

Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future

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Introduction

The success of chemotherapeutic measures in the treatment of small cell lung cancer has tended to overshadow the more common yet more intractable problem of the management of the patient with non-small cell lung cancer (NSCLC). In spite of more than a decade of intensive research, the practising clinician still lacks clear guidelines. A reappraisal of the position of both radiotherapy and chemotherapy in the treatment of the disease is of high priority. With regard to chemotherapy, single agent data are difficult to interpret in view of the heterogeneity of patient populations with respect particularly to prior therapy, extent of disease and performance status. Furthermore the dose and schedule used for individual agents show considerable variation between trials.

The most serious difficulty in interpretation of the data relates to the chosen end-points. Tumour response rates are universally reported, but more basic data on the effect of treatment on the quality of life, the symptoms and ultimately the survival of patients on study is often lacking. Comparative data are surprisingly scanty. Only a handful of studies have compared single-agent with combination chemotherapy (2, 27, 31-34, 43, 49, 80) or chemotherapy with radiotherapy and supportive therapy for limited disease (25, 48). Two studies have compared chemotherapy with placebo in patients with advanced NSCLC (13, 67).

This review attempts to reappraise the data on the activity of chemotherapeutic agents in NSCLC. Published studies have been reviewed only if they have included at least ten patients and if the minimum criterion of response has been defined as a greater than 50% decrease in the size of measurable lesions. The data on response rates for squamous cell, adenocarcinoma and large cell types have been recorded when these can be abstracted from the original publication. "Undifferentiated" or "anaplastic" cell types have not been included.

Single-agent activity in NSCLC

Fifteen drugs have been studied in more than 100 patients with NSCLC. Overall response rates are given in Table 1. Four drugs (ifosfamide, cisplatin, mitomycin C and vindesine) appear to have moderate activity in NSCLC and six drugs (adriamycin, dibromodulcitol, Baker's antifol, etoposide, hexamethylmelamine and methotrexate) show some evidence of activity. The most-studied single agent, cyclophosphamide, has a disappointingly low overall response rate of 8%.

Ifosfamide has been evaluated in four studies (see Table 2). Response rates in three trials to both a divided daily dose schedule (17, 51) and to a single-dose schedule (41) have ranged from 24 to 32% with a median survival time for all three studies of 10 months for responders and three to four months for nonresponders to therapy. Costanzi *et al.* (16) compared the single high-dose with the low-dose five-day regimen, and found a lower incidence of haemorrhagic cystitis with the latter schedule. None of these studies employed 2-mercaptoethane sulphonate, an agent which has been shown to ameliorate the urothelial toxicity.

Five reports have been published on the activity of cisplatin in NSCLC (see Table 2). Doses have ranged from 75 to 120 mg/m² every three to six weeks. Response rates have shown considerable variation and do not appear to relate to dosage. The two largest studies (23, 77) reported response rates of 25% and 32% respectively. The response duration was around 3 months and the median survival time 5 months for both trials. Three smaller studies (4, 9, 58) reported response rates below 10%. Survival data were not recorded for the latter studies.

An early report by Whittington *et al.* (78) on a divided dose schedule of mitomycin C gave a low response rate. Recent data, however, have been more encouraging and a regimen of 20 mg/m² every three to six weeks has produced response rates of 19 to 40% (see Table 2). The median survival time of 3 months described in one study (59) is less impressive.

