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Review

Combination chemotherapy for advanced adenocarcinoma of the lung*

A review

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Summary. Combination chemotherapy has been used widely in the treatment of inoperable adenocarcinoma of the lung (ACL), but without uniform success. This review summarizes current knowledge of combination chemotherapy in ACL, with the aim of establishing critical background material for future studies. Not all the numerous combinations applied in non-randomized studies have produced response rates above 20% when evaluated in randomized trials. This holds true for the following regimens: cyclophosphamide + lomustine + methotrexate (response rates 14%–38%), hexamethylmelamine + doxorubicin + methotrexate (13%–32%), methotrexate + doxorubicin + cyclophosphamide + lomustine (13%–24%), cyclophosphamide + doxorubicin + cisplatin (0–36%), cyclophosphamide + bleomycin + cisplatin (20%), mitomycin C + vinblastine + cisplatin (26%–33%), cyclophosphamide + doxorubicin + etoposide + cisplatin (29%) and vindesine + cisplatin (33%). None of these combinations has been shown to be clearly superior to single-agent treatment. Nor has any specific regimen been shown to have clear advantages over other active combination chemotherapy regimens or over the sequential administration of either single agents or combined treatments. The prognosis for patients with inoperable ACL remains dismal. None of the studies considered in this review revealed median survival times exceeding 47 weeks. High priority should therefore be given to the identification of new compounds with significant activity against ACL.

Introduction

In recent years, adenocarcinoma of the lung (ACL) has presented an increasingly important health problem. Several groups of investigators have reported that the proportion of lung cancer classified as adenocarcinoma is increasing and, in some centers, cases of ACL outnumber those of the other histological cell types of lung cancer [23, 62, 106, 108].

The majority of patients with ACL have metastases at presentation and a significant proportion of those believed to have only limited disease and treated by surgery or radiotherapy will later develop local recurrence or systemic disease. Subgroups of these patients may be treated with chemotherapy, but progress in this field has been disappointing.

Most studies of cytostatic agents in "non-small cell" lung cancer include all cell types, i.e., squamous cell, adeno- and large cell carcinoma. However, it is still unclear whether or not histological cell type is an important determinant of response to cytotoxic drugs, as suggested in some reports [33, 87]. Survival may also be influenced by histological tumor type [18, 33, 43]. Thus, the purpose of this paper is to review the existing literature dealing with combination chemotherapy of ACL, thereby establishing critical background material for future clinical studies in this disease. The literature on single-agent chemotherapy in ACL has already been reviewed [98].

For inclusion in this review, all publications were required to fulfill the following criteria:

1. A minimum of ten evaluable patients with ACL.
2. Information concerning the number of responses or duration of survival. Definitions of response criteria employed were also necessary, and only responses qualifying as partial (PR) or complete remission (CR) according to the WHO criteria [116] were recorded as responses.
3. Detailed information on the applied schedule and dosage of the component drugs should be present.
4. Results presented solely in abstract form were excluded.

Articles dealing with combined treatment modalities, including surgery and radiotherapy, have not been considered.

Non-randomized trials

Combinations of potentially active single agents have been intensively studied in non-randomized studies. The patients in the published series have received a wide variety of treatments with a varying number of drugs (Tables 1–11).

Two-drug regimens

Response rates in the range of 9%–56% have been reported for 11 studies evaluating two-drug regimens without cisplatin (Table 1). Response rates above 30% have been reported for the combinations cyclophosphamide + methotrexate, doxorubicin + lomustine and doxorubicin + ifosfamide, but the study populations were small and the confidence limits wide.

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Table 1. Two-drug regimens without cisplatin

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CTX + ADR	0	12	1	17 (2–48)	34		[46]
CTX + MTX	0	18	2	56 (31–78)		34	[101]
CTX + CCNU	0	32	0	9 (2–25)		15	[88]
ADR + CCNU		15	2	33 (12–62)	30–43	30	[106]
ADR + DBD	0	32	1	9 (2–25)		24	[87]
ADR + MMC		18		16 (4–41)	8		[16]
ADR + MMC		29		22 (10–44)		20	[24]
ADR + IFX		22	0	32 (14–55)			[72]
VBL + MMC	0	21			9	20	[112]
VDS + MMC		44		25 (14–41)			[71]
VP-16 + IFX		34		24 (11–41)			[26]

PC, Prior chemotherapy; ADR, doxorubicin; CCNU, lomustine; CTX, cyclophosphamide; DBD, dibromodulcitol; IFX, ifosfamide; MMC, mitomycin C; MTX, methotrexate; VBL, vinblastine; VDS, vindesine; VP-16, etoposide

Table 2. Two-drug regimens including cisplatin and vinca alkaloids

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CDDP + VDS		17	0	18 (4–43)			[25]
CDDP + VDS	0	15	3	38 (12–62)		25	[10]
CDDP + VPL	0	19		32 (13–57)			[49]

CDDP, cisplatin; see previous table for other abbreviations

Table 3. Two-drug regimens including cisplatin and etoposide

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CDDP + VP-16		22	1	32 (14–55)	17		[54]
CDDP + VP-16		10	0	10 (0–45)			[53]
CDDP + VP-16	0	25		13 (3–31)			[22]
CDDP + VP-16	0	21	0	24 (8–47)			[92]
CDDP + VP-16	0	15	0	33 (12–62)			[108]
CDDP + VP-16	0	10	1	40 (12–74)		35	[100]

See previous tables for abbreviations

Combinations of cisplatin with a vinca alkaloid have resulted in response rates of 18%–33% for cisplatin + vindesine and 32% for cisplatin + vinblastine in small groups of patients (Table 2).

