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Review

Single-agent chemotherapy for advanced adenocarcinoma of the lung

A review

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Summary. Systemic therapy with cytostatic agents has been widely used in the management of inoperable adenocarcinoma of the lung (ACL). However, chemotherapy for this tumor type remains experimental, and the prognosis is still poor. Thus, the literature on single-agent chemotherapy was reviewed in order to establish critical background material for the planning and evaluation of future studies. Only vindesine, dibromodulcitol, doxorubicin and hexamethylmelamine have displayed overall response rates exceeding 10% in randomized studies. Several of the most promising agents with response rates above 20% in non-randomized studies, i.e., 5-fluorouracil, mitomycin C, vinblastine and ifosfamide, have not been adequately evaluated in randomized trials in ACL. There is no published evidence to suggest the superiority of single-agent chemotherapy over the best supportive treatment, with respect either to survival or to quality of life. There are considerable methodological problems in designing, executing, analyzing and reporting these studies. Some of the problems could be solved by use of the internationally accepted guidelines for reporting results of cancer treatment, which might make more rapid progress possible.

Introduction

Systemic chemotherapy has been widely used in the treatment of adenocarcinoma of the lung (ACL), but without similar success to that observed in small cell lung cancer. A vast number of reports on the use of chemotherapy in inoparable non-small cell lung cancer (NSCLC) has been published, though very few have focused exclusively on ACL, a tumor type prognostically and clinically different from squamous cell and large cell carcinoma [14, 41, 87]. It was therefore of interest to review the existing literature to evaluate the present status of single-agent chemotherapy of ACL, thereby establishing critical background material for the planing and evaluation of future studies. Accordingly, we have reviewed the relevant literature for the period 1960–1986.

The major chemotherapeutic goals in ACL are to extend the median survival and to achieve long-term disease-free survival and, if possible, cure. A secondary goal is tumor shrinkage, which may alleviate symptoms and thus improve the quality of life. The observation of a tumor response may also be accompanied by prolonged survival, although this is not always the case. However, tumor shrinkage is essential for cure. Evaluation of the benefical effects of chemotherapy is therefore usually based upon tumor response rate, duration of response, and duration of survival, the last being the most critical.

In order to be considered in this review all publications were required to meet the following criteria:

1. A minimum of ten evaluable patients with ACL.
2. Inclusion of the number of responders or duration of survival. Definition of the response criteria applied was also necessary, and only responses qualifying as partial (PR) or complete remission (CR) according to WHO criteria [101] were considered.
3. Inclusion of detailed information on the schedule and dosage of the component drugs.
4. Presentation of results in more detail than allowed by the abstract form.

Studies satisfying these selection criteria are considered under the following headings: I. Non-randomized trials; II. Randomized trials.

I. Non-randomized trials

The data on the various cytostatic agents are presented according to their mode of action in Tables 1–8.

Alkylating agents (Table 1)

It is noteworthy that only one publication [17] reporting on the activity of cyclophosphamide (CTX) in a non-randomized study meets the aforementioned criteria. No responses were observed in this early trial reported in 1969. Because it is a retrospective review of patients treated during a 10-year period, the study is open to the criticism that it is liekly to refer to a very heterogeneous patient population. No information is given on drug toxicity, and the distribution of patients between the two treatment schedules is not described.

Ifosfamide (IFX), an isomer of CTX, has been evaluated in four studies with different doses and schedules. When the data from these studies are pooled, IFX yields an overall response rate of 21% among 112 patients with 4% CRs, indicating that IFX is an active agent in ACL. The observed response rates range from 9% to 30%. It is interesting that even though Loehrer et al. [63] and Costanzi