Nine published reports are available for vindesine (see Table 2). Doses have ranged from 3 to 4 mg/m² weekly for up to 10 weeks. In spite of the uniformity of dose and schedule,

Table 1 Response rates in NSCLC. Drugs studied in more than 100 patients

Drug	No. of trials	No. of responders (no. evaluable)	Range of response rates (%)	Mean response rate (%)
Ifosfamide	4	62 (237)	7-32	26
Cisplatin	5	28 (140)	6-32	20
Mitomycin C	4	23 (115)	9-40	20
Vindesine	9	49 (288)	6-31	17
Adriamycin	5	34 (261)	6-38	13
Dibromodulcitol	1	15 (115)	-	13
Baker's antifol (Triazinate)	3	14 (119)	5-15	12
Etoposide (VP 16-213)	4	21 (195)	3-21	11
Hexamethylmelamine	3	18 (166)	0-17	11
Methotrexate	6	25 (247)	0-26	10
Cyclophosphamide	5	30 (369)	4-42	8
Mechlorethamine	1	9 (109)	-	8
CCNU	4	12 (161)	2-28	7
AMSA	3	6 (143)	0-7	4
Chlorozotocin	3	3 (128)	0-7	2

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Adriamycin highest response every three schedules and 4 months

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NSCLC. Overall response rates for mitomycin C and vindesine, adriamycin, dibromodulcitol, and cyclophosphamide show some evidence of activity, but as a disappointingly low

response rates in three trials using a high-dose schedule (41) have been reported. Studies of 10 months for cyclophosphamide, Costanzi *et al.* (16) and others, and found a lower response rate. These studies employed schedules that ameliorate the urothelial

in NSCLC (see Table 2). Response rates have been reported. The two largest studies have shown response rates of 10% to 20%. Three smaller studies were not recorded for

schedule of mitomycin C. Response rates are more encouraging and a response rate of 19 to 40% (see Table 2). One study (59) is less

Doses have ranged from 10 to 100 mg/m² of dose and schedule,

response rates have shown considerable variation. Five trials have given response rates ranging from 17 to 31% and four trials have shown response rates of less than 10%. In one of the latter trials (76) the majority of patients had received prior chemotherapy including treatment with vincristine. Survival data are only available for two studies. Gralla *et al.* (39) reported a 9 month median survival time for responders to treatment; Luedke *et al.* (50) reported an overall survival time of 3.5 months.

Adriamycin has shown marginal evidence of activity in NSCLC (see Table 2). The highest response rate of 38% was reported in an early trial employing a dose of 75 mg/m² every three weeks (44). Subsequent published studies have employed divided dose schedules and response rates have varied from 6 to 24%. Median survival times of 3 months and 4 months have been reported in two studies (15, 47).

A single report is available for dibromodulcitol activity in NSCLC (see Table 2). A response rate of 13% with a median survival time of 6 months was described. Baker's antifol (triazinate) has shown marginal activity in three studies (see Table 2). Survival data were not reported. Response rates to etoposide (VP 16-213) have shown considerable variation and do not clearly relate to the dose or schedule employed (see Table 2). Two trials using intravenous and oral divided dose schedules (1, 30) have given 18% and 21% response rates respectively with a median survival time of 6 to 8 months. A further two studies have given response rates of less than 10%. In one of the latter trials (12) half of the patients had received prior chemotherapy. Hexamethylmelamine gave an encouraging 17% response rate in an early trial (24) but this has not been confirmed in later studies (see Table 2).

Methotrexate has been evaluated in six trials (see Table 2). Response rates show considerable variation and again show no clear relation to the dose employed. Three high-dose studies (35, 68, 74) gave response rates respectively of 0%, 4% and 26%. Reported median survival times have ranged from 3 months to a surprising 12 months in the high-dose study of Tornoy *et al.* (74). The response rate in the latter study was zero! The one randomized study reported in which methotrexate was compared with placebo (67) showed no significant difference in overall survival times between the two arms.

Cyclophosphamide is the most studied single agent in NSCLC (see Table 2). Response rates have generally been disappointingly low. A recent study of a higher dose in a small series of patients (73) gave a response rate of 42%. The response duration, however, was short and the median survival time of 4 months was similar to that reported in trials employing a lower dose. A single report is available on mechlorethamine in NSCLC (see Table 2). A response rate of 8% with a median survival time of 3 months was described. With the exception of an early report (72), response rates to CCNU have been less than 10% (see Table 2). Survival data are not available for the four published trials. AMSA (see Table 2) and chlorozotocin (see Table 2) have similarly given disappointing results in terms of response rates. A single AMSA report gave a median survival time of 5 months.

