described in the radiotherapy study as being approximately half the median survival time, i.e. 3 months.[19] With gemcitabine, the duration of improvement was more variable for specific symptoms. There was marked relief for anorexia and haemoptysis (medians of 2–3 months), dyspnoea and cough (medians somewhat longer, 3–4 months) and chest pain (median 5 months), with a median survival of 8–9 months. The relief of disease-related symptoms seen with gemcitabine was achieved without the introduction of troublesome toxicities. Gemcitabine has a modest toxicity profile, the main side effects being transient flu-like symptoms, peripheral oedema and skin rash.

Professional "bias"

It is important to note that patients' and doctors' attitudes to treatment often differ markedly. Chemotherapy for advanced NSCLC was considered to be of little or no value in a survey of 118 Canadian doctors who treated lung cancer. Only 15% of the respondents would have chemotherapy if they had symptomatic metastatic NSCLC,[25] a view which has not changed in a recent repeat investigation.[26] Furthermore, the treatment, if any, which patients with advanced NSCLC receive is extremely variable throughout Europe and elsewhere. Differences in the perceived prognosis which in itself often differs markedly between doctors is reflected in the amount of therapy given.[27]

When treatment preferences of *patients* with cancer were compared with those of radiotherapists, medical oncologists, cancer nurses and general practitioners, interesting results were obtained (Table 9).[28] Intensive chemotherapy in this survey was described as having a considerable number of side effects, including severe nausea and vomiting, hair loss, frequent use of needles, drips, weakness,

repeated admissions to hospital etc., whilst the mild chemotherapy regimen was described as having many fewer side effects with only occasional use of needles, admission to hospital about once a month, etc. Substantial differences were shown between the cancer patients, doctors and cancer nurses. Patients with cancer were much more likely to accept intensive chemotherapy, let alone mild chemotherapy, for what are perceived by health care professionals to be potentially small benefits (Table 9). After completing 3 months of chemotherapy the responses were again compared on a repeat questionnaire, with little change.

Conclusions

At present only a few agents have reliably demonstrated response rates of more than 15% in advanced NSCLC patients. It is therefore very important to identify active new agents which provide not only objective tumour shrinkage but also measurable patient benefit (e.g. reduction of disease-related symptoms, improvements in performance status, survival), and which can achieve this with a more attractive side-effect profile. Gemcitabine, the novel nucleoside analogue, fulfils these criteria with a response rate of 20% and significant symptom relief; and is also of considerable interest as it lacks the myelosuppression and alopecia associated with most chemotherapeutic agents, the main side effects being transient flu-like symptoms with occasional peripheral oedema and skin rash. These symptoms may be relieved with low-dose prednisolone. Finally, health care professionals should be aware of inherent bias concerning the use of chemotherapy in advanced NSCLC. Treatment options should be presented to patients without prejudging what they will or will not accept.

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