Six studies with a total of 103 patients have evaluated a combination of cisplatin + etoposide with inconsistent results (range of response rates, 10%–40%; Table 3). It is noteworthy that all four of the studies that included only untreated patients used different drug doses or schedules. The lowest order of activity (response rate 13%) was observed by Dhingra et al. [22], who used the lowest doses of cytostatic agents (etoposide 120 mg/m^2 i.v. on days 4, 6 and 8; cisplatin 60 mg/m^2 on day 1 every 3–4 weeks). Scagliotti et al. [92] used the same dose of etoposide but a higher dose of cisplatin (100 mg/m^2) and observed a response rate of 24%. After further increasing the dose and altering the schedule to etoposide 60 mg/m^2 per day for 5 days and cisplatin 20 mg/m^2 per day for 5 days, Villalon et al. [108] observed a response rate of 33%. The doses of etoposide were further increased to 100 mg/m^2 i.v. on days 1 and 2, and etoposide 200 mg/m^2 p.o. on days 3 and 5 by Splinter et al. [100]. The cisplatin dose was 80 mg/m^2 on day 1 every 4 weeks. The response rate observed was 40%, and median survival was 35 weeks. The overall data suggest a dose-response effect, although some of the differences observed in treatment results may, in part, reflect heterogeneity of the study populations with respect to other prognostic factors than previous treatment.

Only two studies have explored the activity of 2-drug regimens with cisplatin in combination with agents other than vinca alkaloids or etoposide (Table 4). The response rate was 20% among 20 patients receiving cisplatin + hexamethylmelamine and 29% among 25 patients treated with cisplatin + ifosfamide.

Table 4. Two-drug regimens including cisplatin but without vinca alkaloids or etoposide

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CDDP+HMM		20	0	20 (6–44)		34 (responders) 10 (non-responders)	[57]
CDDP+IFX		25		29 (12–49)			[26]

HMM, hexamethylmelamine, see previous tables for other abbreviations

Table 5. Three-drug regimens without cisplatin

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
VCR+PCZ+HUR	14	14	0	7 (0–34)	33		[45]
5-FU+ADR+MTX		11	1	45 (17–77)			[70]
5-FU+VCR+Me-CCNU		16	0	0 (0–21)			[5]
5-FU+CTX+CCNU	3	23	1	22 (7–44)	21	36	[4]
5-FU+ADR+MMC	0	25	1	36 (18–57)	28	29	[9]
5-FU+ADR+MMC	0	30	1	33 (17–53)	28	24	[86]
5-FU+ADR+MMC	0	20	0	20 (6–44)		32	[65]
futraful+ADR+MMC	0	20	0	0 (0–17)		22	[65]
5-FU+VCR+MMC	0	46	3	41 (27–57)		24	[73]
5-FU+VCR+MMC	0	23	0	9 (0–21)	22	24	[75]
5-FU+VDS+MMC	0	40	2	20 (9–36)		23	[74]
CTX+ADR+MMC		28	0	25 (11–45)	14	39 (resp.) 17 (non-resp.)	[37]
CTX+ADR+MTX (+CF)		18	3	39 (17–64)		28	[85]
CTX+ADR+5-FU	0	10	0	10 (0–45)		24	[105]
ADR+VCR+MTX		13		15 (2–45)			[38]
ADR+VCR+Me-CCNU		19	0	0 (0–18)			[41]
MMC+5-FU+Ara C		23	0	0 (0–15)			[41]
DTIC+MTX+IFX		21	1	19 (5–42)		24	[2]
MMC+MTX+VCR	8	21	0	19 (5–42)	12	12	[94]

Ara C, Cytanabinoside C; CF, citrovorum factor; DTIC, dicarbazine; 5-FU, 5-fluorouracil; HUR, hydroxyurea: Me-CCNU, methyl-CCNU; PCZ, procarbazine; VCR, vincristine; resp., responders; see previous tables for other abbreviations

Three-drug regimens

Table 5 summarizes the results of 19 trials of three-drug regimens without cisplatin. Once again there are marked variations in the results reported.

Of interest is the 41% response rate among 46 previously untreated patients reported by Miller et al. [73] with a regimen of 5-fluorouracil, vincristine and mitomycin C. However, a similar regimen, but with vindesine in place of vincristine, produced a response rate of only 20% in a comparable group of 40 patients [74]. The same group performed a confirmatory study employing 5-fluorouracil + vincristine + mitomycin C in 23 previously untreated patients with bronchiolo-alveolar carcinoma, a separate histopathological subtype of ACL according to the WHO criteria [117]. The observed response rate was only 9%. Whether this low order of activity was attributable to greater resistance of the histopathologic subtype to the combination or to other differences between the study populations cannot be made clear from these results.