Minimal data are available on a further 20 drugs studied in less than 100 patients (see Table 3). Response rates above 10% have only been reported for two drugs, vinblastine and procarbazine. In each case only one report on a small series of patients is available.

In summary, objective response and survival data suggest that ifosfamide, cisplatin, mitomycin C and vindesine are agents with some degree of activity in NSCLC. Adriamycin, dibromodulcitol, Baker's antifol, etoposide, hexamethylmelamine, methotrexate, vinblastine and procarbazine may be active agents, but further data on optimal doses and schedules are required.

With regard to the effect of single-agent chemotherapy on the quality of life of individual

RESULTS

Response (%)	Mean response rate (%)
32	26
32	20
40	20
11	17
38	13
5	13
11	12
7	11
6	10
2	8
8	8
	7
	4
	2

Table 2. Single agents in NSCLC

Reference	Regimen	No. of responders (no. evaluable)				Response		
		Squa- mous	Adeno- carcin- oma	Large cell	Totals	Rate (%)	Duration (months)	Median survival (months)
<i>Ifosfamide</i>								
51	1.2 g/m ² /d i.v. × 5, then once weekly	4 (13)	5 (16) all cell types	1 (2)	10 (31)	32	NR	10 ⁺ , 4 ^a
61	1.2 g/m ² /d i.v. × 5 q 4 wks	15 (55)	9 (38)	8 (19)	32 (112)	7	NR	NR
17	1.2 g/m ² /d i.v. × 5 q 4 wks	12 (39)	7 (34)	0 (7)	19 (80)	29	NR	10 ⁺ , 3 ^b
41	4.0 g/m ² i.v. q 3 wks	29 (94)	21 (88)	9 (28)	52 (237)	24	6 (med.)	10 ⁺ , 3 ^b
	Totals	31	24	32	26	26		
	Response rate (%)							
<i>Cisplatin</i>								
58	75 mg/m ² i.v. q 3 wks	0 (1)	1 (5)	0 (5)	1 (11)	9	NR	NR
4	15 mg/m ² i.v. × 5 days q 4 wks	—	2 (22)	—	2 (22)	9	1, 1	NR
23	120 mg/m ² i.v. q 3 wks	7 (39)	7 (20)	1 (2)	15 (61)	25	3.5 (med.)	5
9	120 mg/m ² i.v. q 4-6 wks	1 (6)	0 (9)	0 (3)	1 (18)	6	5	NR
77	75 mg/m ² i.v. weekly for 3 wks, then q 3 wks	6 (15)	3 (12)	0 (1)	9 (28)	32	3 (med.)	5 ^a , 3 ^b
	Totals	14 (61)	13 (68)	1 (11)	28 (140)	20		
	Response rate (%)	23	19	9	20			
<i>Mitomycin C</i>								
78	0.05 mg/kg i.v. × 10 days, repeat after 2 wks	0 (22)	3 (11)	—	3 (33)	9	NR	NR
63	20 mg/m ² i.v. days 1, 42, then 10 mg/m ² i.v. q 6 wks	—	5 (20)	2 (15)	7 (35)	20	3 (med.)	NR
46	20 mg/m ² i.v. q 4 wks	8 (20)	—	—	8 (20)	40	3 (mean)	NR
59	20 mg/m ² i.v. q 3 wks	5 (27)	—	—	5 (27)	19	NR	3
	Totals	13 (69)	8 (31)	2 (15)	23 (115)	20		
	Response rate (%)	19	26	13	20			
<i>Vindesine</i>								
39	3-4 mg/m ² i.v. weekly	3 (14)	6 (29)	1 (3)	10 (46)	22	5 (med.)	9 ^a , 4 ^b
52	3-4 mg/m ² i.v. weekly	0 (21)	1 (7)	2 (9)	3 (37)	8	NR	NR
36	3-4 mg/m ² i.v. weekly	5 (15)	3 (8)	0 (3)	8 (26)	31	NR	NR
56	4 mg/m ² i.v. weekly × 8 then q 2 wks	2 (19)	6 (22)	1 (13)	9 (54)	17	7 (med.)	NR
<i>Etoposide</i>								
50	3-4 mg/m ² i.v. weekly × 10 then q 2 wks	9 (35)	2 (10)	—	11 (45)	24	2 (med.)	3.5
60	3 mg/m ² i.v. weekly	0 (10)	0 (11)	2 (5)	2 (26)	8	NR	NR
61	2 mg/m ² i.v. day 1, 1 mg/m ² i.v. day 2, q 7-10 days	—	all cell types	—	4 (20)	20	NR	NR
34	3-4 mg/m ² i.v. weekly × 8 then 4 mg/m ² i.v. q 2 wks	—	all cell types	—	1 (18)	6	NR	NR
76	3 mg/m ² i.v. weekly	1 (7)	0 (7)	0 (2)	1 (16)	6	NR	NR