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Table 1. Alkylating agents

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Aziridinylbenzoquinone							
20 mg/m² i.v. weekly × 4, then every 2 weeks	8	18	0 (0–19)	0		9	[18]
Cyclophosphamide							
400 mg/day i.v. (total 30–40 mg/kg monthly) or 1600–2000 mg i.v., then 100–200 mg/day		20	0 (0–17)	0		23 (mean)	[17]
Dianhydrogalactitol							
15–30 mg/m² daily i.v. × 5 every 4 weeks	19	33	9 (2–24)	0	28		[43]
Dibromodulcitol							
175–225 mg/m² daily × 10 every 4–5 weeks	23	31	6 (1–21)	0	22	20	[27]
Dihydroxyanthracenedione							
3–4 mg/m² daily i.v. × 5 every 4 weeks	11	18	17 (4–41)	0			[96]
Guanazole							
4 mg/m² every 8 h i.v. for 5 days every 3 weeks		11	0 (0–28)	0			[60]
Ifosfamide							
1.2 g/m² daily i.v. × 5, then once weekly		16	30 (11–59)	1	30 (CRs)		[68]
1.2 g/m² daily i.v. × 5 every 4 weeks		38	24 (10–40)	1			[13]
4 g/m² i.v. every 3 weeks		35	20 (8–37)	2	19	17	[45]
1.2 g/m² daily i.v. × 5		23	9 (1–28)	0			[63]
Total		112	21 (14–30)	4			
Melphalan							
20–40 mg/m² once	9	20	0 (0–17)	0			[90]

* Prior chemotherapy

et al. [13] used similar doses and schedules, widely different response rates were observed – 24% and 9%, respectively. Apparently there are no randomized studies comparing CTX and IFX in ACL. The relative activity of the two agents when given in equitoxic doses therefore remains open to question.

Among the other alkylating agents, the hexitols dianhydrogalactitol and dibromodulcitol have shown only minor activity, with response rated of 6%–9% in studies which have included primarily pretreated patients. Similarly, neither guanazole nor the aziridinylbenzoquinone derivatives AZQ and melphalan have shown any activity in 11, 18 and 20 patients, respectively with ACL.

Dihydroxanthracenedione (DHAD) is a new anthraquinone compound. Valdivieso et al. [96] observed one PR among 11 pretreated patients and two PRs among 7 patients without prior chemotherapy, resulting in an overall 17% response rate for DHAD.

Nitrosoureas (Table 2)

The nitrosoureas were extensively tested in the early 1970s with lomustine (CCNU), showing a cumulated response rate of 14% among 44 patients treated in two trials. Another nitrosourea, methyl-CCNU (Me-CCNU), yielded a response rate of only 5% in a clinical trial conducted by Tranum et al. [95] in 38 patients.

Among the non-myelosuppressive nitrosoureas, chlorozotocin has been tested in four trials using doses in the range 120–225 mg/m² i.v. every 5–6 weeks. The overall response rate was only 3% among 97 patients treated.

A more recently developed nitrosourea, the water-soluble ACNU, has undergone initial clinical evaluation in Japan. Saijo et al. [80] did not detect any activity among 13 patients treated with ACNU. It was not reported whether or not the patients had received prior chemotherapy. A subsequent study by Sasaki et al. [85] was also negative.

Another recently developed nitrosourea is the lipid-soluble PCNU. In a trial by Kalman et al. [55] no responses were observed among 14 patients. Higher activity was reported by Ratanatharathorn et al. [77], but the overall response rate for PCNU among 36 patients treated in the two trials was only 6%.

Antibiotics (Table 3)

The most commonly used anthracycline doxorubicin (ADR) has been evaluated in four studies, each using different dose schedules. Noteworthy is the observation by

Table 2. Nitrosoureas

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
ACNU							
0.4–1.0 mg/kg daily		1					[80]
or 2 mg/kg weekly		6 } 13	0 (0–25)	0			
or 3 mg/kg every 6 weeks		6					
67–100 mg/m² every 4–6 weeks		11	0 (0–29)	0			[85]
Total		24	0 (0–14)	0			
Chlorozotocin							
150–200 mg/m² daily i.v. × 5 every 6 weeks		18	6 (0–27)	0	10		[6]
125 mg/m² i.v. every 5 weeks	20	28	3 (0–18)	0	24		[15]
120 mg/m² i.v. every 6 weeks		27	0 (0–13)	0			[11]
200–225 mg/m² i.v. every 6 weeks		24	4 (0–21)	0			[44]
Total		97	3 (1– 9)	0			
Lomustine							
130 mg/m² p.o. every 3 weeks		14	28 (8–58)	1			[93]
130 mg/m² p.o. every 6 weeks		30	7 (1–22)	0			[92]
Total		44	14 (5–27)	1			
Methyl-CCNU							
150–200 mg/m² p.o. every 6 weeks		38	5 (1–18)				[95]
PCNU							
20–25 mg/m² daily i.v. × 5 every 6 weeks		14	0 (0–23)	0			[55]
75–100 mg/m² i.v. every 6 weeks	7	22	9 (1–29)	0			[77]
Total		36	6 (1–19)	0			