Combinations of cisplatin with a vinca alkaloid and a third cytotoxic agent have been extensively evaluated (Table 6). Eight of the 12 trials using such a combination have included solely previously untreated patients. All 8 trials have reported a response rate equal to or over 30%, irrespective of whether the vinca alkaloid was vinblastine [79, 102], vincristine [14] or vindesine [7, 50, 59, 77]. Kris et al. [59] reported the largest study, including 54 patients without previous chemotherapy receiving a regimen of cisplatin + vindesine + mitomycin C. The observed response rate was 50% (95% confidence limits: 36%–64%) with a median survival of 47 weeks. The same combination was also evaluated by Miller et al. [77], who observed a similar response rate (42%) but a lower median survival (27 weeks). This promising combination deserves further evaluation in randomized comparative trials against other chemotherapeutic regimens.

Three-drug combinations including cisplatin and etoposide have also been evaluated in several studies (Table 7). However, only two have included exclusively previously untreated patients [7, 21]. A 60% response rate was observed with a combination of cisplatin + etoposide + vindesine, but only 10 ACL patients were included in this

Table 6. Three-drug regimens including cisplatin and vinca alkaloids

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CDDP+VBL+MMC		15	2	40 (16–68)			[93]
CDDP+VBL+MCC	0	11	0	27 (2–52)			[79]
CDDP+VBL+BLM	0	10	0	30 (7–65)			[102]
CDDP+VCR+MMC	0	25	1	40 (21–61)			[14]
CDDP+VDS+BLM	0	34	3	38 (22–56)			[51]
CDDP+VDS+BLM	0	10	1	40 (12–74)			[3]
CDDP+VDS+MCC	0	43	5	42 (27–58)		27	[77]
CDDP+VDS+MCC	0	54		50 (36–64)		47	[58]
CDDP+VDS+VP-16	2	17	3	24 (7–50)			[55]
CDDP+VDS+VP-16	11	11	0	0 (0–29)			[1]
CDDP+VDS+VP-16		36		14 (5–30)			[44]
CDDP+VDS+VP-16	0	10	0	60 (26–88)			[6]

BLM, bleomycin; see previous tables for other abbreviations

Table 7. Three-drug regimens including cisplatin and etoposide

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CDDP+VP-16+BLM		18	0	22 (6–48)		19	[82]
CDDP+VP-16+MMC	0	12	1	58 (28–85)			[21]
CDDP+VP-16+VDS	2	17	3	24 (7–50)			[55]
CDDP+VP-16+VDS	11	11	0	0 (0–29)			[1]
CDDP+VP-16+VDS		36		14 (5–30)			[44]
CDDP+VP-16+VDS	0	10	0	60 (26–88)			[7]

See previous tables for abbreviations

Table 8. Three-drug regimens including cisplatin but without vinca alkaloids or etoposide

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CTX+ADR+CDDP	0	22	0	45 (24–68)			[31]
CTX+ADR+CDDP		30	0	27 (12–46)			[40]
CTX+ADR+CDDP	0	58	1	24 (14–37)		14	[36]
CTX+ADR+CDDP	0	17	0	24 (7–50)			[56]
CTX+ADR+CDDP		15	0	20 (4–48)			[118]
5-FU+ADR+CDDP	0	39	0	26 (13–42)		27	[88]
5-FU+ADR+CDDP	0	31	1	3 (2–26)	25	45	[11]

See previous tables for abbreviations

trial. Similarly, the 58% response rate in a trial with cisplatin + etoposide + mitomycin C occurred among only 12 ACL patients.

Among three-drug regimens including cisplatin but without vinca alkaloids or etoposide, a combination of cyclophosphamide + doxorubicin + cisplatin is the one that has been most extensively studied (Table 8). Five trials including a total of 142 patients yielded response rates ranging from 20% to 45%.

The combination of 5-fluorouracil + doxorubicin + cisplatin produced response rates of 3%–26% in two studies which included a total of 70 previously untreated patients. Although a response rate of only 3% was observed in the study by Cazap et al. [11], the overall median survival was 45 weeks.

Four-drug regimens

Eleven studies have exploited the activity of four-drug regimens without cisplatin (Table 9). The highest response rate was 58%, recorded among 26 patients by Chahinian et al. [12], who employed a combination of methotrexate + doxorubicin + cyclophosphamide + lomustine (MACC). However, lower activity was noted in three subsequent studies employing the same regimen [65, 78, 88], with response rates of only 28% among 29 patients, 7% among 15

Table 9. Four-drug regimens without cisplatin

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
MTX + ADR + CTX + CCNU		26	1	58 (37–77)	29	29	[12]
MTX + ADR + CTX + CCNU	5	29	0	28 (13–47)	12	32	[78]
MTX + ADR + CTX + CCNU	0	15	0	7 (0–32)		14	[88]
MTX + ADR + CTX + CCNU	0	17	0	0 (0–20)			[64]
CTX + ADR + MTX + PCZ	0	12	1	42 (15–72)			[110]
CTX + ADR + MTX + PCZ	0	22		36 (17–59)			[6]
CTX + ADR + MTX + PCZ		12		33 (10–65)			[63]
CTX + ADR + MTX + PCZ	0	70		37 (26–50)		39	[95]
CTX + ADR + MTX + 5-FU		15	0	0 (0–22)			[41]
MTX + CTX + HMM + CCNU	0	44		9 (10–35)		17	[42]
CTX + VCR + Me-CCNU + BLM		28	0	11 (2–28)		22	[69]