46	20 mg/m ² i.v. q 4 wks	8 (20)	5 (20)	2 (15)	7 (35)	20	3 (med.)	NR
59	20 mg/m ² i.v. q 3 wks	5 (27)	—	—	8 (20)	40	3 (mean)	NR
	Totals	13 (69)	8 (31)	2 (15)	23 (115)	19	NR	3
	Response rate (%)	19	26	13	20			
<i>Flutamine</i>								
39	3-4 mg/m ² i.v. weekly	3 (14)	6 (29)	1 (3)	10 (46)	22	5 (med.)	9*, 4*
52	3-4 mg/m ² i.v. weekly	0 (21)	1 (7)	2 (9)	3 (37)	8	NR	NR
36	3-4 mg/m ² i.v. weekly	5 (15)	3 (8)	0 (3)	8 (26)	31	NR	NR
56	4 mg/m ² i.v. weekly × 8 then q 2 wks	2 (19)	6 (22)	1 (13)	9 (54)	17	7 (med.)	NR
	Totals	9 (35)	2 (10)	—	11 (45)	24	2 (med.)	3.5
	Response rate (%)	0 (10)	0 (11)	2 (5)	2 (26)	8	NR	NR
50	3-4 mg/m ² i.v. weekly × 10 then q 2 wks	0 (10)	all cell types	—	4 (20)	20	NR	NR
69	3 mg/m ² i.v. weekly	1 (7)	0 (7)	0 (2)	1 (16)	6	NR	NR
61	2 mg/m ² i.v. day 1, 1 mg/m ² i.v. day 2, q 7-10 days	20 (121)	18 (94)	6 (35)	49 (288)	17	NR	NR
34	3-4 mg/m ² i.v. weekly × 8 then 4 mg/m ² i.v. q 2 wks	17	19	17	17			
76	3 mg/m ² i.v. weekly	11 (30)	0 (2)	2 (2)	13 (34)	38	NR	NR
	Totals	2 (18)	3 (18)	—	5 (36)	14	NR	NR
	Response rate (%)	0 (9)	0 (6)	2 (11)	2 (26)	8	NR	NR
<i>Adriamycin</i>								
44	75 mg/m ² i.v. q 3 wks	0 (2)	5 (17)	1 (6)	6 (25)	24	NR	4
55	20-25 mg/m ² i.v. × 3 days q 3 wks or	4 (58)	2 (45)	2 (37)	8 (140)	6	NR	3
3	60-75 mg/m ² i.v. q 3 wks	17 (117)	10 (88)	7 (56)	34 (261)	13		
	Totals	15	11	13	13			
	Response rate (%)	6 (70)	9 (45)	—	15 (115)	13	NR	6
79	NR	9	20	—	13			
<i>Dibromodulcitol</i>								
	Response rate (%)	0 (6)	4 (31)	—	4 (37)	11	NR	NR
<i>Baker's azotofol (Triazine)</i>								
57	100-150 mg/m ² /day × 5 i.v. q 2-3 wks or	0 (15)	1 (21)	1 (5)	1 (20)	5	1	NR
18	150-250 mg/m ² /day × 3 i.v. q 2-3 wks	5 (22)	—	3 (19)	9 (62)	15	NR	NR
21	250 mg/m ² /day × 3 i.v. q 3-4 wks	5 (43)	5 (52)	4 (24)	14 (119)	12	NR	
	Totals	12	10	17	12			
	Response rate (%)	5 (20)	3 (24)	—	8 (44)	18	5 (med.)	6*, 8*
<i>Etoposide (VP-16-213)</i>								
30	140 mg/m ² i.v. days 1, 3, 5 q 4-5 wks	5 (20)	all cell types	—	2 (60)	3	NR	NR
54	60 mg/m ² i.v. twice weekly or	1 (7)	1 (42)	—	2 (49)	4	5, 6	NR
	90 mg/m ² i.v. twice weekly or							
12	135 mg/m ² i.v. twice weekly							
	120-200 mg/m ² i.v. days 1, 3, 5 q 3 wks							