* Prior chemotherapy

Knight et al. [57], who found only 2 PRs among 45 patients when they used a dosage of 20 mg/m² daily ×3 every 3 weeks, while Cortes et al. [12] reported a response rate of 29% with an ADR dosage of 30–35 mg/m² daily ×3 every 3–4 weeks. This suggests a dose-response relationship, but the difference might also reflect prognostic variations in the study populations, e.g., the extent of prior treatment. All patients in the study by Knight et al. had received prior chemotherapy, while the proportion of previously treated patients is not reported in the study by Cortes et al. Overall, the response rate for ADR is 10%, based on a total of 96 patients treated.

A more recently developed anthracycline antibiotic is aclarubicin, which was evaluated in 60 patients in three studies with varying doses and schedules. No responses were reported.

Epirubicin is another isomer of ADR, which yielded a response rate of 10% among 20 patients in a trial performed by the Early Clinical Trial Group of EORTC [54]. Similar activity was observed in a later study by Meyers et al. [67]. None of the patients in either trial had received prior chemotherapy.

Mitomycin C (MMC) is an antibiotic which is commonly used in combination chemotherapy regimens in the treatment of ACL. A consistently high response rate of 25%–27% has been observed in two studies in which MMC was given as a single agent [82, 100] with one-quarter of the responses being CRs. Thus, MMC has a predicted activity of 12%–45% within 95% confidence limits.

Miscellaneous alkylator-like agents (Table 4)

Cisplatin (CDDP) has been evaluated in five studies including 105 patients, yielding an overall response rate of 19%. Major differences in response rates have been observed, ranging from zero in the study by Bhuchar et al. [1] to 35% in the study by De Jager et al. [19]. No CRs were reported. Only two studies report information about prior treatment. Vogl et al. [99] observed three PRs among 12 patients without prior chemotherapy, while De Jager et al. reported a 35% response rate in 20 patients, 9 of whom were previously untreated.

Different dose schedules were employed in all five studies. The highest dose (120 mg/m²) was administered by De Jager et al., who also found the highest response rate. The results are in contrast to the findings of Bhuchar et al., who found no responses when giving doses of 100 mg/m², 120 mg/m² or 140 mg/m². Unfortunately, no details are given about the respective numbers of ACL patients treated at these three dose levels. The observed differences in activity are conceivably due to differences in various prognostic features in the patient samples, but none of the above -mentioned studies gives details on this subject.

Carboplatin is a new CDDP analogue with lower nephrotoxicity and emetogenic effect. Olver et al. [74] recorded no responses among 23 patients following bolus infusion of carboplatin.

Table 3. Antibiotics

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Aclarubicin							
120 mg/m² as 24-h infusion every 3–4 weeks		13	0 (0–25)	0			[10]
65–85 mg/m² i.v. weekly		21	0 (0–16)	0			[94]
75–100 mg/m² i.v. every 3 weeks		26	0 (0–13)	0			[58]
Total		60	0 (0– 6)	0			
Doxorubicin							
20–25 mg/m² daily i.v. × 3 every 3 weeks or 60–75 mg/m² i.v. every 3 weeks		18	17 (4–41)				[73]
30–35 mg/m² daily i.v. × 3 every 3–4 weeks		17	29 (10–56)	0	28		[12]
20 mg/m² daily i.v. × 3 every 3–4 weeks	45	45	4 (2–21)	0			[57]
30 mg/m² daily i.v. on days 1 + 2 once		16	0 (0–21)	0			[35, 36]
Total		96	10 (5–18)	0			
Epirubicin							
90 mg/m² i.v. every 3 weeks		20	10 (1–32)	0			[53, 54]
75 mg/m² i.v. every 3 weeks	0	17	6 (0–29)	0			[67]
Total		37	8 (2–21)	0			
Mitomycin C							
0.05 mg/kg daily i.v. × 10 every 2 weeks		11	27 (6–61)	1			[100]
20 mg/m² i.v. on days 1 + 42, then 10 mg/m² every 6 weeks		20	25 (9–49)	1			[82]
Total		31	26 (12–45)	2			