See previous tables for abbreviations

Table 10. Four-drug regimens including cisplatin

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
VP-16 + CTX + ADR + CDDP	0	20	0	35 (15–59)	9–30	24	[30]
TZT + CTX + ADR + CDDP	0	35		57 (39–74)	36	29	[32]
FT + CTX + ADR + CDDP		48	4	31 (19–46)		56 (resp.) 28 (non-resp.)	[52]
VCR + CTX + ADR + CDDP	0	20				40	[68]
MMC + MTX + VBL + CDDP	0	16	0	50 (25–75)		24 (resp.) 16 (non-resp.)	[80]
MMC + VP-16 + HMM + CDDP	18	18	0	11 (1–35)			[13]

FT, ftorafur; TZT, triazinate; resp., responders; see previous tables for other abbreviations

Table 11. Five-drug regimens

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
BLM + CTX + VCR + MTX + 5-FU		17	0	35 (14–62)			[66]
CDDP + ADR + VCR + CTX + CCNU		11	2	64 (31–89)		30	[103]
CDDP + ADR + VCR + MTX + 5-FU		15		33 (12–62)		45	[104]
CDDP + ADR + VCR + CTX + CCNU		19	2	42 (20–67)			[83]

See previous tables for abbreviations

untreated patients, and zero among 17 untreated patients, respectively (Table 9).

The most consistent activity has been observed in studies using a regimen of cyclophosphamide + doxorubicin + methotrexate + procarbazine. Four studies, including a total of 116 patients, yielded response rates of 42%, 36%, 33% and 37% (Table 9).

Four-drug regimens including both cisplatin and etoposide have been evaluated by Eagan et al. [29] and Chahinian et al. [13], with response rates of 35% among 20 untreated patients and 11% among 18 pretreated patients, respectively (Table 10). This is in the same order of activity as observed with cisplatin + etoposide alone (Table 3).

Five-drug regimens

Four studies have evaluated five-drug regimens in ACL (Table 11). The highest activity rates have been reported by Takita et al. [103] and by Pearlman et al. [83], using a combination of cisplatin + doxorubicin + vincristine + cyclophosphamide + lomustine, with response rates of 64% and 42% among 11 and 19 patients, respectively.

Randomized trials

The relative efficacy of different combination chemotherapy regimens and their efficacy in relation to single-agent chemotherapy or to optimum supportive care (without chemotherapy) cannot be determined from phase II studies. Neither is it possible to assess potential survival benefits from chemotherapy in relation to the natural course of the disease. These questions can only be clarified by randomized studies. Altogether, 25 randomized trials have been published on the activity of combination chemotherapy in ACL (Tables 12–14). Almost all these studies also included other histological types of lung cancer. Studies

dealing with comparisons against single-agent treatments, comparisons between different combination chemotherapy regimens, and comparisons with sequential chemotherapy are analyzed separately.

Combination chemotherapy versus single-agent treatment

Combination chemotherapy has been evaluated against single-agent chemotherapy in six trials (Table 12).

A combination of vincristine + bleomycin + doxorubicin was compared with ICRF 159 by Eagan et al. [27] in 16 and 25 patients. There was minor activity for both treatments, with response rates of 13% and 8%, respectively.

The same group of investigators has also compared the alkylating agent dianhydrogalactitol (DAG) with a combination of cyclophosphamide + doxorubicin + cisplatin (CAP) [28]. Responses to CAP were observed in 8 of 22 patients. This was significantly better than the activity observed with DAG, which yielded no responses among 12 patients ($P < 0.01$). For those receiving CAP the response rate among the 14 patients without prior chemotherapy was 43%. Unfortunately, the study report gave no information on survival of patients with ACL.

The alkylating agent cyclophosphamide was compared with three two-drug regimens by Wolf et al. [115] (Table 12). None of the three combinations including cyclophosphamide, doxorubicin or lomustine was superior to the single agent with respect to either response rate or survival. All regimens yielded response rates below 9%.

Ruckdeschel et al. [87] demonstrated the superiority of the three-drug regimen doxorubicin + 5-fluorouracil + cisplatin to single-agent therapy. This combination yielded a 26% response rate among 39 patients, which was superior to the 7% response rate among 27 patients with piperazinedione ($P < 0.05$) and the 3% response rate among 33 patients with ftorafur ($P < 0.01$). A superior median survival was observed among patients receiving the combination (27 weeks vs 14 and 15 weeks for ftorafur and piperazinedione). This interpretation is, however, subject to a number of potential biases, because each treatment group is characterized by a different mix of prognostic factors affecting patient survival. For example, 81% of the patients receiving three-drug combination chemotherapy were ambulatory, as against 54% of the patients receiving ftorafur. Using a Cox multivariate analysis, none of the treatments was found to be superior with respect to survival [87].

Creech et al. [19] compared the antimetabolite triazinate with four separate combination chemotherapy regimens (Table 12). Although a response rate of only 5% was observed in 21 patients receiving triazinate, this was not significantly inferior to the 32% responders among 19 patients receiving a combination of hexamethylmelamine + doxorubicin + methotrexate. The statistical power of the study was low due to small numbers of patients.