continued

Table 2. (continued)

Reference	Regimen	No. of responders (no. evaluable)				Response		
		Squa- mous	Adeno- carcin- oma	Large- cell	Totals	Rate (%)	Duration (months)	Median survival (months)
1	100 mg bd p.o. x 5 days q 4 wks	5 (34)	4 (8)	—	9 (42)	21	NR	6 ^a
	Totals	11 (61)	8 (74)	—	21 (195)	11		
	Response rate (%)	18	11	—	11			
<i>Hexamethylmelamine</i>								
24	10-12 mg/kg/day x 21 p.o. or 8 mg/kg/day x 90 p.o.	4 (27)	1 (9)	3 (12)	8 (48)	17	NR	NR
71	NR	0 (9)	0 (7)	—	0 (16)	0	NR	NR
79	NR	4 (65)	6 (37)	—	10 (102)	10	NR	NR
	Totals	8 (101)	7 (53)	3 (12)	18 (166)	11		
	Response rate (%)	8	13	25	11			
<i>Melbrosate</i>								
75	0.2-0.9 mg/kg im i.v. or p.o. twice weekly or 5-10 mg/kg i.v. q 3 wks	4 (71)	2 (28)	0 (28)	6 (127)	5	NR	8 ^a , 4 ^b
67	0.2-0.6 mg/kg i.v. twice weekly	9 (34)	0 (7)	—	9 (40)	23	NR	4
74	200 mg p.o. q 6 h for 4 doses weekly	0 (13)	—	—	0 (13)	0	—	12
35	1500 mg/m ² i.v. day 1, escalated by 1500 mg/m ² i.v. at 2 weekly intervals	0 (5)	1 (18)	0 (5)	1 (28)	4	2	4
68	400 mg/m ² i.v. q 3 wks	7 (27)	—	—	7 (27)	26	3.5 (mean)	NR
60	40 mg/m ² i.v. weekly	—	all cell types	—	2 (12)	17	NR	3
	Totals	20 (150)	3 (53)	0 (33)	25 (247)	10		
	Response rate (%)	13	6	0	10			
<i>Cyclophosphamide</i>								
32	1 g/m ² i.v. q 3 wks	—	10 (79)	—	10 (79)	13	3.5 (med.)	4
2	1.1 g/m ² i.v. q 3 wks	1 (27)	—	—	1 (27)	4	2	4
80	1.1 g/m ² i.v. q 3 wks	3 (70)	4 (50)	2 (55)	9 (175)	5	NR	3 ^a , 5 ^a
22	600 mg/m ² i.v. q 3 wks	—	all cell types	—	2 (41)	5	NR	5
7	1.1 g/m ² i.v. q 3 wks	3 (17)	0 (2)	0 (16)	3 (35)	9	NR	2
73	1.5-3.5 g/m ² i.v. q 3 wks	—	all cell types	—	5 (12)	42	2.5 (med.)	4