* Prior chemotherapy

Table 4. Miscellaneous alkylatorlike agents

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Carboplatin							
60–80 mg/m² daily × 5 every 4 weeks		23	0 (0–15)	0			[74]
Cisplatin							
120 mg/m² i.v. every 3 weeks		20	35 (15–59)	0			[19]
75 mg/m² i.v. weekly for 3 weeks, then every 3 weeks	0	12	25 (5–57)	0			[99]
100–140 mg/m² i.v. every 4 weeks		16	0 (0–21)	0			[1]
50 mg/m² i.v. on days 1 + 8 every 4 weeks		27	14 (4–34)	0		21	[76]
80 mg/m² i.v. every 3 weeks		30	17 (6–35)	0			[35, 36]
Total		105	18 (11–27)	0			
Hexamethylmelamin							
12 mg/kg daily p.o. × 21		10	30 (7–65)	0			[102]
12 mg/kg daily p.o. × 21 every 4 weeks		11	0 (0–28)	0			[91]
Total		21	14 (3–36)	0			

* Prior chemotherapy

Inconsistent data about the activity of hexamethylmelamine (HMM) in ACL are noted in the studies by Wilson et al. [103] and Stolinsky et al. [91], who report response rates of 30% and zero, respectively. The dose were similar, but both trials had small patient populations (10 and 11 patients), which were not characterized in detail.

Antimetabolites (Table 5)

The folate antagonist methotrexate (MTX) has been shown to possess minor activity as single agent, both in a conventional dosage [98] and in a high dosage with citrovorum factor rescue [3, 29]. The overall response rate in 68 patients treated with MTX was only 6%, the response rate apparently being independent of both the actual dose and the schedule.

Another antimetabolite is triazinate (TZT). One study has been performed in 31 patients with ACL, yielding a response rate of 13% [78].

Among the other antimetabolites, the folate antagonist 6-mercaptopurine and the pyrimidine antagonists *N*-(phosphonacetyl)-L-aspartic acid (PALA), acivicin and pyrazofurin all appear to be inactive as single agents in the treatment of ACL, with response rates of 0–6% [8, 39, 59, 65].

With respect to the established antimetabolite 5-fluorouracil (5-FU), in 1974 Faulkner et al. [32] published the results of an interesting phase II trial in ACL. Responses were seen in 4 of 10 treated patients, with 2 CRs and 2 PRs lasting a median of 13 months. All patients were previously untreated. The treated patient population is therefore small, but response rates obtained using 5-FU exceed 12% with a confidence level of 95%. Unfortunately, there are no more recent studies that have evaluated the activity of 5-FU in a sufficient number of patients with ACL.

Plant alkaloids (Table 6)

The cumulated response rate from two studies [22, 51] in a total of 66 patients treated with the semisynthetic plant alkaloid etoposide (VP-16-213) (VP-16) is only 6%. The highest response rate (13%) was observed in the study by Eagan et al. [25] in which none of the patients had received prior chemotherapy.

The other podophyllotoxin derivative teniposide (VM-26) did not yield any responses in a study by Samson et al. [81], which included mainly pretreated patients. The dosage of teniposide was however relatively low, being 20–30 mg/m^2 i.v. daily for 5 days every 3–4 weeks. The majority of the 19 patients had been pretreated with chemotherapy (14 patients) and radiotherapy (13 patients), and the mean performance status was only 63% (Karnofsky scale). The possibility cannot be excluded that teniposide would be effective in patients who had more favorable prognostic features and were treated more intensively.

Another plant alkaloid, maytansine (MAYT) was given according to a schedule of 0.6 mg/m^2 daily ×3 every

Table 5. Antimetabolites

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Acivicin							
12 mg/m^2 daily i.v. × 5 every 3 weeks	18	36	6 (0–19)	0			[59]
5-Fluorouracil							
12 mg/kg daily i.v. × 4, then once weekly	0	10	40 (12–74)	2			[32]
Methotrexate							
0.2–0.9 mg/kg i.m., i.v. or p.o. twice weekly or 5–10 mg/kg i.v. every 3 weeks	0	31	6 (1–21)	0			[98]
1500–7500 mg/m^2 i.v. in 6 h every 2 weeks	0	18	6 (0–27)	0			[29]
1500–12 000 mg/m^2 i.v. in 6 h or 50 mg/m^2 bolus followed by 1500 mg/m^2 in 30 h		19	5 (0–26)	0			[3]
Total		68	6 (2–14)	0			
PALA							
3.75–4.25 mg/m^2 i.v. weekly		12	0 (0–26)	0			[7]
Pyrazofurin							
200 mg/m^2 i.v. weekly		10	0 (0–31)	0			[39]
Triazinate							
100–150 mg/m^2 daily i.v. × 5 every 2–3 weeks or 150–250 mg/m^2 daily i.v. × 3 every 2–3 weeks		31	13 (4–30)	1			[78]
Metoprine							
150–225 mg/m^2 p.o. every 2–3 weeks		28	0 (0–12)	0			[65]