The preceding five studies all evaluated agents which do not have major single-agent activity in ACL [98]. The only study to have included one of the most active single agents in ACL (vindesine) has been published by Sørensen et al. [99]. In a randomized trial, they compared vindesine alone (in 71 patients) with cyclophosphamide + lomustine + methotrexate (in 74 patients) with the combination of all four drugs (in 73 patients). Similar response rates (22%, 23% and 27%, respectively) and median survivals (29, 29 and 34 weeks, respectively) were observed. The median response durations were short, being 12–16 weeks (Table 12).

Table 12. Randomized trials comparing combination chemotherapy and single-agent treatment

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
ICRF 159 vs		25	0	8 (1–26)			[27]
VCR + BLM + ADR		16	0	13 (2–38)			
DAG vs	2	18		0 (0–19)			[28]
CTX + ADR + CDDP	8	22		36** (17–59)			
CTX vs		50		8 (2–19)		19	[115]
CTX + CCNU vs		60		2 (0– 9)		21	
CTX + ADR vs		53		0 (0– 7)		21	
CCNU + ADR		57		4 (0–12)		23	
CTX + CCNU vs	0	32	0	9 (2–25)		15	[87]
MTX + ADR + CTX + CCNU vs	0	15	0	7 (0–32)		14	
DBD + ADR vs	0	32	1	9 (2–25)		24	
FT vs	0	33	0	3 (0–16)		14	
Piperazinedione vs	0	27	0	* 7 (1–24)		15	
ADR + 5-FU + CDDP	0	39	0	** 26 (13–42)		27	
TZT vs		21		5 (0–24)			[19]
CTX + MTX vs		19		5 (0–26)			
CTX + CCNU vs		23		9 (1–28)	16	19	
5-FU + PCZ vs		19		11 (1–33)			
HMM + ADR + MTX		19		32 (13–57)			
VDS vs	0	71	5	22 (13–34)	12	29	[98]
CTX + CCNU + MTX vs	0	74	2	23 (14–34)	16	29	
CTX + CCNU + MTX + VDS	0	73	2	27 (18–39)	16	34	

*$P < 0.05$; **$P < 0.01$

DAG, dianhydrogalactitol; see previous tables for other abbreviations

Table 13. Randomized trials comparing combination chemotherapy regimens

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CTX + MTX vs	0	17		6 (0–29)	16	17	[45]
CCNU + CTX + MTX	0	21		38* (18–62)	16	29*	
CCNU + CTX + MTX vs	10	28		25 (11–45)		23	[84]
5-FU + ADR		26		15 (4–35)		15	
CTX vs		50		8 (2–19)		19	[114]
CTX + CCNU vs		60		2 (0– 9)		21	
CTX + ADR vs		53		0 (0– 7)		21	
CCNU + ADR		57		4 (0–12)		23	
CCNU + CTX + MTX vs	0	56		14 (6–26)			[110]
PCZ + ADR	0	56		7* (2–17)			
HMM + ADR + MTX vs	0	30	0	13 (4–31)		23	[88]
CTX + ADR + MTX + PCZ	0	33	1	18 (7–35)		22	
CTX + CCNU vs	0	32	0	9 (2–25)		15	[87]
MTX + ADR + CTX + CCNU vs	0	15	0	7 (0–32)		14	
DBD + ADR vs	0	32	1	9 (2–25)		24	
FT vs	0	33	0	3 (0–16)		14	
Piperazinedione vs	0	27	0	** 7 (1–24)		15	
ADR + 5-FU + CDDP	0	39	0	* 26 (13–42)		27	
TZT vs		21		5 (0–24)			[19]
CTX + MTX vs		19		5 (0–26)			
CTX + CCNU vs		23		9 (1–28)	16	19	
5-FU + PCZ vs		19		11 (1–33)			
HMM + ADR + MTX		19		32 (13–57)			
PLM + CQ vs	0	17	0	18 (4–43)			[91]
PLM + MMC	0	17	0	14 (7–50)			
CTX + ADR + CDDP (50 mg/m²) vs	0	10	0	0 (0–31)			[20]
CTX + ADR + CDDP (100 mg/m²)	0	17	0	12* (1–36)			
CTX + ADR + CDDP vs	0	37		35 (20–53)			[60]
MTX + ADR + CTX + CCNU	0	33		24 (11–42)			
5-FU + ADR + MMC vs	0	41	0	17 (7–32)		29	[61]
MTX + ADR + CTX + CCNU	0	40	0	13 (4–27)		22	
CTX + ADR + VP-16 vs	0	20	1	15 (3–28)			[39]
CTX + ADR + VP-16 + CDDP	0	24	4	29 (13–51)			
CTX + BLM + CDDP vs	0	47	0	20 (8–31)		24	[89]
ADR + 5-FU + CDDP vs	0	43	0	17 (8–33)		24	
MMC + VBL + CDDP vs	0	45	1	26 (16–44)		28	
CTX + ADR + CDDP	0	45	0	23 (15–42)		26	
VDS + CDDP vs	0	29		32 (21–44)			[59]
VBL + CDDP	0	38					
VDS + CDDP vs	0	18	0	33 (13–59)		43	[96]
VDS + MMC	0	21	0	14 (3–36)			
ADR + CTX + CCNU + VCR vs	0	11		9 (0–41)			[15]
ADR + CTX + CCNU + VCR + CDDP	0	14		21 (5–51)			
5-FU + VCR + MMC vs	0	90		27 (18–37)		17	[76]
CTX + ADR + CDDP vs	0	95		15 (2–23)		23	
5-FU + VCR + MMC alternating with CTX + ADR + CDDP	0	94		20 (13–30)		24	
CTX + ADR + MTX + PCZ vs	0	47	1	21 (11–36)		25	[90]
MMC + VBL + CDDP vs	0	52	3	33 (20–47)	12	26	
VP-16 + CDDP vs	0	54	1	7 (2–18)		27	
VDS + CDDP	0	54	4	18 (9–31)		20	
VDS vs	0	71	5	22 (13–34)	12	29	[99]
CTX + CCNU + MTX vs	0	74	2	23 (14–34)	16	29	
CTX + CCNU + MTX + VDS	0	73	2	27 (18–39)	16	34	