Table 3. Response rates in NSCLC. Drugs studied in less than 100 patients

Drug	Regimen	No. of responders (no. evaluable)				
		Squa- mous	Adeno- carcin- oma	Large cell	Totals	Response rate (%)
Vinblastine	2.4 mg/m ² i.v. q 6 h x 2 days, then 1.2 mg/m ² i.v. q 6 h x 2 days q 2 wks	2 (3)	4 (16)	0 (3)	6 (22)	27
Procarbazine	100-250 mg/m ² p.o. daily	3 (13)	3 (9)	1 (5)	7 (27)	26
Vincristine	1 mg/m ² i.v. weekly or 1.5 mg/m ² i.v. infusion over 4-6 h weekly or 2 mg i.v. weekly	1 (21)	7 (48)	0 (15)	8 (84)	10
Maytansine	0.6 mg/m ² /d x 3 q 3 wks	1 (12)	2 (17)	1 (13)	4 (42)	10
5-Fluorouracil	600 mg/m ² /d i.v. infusion x 5 days q 2 wks	3 (21)	0 (2)	0 (11)	3 (34)	9
Mitolactol	175-225 mg/m ² /d p.o. x 10 days q 4-5 wks	2 (20)	2 (31)	1 (12)	5 (63)	8
ICRF 159	1 g/m ² /day p.o. x 3 days (divided into 9 doses given every 8 h) q 4-5 wks	1 (17)	2 (25)	1 (10)	4 (52)	8
Dianhydrogalactitol	30 mg/m ² /d i.v. x 5 days q 3-5 wks	4 (57)	0 (18)	2 (14)	6 (89)	7
Mgbgh ^a	500 mg/m ² i.v. weekly	1 (14)	1 (20)	1 (10)	3 (44)	7
Piperazone	15 mg/m ² i.v. q 3 wks	—	2 (27)	0 (3)	2 (30)	7
Dactinomycin	2.5 mg/m ² i.v. q 3 wks	3 (47)	—	—	3 (47)	7
Methyl-CCNU	200 mg/m ² p.o., then 150 mg/m ² p.o. q 7 wks	1 (18)	0 (23)	1 (12)	2 (53)	4
PALA	3.75-4.5 g/m ² i.v. infusion weekly or 5-6 g/m ² i.v. infusion q 3-4 wks	0 (5)	0 (12)	0 (1)	2 (75) ^b	3
Bleomycin	10-30 mg/m ² i.v. or im twice weekly or 15 mg/m ² /day x 5-8 days	1 (47)	1 (12)	—	2 (59)	3
Florafur	4 g/m ² i.v. q 2 wks	—	1 (33)	0 (3)	1 (36)	3
VM-26	20-30 mg/m ² i.v. infusion q 3-4 wks	1 (25)	0 (19)	—	1 (44)	2
Pyrazofurin	200 mg/m ² i.v. weekly	0 (14)	0 (10)	—	0 (24)	0
Melphalan	3.5 mg/m ² p.o. b.d. x 5 days q 5 wks	0 (18)	—	—	0 (18)	0
Rubidazole	120-150 mg/m ² i.v. q 3 wks	0 (16)	—	—	0 (16)	0

^aMgbgh = methyl-glyoxal-bis-guanyl-hydrazine.

^bIncludes 57 patients of undefined cell type.

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patients, data from the literature are surprisingly scanty. Durrant *et al.* (25) devised a "palliation index" which reflected the length and the quality of life of patients on study. In a randomized study, neither radiotherapy nor mechlorethamine therapy appeared to have any influence on the "palliation index" although data on the relief of symptoms by treatment were not reported.