*$P < 0.05$; **$P < 0.01$

CQ, Carbaxilquinone; PLM, peplomycin; see previous tables for other abbreviations

Trials comparing combination chemotherapy regimens

A summary of the randomized trials comparing various combination chemotherapy regimens is given in Table 13.

In 1976, Hansen et al. [45] indicated a high degree of sensitivity to combination chemotherapy in ACL. A combination of lomustine + cyclophosphamide + methotrexate was found to be superior to cyclophosphamide + methotrexate with regard to objective response rate ($P = 0.05$) and median survival ($P = 0.007$). Patients in both treatment arms, numbering 21 and 17 respectively, were previously untreated and all had advanced disease. The activity of this three-drug regimen was later confirmed by Richards et al. [84], who demonstrated its superiority, in terms of response rate but not in terms of survival, over 5-fluorouracil + doxorubicin. The 25% response rate was somewhat lower than the 38% in the study of Hansen et al., but some patients, in contrast to the latter study, had received prior chemotherapy.

Vincent et al. [110] compared the same three-drug regimen with a combination of doxorubicin + procarbazine in a multicenter study. Although only 14% responded among the 56 patients treated with the three-drug combination, this was significantly superior to the 7% response rate among 56 patients receiving the two-drug regimen ($P < 0.05$).

As mentioned above, the combination of lomustine + cyclophosphamide + methotrexate has also been compared with vindesine alone and with all four drugs in a trial by the Copenhagen Group [99]. There were no differences in response rate (22%, 23% and 27%) or median survival (29, 29 and 34 weeks). These studies imply that the combination of lomustine + cyclophosphamide + methotrexate is active in ACL but that this activity is not increased by the addition of vindesine. However, the doses of lomustine and cyclophosphamide were slightly lower in this four-drug treatment than in the original three-drug regimen.

In an attempt to further improve the regimen of cyclophosphamide + doxorubicin + cisplatin (CAP), which was originally described by Eagan et al. [28] (Table 12), Davis et al. [20] initiated a randomized study of CAP with either "low-dose" (50 mg/m^2) or "high-dose" (100 mg/m^2) cisplatin in patients with extensive non-small cell lung cancer. No activity was seen among 10 ACL patients treated with low-dose cisplatin, and only 12% of 17 ACL patients responded to high-dose cisplatin.

It must be stressed, however, that the low order of activity observed with the CAP regimen in this last study may be due to the inclusion of a higher proportion of patients who had received prior irradiation or who had a Karnofsky performance status below 80 (76% and 78% of all 50 patients in the study). In the original study be Eagan et al. only 27% of the ACL patients had previously been irradiated, and only 23% had ECOG performance status below 1. The small number of CAP-treated patients given cisplatin at a conventional (low) dose in the study by Davis et al. also results in wide 95% confidence limits (0–31%). Firm conclusions concerning the impact of cisplatin dose level in the CAP regimen cannot therefore be drawn for ACL on this basis alone.

In a larger study, Krook et al. [61] compared CAP with a regimen of methotrexate + doxorubicin + cyclophosphamide + lomustine (MACC) in a total of 70 previously untreated patients (Table 13). The latter regimen had previously been shown to possess activity in ACL in non-randomized trials by Chahinian et al. [12] and by others [78, 87] (Table 9). Both CAP and MACC were shown to be active combinations (response rates: 35% and 24%, respectively), with no indication that either combination was superior to the other.

MACC was associated with less nausea and vomiting, however, and was therefore chosen as the basis for another comparative trial by Krook et al. [61]. The MACC regimen was compared with 5-fluorouracil + doxorubicin + mitomycin C (FAM), which had yielded encouraging results in a non-randomized trial by Butler et al. [9]. No significant differences were found in the randomized trial with regard to response rates, which were 17% for FAM and 13% for MACC. Survival was also similar for the two treatments, at 22 and 29 weeks, respectively. However, the pattern of toxicity was different. MACC produced a higher incidence of nausea and vomiting, whereas FAM produced more frequent and severe thrombocytopenia related to the use of mitomycin C.

Further studies of cisplatin containing regimens were reported by Fuks et al. [39]. Regimens of cyclophosphamide + doxorubicin + etoposide given with (CAE-P) or without (CAE) cisplatin 40 mg/m^2 were studied in 24 and 20 patients (Table 13). The CAE-P regimen showed an advantage with respect to response rate (29% versus 15%), including more complete remissions, though this was not significant. The authors concluded that there might be synergism between cisplatin and at least one of the agents in the CAE regimen.

A large multicenter study has recently been conducted by ECOG [89], comparing four CDDP-containing regimens which have all shown activity in single institutional trials. The regimens employed included cyclophosphamide + bleomycin + cisplatin (CBP), doxorubicin + 5-fluorouracil + cisplatin (AFP), mitomycin C + vinblastine + cisplatin (MVP) and CAP (Table 13). A total of 47, 43, 45 and 45 patients, all previously untreated, were randomized to the respective treatment arms. Although MVP resulted in a higher response rate (26%) than CBP (20%), AFP (17%) or CAP (23%), the difference was not significant. Survival did not differ significantly among the treatment groups, median survival being 24–48 weeks.

Another randomized study employing cisplatin was reported by Kris et al. [58]. In this study, 29 patients received a combination of vindesine + cisplatin, while 38 patients were treated with vinblastine + cisplatin. Response rates were not significantly different, with the overall response rate being 32% (Table 13). The combination of vindesine + cisplatin was also exploited by Shinkai et al. [96] and compared with vindesine + mitomycin C. Vindesine + cisplatin resulted in a 33% response rate, which was not significantly better than the 14% response rate observed with vindesine + mitomycin C. Overall survival for the two treatment arms was 43 weeks.

Sequential chemotherapy

In view of the disappointing results achieved with both single-agent and combination chemotherapy, other treatment strategies have been exploited. One approach has been the use of sequential treatment, employing potentially "non-cross-resistant" agents or combinations as a possible means of inducing a response after resistance to the initial treatment has occurred.

Table 14. Randomized trials comparing combination chemotherapy and sequential chemotherapy

Treatment	Evaluable patients		Complete responses (no.)	Response rate % (Range)	Median duration (weeks)		Reference
	PC	Total			Response	Survival	
CTX sequ	0	79	1	12 (6–22)		17	[34]
CCNU vs	16	16		13 (2–38)	14		
CTX + CCNU	0	83	3	12 (6–21)	17	26	
CTX + ADR + MTX vs		13		15 (2–45)		34	[35]
CTX sequ ADR sequ MTX		19		5 (0–26)		26	
MTX + CTX + ADR + PCZ vs	0	14	0	13 (4–29)		40	[47]
MTX sequ CTX + ADR sequ PCZ	0	18	0			11**	
CDDP sequ with	0	22	1	9 (1–29)	4	25	[8]
CTX + ADR vs	17	17	1	29 (10–56)	38		
CDDP + CTX + ADR	0	19	1	26 (9–51)	14*	29	

*$P < 0.05$; **$P < 0.01$
sequ: given sequentially with; see previous tables for other abbreviations

Four randomized trials have evaluated combination chemotherapy against sequential chemotherapy (Table 14). In 1976, Edmonson et al. [34] showed a minor survival advantage (26 weeks vs 17 weeks) for a combination of cyclophosphamide + lomustine (83 patients) compared with cyclophosphamide alone (79 patients) followed by lomustine at progression (16 patients). However, this difference did not reach statistical significance ($P = 0.07$). The limited data available failed to indicate whether or not previous treatment with cyclophosphamide affected the likelihood of responding to subsequent treatment with lomustine.

In an attempt to evaluate the contribution of cisplatin to the activity of CAP, the Mayo Clinic performed a study [8] comparing CAP with cisplatin as a single agent followed by cyclophosphamide + doxorubicin at the time of progression. There was a higher response rate with CAP (26% among 19 patients) than with cisplatin alone (9% responses among 22 patients) ($P < 0.025$), but no significant difference between cisplatin followed by cyclophosphamide + doxorubicin (29% responses in 17 patients) versus CAP. Median survival times were identical with 25–29 weeks, but there was a longer median duration of response in patients responding to cyclophosphamide + doxorubicin following cisplatin (38 weeks) than in patients responding to CAP (14 weeks) ($P = 0.05$).

Einhorn et al. [35] compared a combination of cyclophosphamide + doxorubicin + methotrexate (CAM) in 13 patients with single-agent sequential chemotherapy using the same three agents in 19 patients. There were no significant differences with respect to response rate (15% vs 5%) or survival (34 vs 26 weeks). These observations are in contrast to those of Hoffmann et al. [47], who compared a combination of cyclophosphamide + doxorubicin + methotrexate + procarbazine with leucovorin rescue (CAMP-L) against a regimen in which the same drugs were given sequentially (Table 14). The median survival of 11 weeks among 18 sequentially treated patients was shorter ($P < 0.01$) than the 40-week survival among the 14 patients treated with the combination regimen.

Discussion

The majority of the studies that have evaluated combination chemotherapy in ACL have been phase II trials. Interpretation of the treatment data requires consideration of several factors that may contribute to variations in the reported results even for similar cytostatic regimens. This variability may be attributed to such factors as differences in patient selection, response assessment, treatment intensity or reporting procedures. In addition, the size of the trial influences the statistical interpretation.