Wolf *et al.* (80) analysed the improvement in performance status of patients in relation to the chemotherapy regimen administered. For adenocarcinoma patients treated with cyclophosphamide although not for those with other cell types, an improvement of 20 or more units on the pretreatment Karnofsky score was seen in 21%. The tumour response rate for this cell type was, however, only 8% and the authors did not attempt to correlate objective tumour response with an improvement in performance status. The report by Anderson *et al.* (1) on a trial of etoposide in NSCLC did attempt to define more closely the possible benefits of treatment for the patients. Of 24 responders to etoposide, 15 showed an increase in Karnofsky score, the mean maximum improvement being 23%. Fourteen of the responders gained weight. Unfortunately non-small cell and small cell histological types were included together in this analysis and furthermore the change in Karnofsky scores of nonresponding patients was not recorded.

The question of whether chemotherapy can favourably influence the quality of life of patients with NSCLC therefore remains to be answered. Similarly, whether or not chemotherapy can palliate symptoms is, even now, an issue for debate. One assumes that objective tumour response must be associated with symptom palliation but, unfortunately, documentation of this is sadly lacking in the majority of reports on NSCLC trials.

Combination chemotherapy in NSCLC

The lack of adequate documentation of single-agent activity in NSCLC extends to that of combination chemotherapy. Not only is there an almost exclusive concentration on the reporting of tumour regression rates rather than on symptom palliation or on changes in quality of life, but few trials directly comparing combinations with single-agent activity have been published.

Nine prospective randomised trials (see Table 4) are available for review. Of these, only two studies show unequivocal evidence of higher response rates for the combination under test and only one study claims an improved survival time for patients treated with a combination regimen. The former two studies compared respectively cyclophosphamide, adriamycin and cisplatin with dianhydrogalactitol (31) and vindesine plus cisplatin with vindesine alone (34). Each reported a significant improvement in response rates for patients on the platinum-containing combinations although survival times were the same in one of the studies (31). A third study (49) actually demonstrated a higher response rate for the single agent tested (vindesine) as compared to the combination (adriamycin plus cyclophosphamide). Median survival times were identical (3.5 months).

The one study showing a superior survival time for a combination was that of Wolf *et al.* (80), in which adriamycin plus cyclophosphamide produced a longer duration of survival in squamous cell patients compared with cyclophosphamide alone (6 months *vs* 3 months). It is interesting to note that an identical schedule of adriamycin and cyclophosphamide in the Luedke *et al.* study (49) produced a median survival time of only 3.5 months. Further conflicting data on survival are apparent from the analysis of the trial comparing

	10-12 mg/m ² /day x 5-8 days	4 g/m ² i.v. q 2 wks	20-30 mg/m ² i.v. infusion q 3-4 wks	200 mg/m ² i.v. weekly	3.5 mg/m ² p.o. b.i.d. x 5 days q 5 wks	120-150 mg/m ² i.v. q 3 wks	* (77)	1 (12)	2 (59)	3	3, 40
Fluorouracil											
VM-26											
Pyrazofurin							1 (25)	1 (33)	1 (36)	3	59
Melphalan							0 (14)	0 (19)	1 (44)	2	62
Rubidazole							0 (18)	0 (10)	0 (24)	0	38
							0 (16)	—	0 (18)	0	21
								—	0 (16)	0	37

*Mgbh = methyl-glyoxal-bis-guanyl-hydrazine.

*Includes 57 patients of undefined cell type.

Table 4. Prospective randomized trials comparing single agent with combination chemotherapy in NSCLC

Reference	Treatment ^a	No. of responders (no. evaluable)			Response		Median survival (months)
		Squa-mous	Adeno-carcin-oma	Large cell	Totals	Rate (%)	Duration (months)
43	CCNU <i>vs</i>	0 (10)	—	—	0 (10)	0	NR
	BLM <i>vs</i>	0 (13)	—	—	0 (13)	0	NR
	CCNU + BLM	2 (17)	—	—	2 (17)	12	NR
32	CTX <i>vs</i>	—	10 (79)	—	10 (79)	12	4 (med.)
	CTX + CCNU	—	10 (83)	—	10 (83)	12	4 (med.)
33	HN ₂ <i>vs</i>	6 (70)	—	3 (39)	9 (109)	8	NR
	HN ₂ + CCNU	2 (68)	—	5 (46)	7 (114)	6	NR
27	ICRF159 <i>vs</i>	1 (15)	2 (20)	1 (8)	4 (43)	9	5
	VCR + BLM + ADR	0 (7)	2 (8)	2 (5)	4 (20)	20	6
31	DAG <i>vs</i>	4 (26)	0 (16)	2 (13)	6 (55)	11**	NR
	CTX + ADR + CDDP	8 (18)	6 (14)	2 (9)	16 (41)	39***	NR
2	CTX <i>vs</i>	1 (27)	—	—	1 (27)	4	2
	<i>vs</i> COMB	1 (20)	—	—	1 (20)	5	8
80	CTX <i>vs</i>	1 (70)	4 (50)	2 (55)	7 (175)	4	NR
	CTX + CCNU <i>vs</i>	2 (67)	1 (60)	2 (46)	5 (173)	3	NR
	CTX + ADR <i>vs</i>	3 (74)	0 (53)	3 (36)	6 (163)	4	NR
	CCNU + ADR	4 (77)	2 (57)	2 (40)	8 (174)	5	NR
34	VDS <i>vs</i>	all cell types			1 (18)	6	NR
	VDS + CDDP				8 (15)	53	NR
49	VDS <i>vs</i>	7 (28)	—	—	7 (28)	25***	2
	ADR + CTX	1 (19)	—	—	1 (19)	5***	7

^aADR, adriamycin; BLM, bleomycin; CDDP, cisplatin; CTX, cyclophosphamide; DAG, dianhydrogalactitol; DDP, cisplatin; HN₂, mechlorethamine; VCR, vincristine; VDS, vindesine; ICRF159, razoxane.

^bThe survival values are for squamous, adenocarcinoma, and large cell, respectively.

P* = < 0.05; *P* = < 0.001; ****P* < 0.008. NR = not recorded.

cyclophosphamide with COMB (cyclophosphamide, vincristine, methyl CCNU and bleomycin). Survival time in this study was significantly shorter for ambulatory patients treated with COMB (2) as compared with those receiving cyclophosphamide alone (2.5 months *vs* 5 months).

The lack of convincing data in these studies may relate to the choice, with the exception of cisplatin and vindesine, of agents with minimal activity in NSCLC. It is probable that meaningful comparisons can only be made between the more active single agents and combinations of these active drugs.

Future studies

The question as to whether chemotherapy is of benefit to patients in terms of palliation of symptoms, an improvement in the quality of life and increased longevity *irrespective of tumour shrinkage* is one that needs an urgent answer. At the same time, the optimal doses and

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Response		Median survival (months)
Rate (%)	Duration (months)	
0	—	NR
0	—	NR
2	NR	NR
2	4 (med.)	4
2	4 (med.)	6
8	NR	3
6	NR	3
9	5	7
0	6	8
1**	NR	5
9**	NR	6
4	2	4
5	8	3
1	NR	3 ^a , 5, 5 ^b
3	NR	3, 5, 4 ^b
1	NR	6, 5, 3 ^b
1	NR	4 ^a , 6, 4 ^b
	NR	NR
	NR	NR
***	2	3.5
***	7	3.5

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schedules need to be defined more clearly for each of the agents with apparent activity in NSCLC. Only after the limitations of single-agent chemotherapy have been clearly defined, can the contribution of combinations of agents to the management of NSCLC be adequately assessed. Finally, the role of chemotherapy as a possible alternative to radiotherapy for the control of both limited disease and of lesions such as painful bony deposits, needs to be evaluated.

The objective of these studies must, in the final analysis, be to relieve suffering. Even if chemotherapy cannot offer the hope of cure, palliation must surely be a worthwhile goal.

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