With respect to the patient population, a number of prognostic factors are known to influence the results obtained in clinical trials. The extent of prior chemotherapy is a major prognostic factor. This issue has been elucidated by Wittes et al. [114] in patients with non-small cell lung cancer. Among patients treated with vindesine as a single agent, the response rate was 28% among 130 previously untreated patients, as against only 5% among 48 pretreated patients ($P < 0.01$). This clearly demonstrates that pretreatment with chemotherapy exerts a deleterious influence on the probability of response. Whether or not the prognostic impact of prior chemotherapy is independent of other potentially important prognostic variables, such as performance status, weight loss and extent of disease, is less clear, because these variables may well be significantly correlated. A multivariate analysis is necessary to determine the independent prognostic impact of the individual variables.

Thus, reported differences between similar treatments may be due to variations inherent in patients' characteristics, but variability in response rates may also arise artifactually. This variability may arise from differences in criteria for assessment of tumor response and the associated errors of measurement [111]. The adoption of standard criteria in the evaluation of response is necessary, as has been proposed by the World Health Organization [116] and the Eastern Cooperative Oncology Group (ECOG) [81].

The doses and scheduling of cytotoxic drugs also vary in many of the trials evaluating the same regimen, e.g., the combination of cisplatin + etoposide (Table 3), which hampers direct comparison of treatment results. The importance of dose in achieving a maximal therapeutic effect has been demonstrated in responsive tumors, e.g., small cell lung cancer [17] and breast cancer [48]. It is not yet firmly documented in ACL, although at least one of the studies considered in this review does suggest such a relation [99].

Lee and Wesley [67] have emphasized the importance of trial size if safe conclusions are to be made concerning the activity of any particular regimen. Small study populations give wide confidence limits and increase the risk of type II statistical errors, i.e., overlooking a clinically useful activity. This point is of equal importance in randomized trials. In the design of randomized studies it is necessary to decide how large a difference one wishes to detect [97]. It will often be necessary to perform the study within a multicenter cooperative treatment group, as most single institutions cannot provide sufficient numbers of patients to answer the questions in prospective randomized trials with a high degree of statistical confidence.

With these difficulties in mind, we have drawn the following cautious conclusions from this review. Among the randomized studies employing combination therapy, several regimens have documented a response rate above 20%: lomustine + cyclophosphamide + methotrexate (response rates 14%–38%), hexamethylmelamine + doxorubicin + methotrexate (response rates 13%–32%), and methotrexate + doxorubicin + cyclophosphamide + lomustine (response rates 13%–24%). Among combinations including cisplatin, noteworthy activity has been reported for cyclophosphamide + doxorubicin + cisplatin (response rates 0–36%). The latter regimen has been extensively studied in six trials, with four yielding a response rate above 20%. Other active combinations are cyclophosphamide + bleomycin + cisplatin (20% responses), mitomycin C + vinblastine + cisplatin (26%–33% responses), cyclophosphamide + doxorubicin + etoposide + cisplatin (29% responses) and vindesine + cisplatin (33% responses).

When looking at the relative activity of a wide variety of treatments, combination chemotherapy regimens have been advantageous compared to single agent chemotherapy in few trials. Only the CAP regimen has shown a significantly higher response rate [8, 28] and longer duration of response [8] than cisplatin alone and dianhydrogalactitol alone, but survival was similar. The majority of combinations, mostly two-drug regimens, were not superior to single agents with respect to response rates. Nor has combination chemotherapy resulted in prolonged survival compared with single-agent therapy. However, most of the single agents that have been compared with combination chemotherapy regimens possess only minor activity against ACL. The only active single agent to have been evaluated in this fashion is vindesine, which has equal activity, based on response rate, duration of response and overall survival, to a three-drug regimen (cyclophosphamide + lomustine + methotrexate) and to a regimen including all four drugs.

Comparisons between various combination chemotherapy regimens have revealed the superiority of one combination over others in only a few instances. The three-drug regimen of lomustine + cyclophosphamide + methotrexate was found to be superior to a 2-drug regimen of cyclophosphamide + methotrexate, with regard to both response rate and survival [45]. Another study showed a combination of cyclophosphamide + doxorubicin + methotrexate + procarbazine to be associated with more prolonged survival than methotrexate given sequentially with cyclophosphamide + doxorubicin and with procarbazine. The trend in the other sequential studies is an advantage for the combination chemotherapy regimens, CAP versus cisplatin given sequentially with cyclophosphamide + doxorubicin being the exception [8].

The prognosis for patients with inoperable ACL is still dismal, as illustrated by the fact that none of the non-randomized trials in this review has demonstrated a median survival above 47 weeks and none of the randomized trials have documented median survivals exceeding 43 weeks. Most trials have shown considerably shorter survivals, but obviously differences in prognostic factors among the study populations have a major impact.

All cytostatic regimens are associated with morbidity attributable to toxicity, and because a survival advantage has not yet been documented patients should only receive cytotoxic chemotherapy within a clinical trial. Accordingly, chemotherapy for adenocarcinoma of the lung remains experimental. There is a pressing need, first of all, to identify new compounds or combinations of agents that have significant activity in ACL as measured by percentage of patients achieving complete or partial remission. Only when this has been achieved should comparative studies be initiated.

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