* Prior chemotherapy

3–4 weeks in a study conducted by Eagan et al. [26]. A different schedule of 0.5–1.25 mg/m^2 weekly was used by Franklin et al. [34]. Both studies gave similar results, with the overall response rate in 30 patients being 10%.

Vinca alkaloid (Table 7)

Among the vinca alkaloids, vinblastine (VBL), vindesine (VDS) and vincristine (VCR) have shown interesting results as single agents. Vinblastine (VBL) has been evaluated in only one study with adequate reporting of results for ACL patients [86]. This study utilized a divided dose schedule with four doses of VBL given every 6 h for 2 days every 2 weeks. The schedule was based on pharmacokinetic studies which demonstrated that VBL is rapidly cleared from the plasma [71]. The results were encouraging, with a response rate of 25% in 16 patients even though the study included both untreated and previously treated patients.

There is some controversy regarding the activity of VCR. Brugarolas et al. [4] initially reported a response rate

Table 6. Plant alkaloids

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Etoposide							
140 mg/m^2 i.v. on days 1–3–5 every 4 weeks	0	24	13 (3–32)	0	15	25	[25]
120–150 mg/m^2 i.v. on days 1–3–5 every 3 weeks		42	2 (0–13)	0	24		[51]
Total		66	6 (2–15)	0			
Maytansine							
0.6 mg/m^2 daily i.v. × 3 every 3–4 weeks	12	17	12 (1–36)	0		19	[26]
0.5–1.25 mg/m^2 i.v. weekly		13	8 (0–36)	0	4		[34]
Total		30	10 (2–27)	0			
Teniposide							
20–30 mg/m^2 daily i.v. × 5 every 3–4 weeks	14	19	0 (0–18)	0			[81]

* Prior chemotherapy

Table 7. Vinca alkaloids

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Vinblastine							
2.4 mg/m^2 i.v., then 1.2 mg/m^2 i.v. every 6 h in 2 days every 2 weeks		16	25 (7–52)	0			[86]
Vincristine							
1.5 mg as 4- to 6-h infusion weekly in 10 weeks	0	15	33 (12–62)	0			[4]
1.0 mg i.v. bolus weekly in 8 weeks	2	30	7 (1–22)				[5]
Total		45	16 (6–30)	0			
Vindesine							
1.0–1.4 mg/m^2 daily i.v. as 8-h infusion × 3 every 3 weeks		14	0 (0–23)	0			[21]
3 mg/m^2 i.v. weekly	19	29	21 (8–40)	0			[69]
3 mg/m^2 i.v. weekly	4	14	0 (0–23)	0			[33]
3 mg/m^2 i.v. weekly × 10, then every 2 weeks		10	20 (0–45)	0			[64]
4 mg/m^2 i.v. weekly × 8, then every 2 weeks	1	22	27 (11–52)	1	28		[75]
3 mg/m^2 i.v. weekly × 6, then every 2 weeks	0	17	29 (10–56)	0	9		[48]
3 mg/m^2 i.v. weekly	0	17	6 (0–29)	0			[88]
3 mg/m^2 i.v. weekly		15	13 (2–40)	0			[37]
Total		138	16 (10–23)	1			

* Prior chemotherapy

of 33% in a single institutional study, while the same author found only 7% responders in a subsequent multi-institutional study performed within the Early Clinical Trial Group of EORTC [5]. Both trials included mainly untreated patients. In addition to the stricter response criteria applied in the multi-institutional trial, differences in the dose of VCR may have contributed to the observed difference in activity. A dose of 1.5 mg VCR was given as a 4- to 6-h infusion in the first study, whereas the later study used a dose of 2.0 mg VCR by bolus injection. The overall response rate for VCR among 45 patients in both studies was 16%.

In contrast to VCR and VBL, substantial data are available on the activity of VDS, with an overall response rate of 16% observed in eight studies including 138 patients. This overall response rate covers major discrepancies among the individual studies, with response rates ranging from zero to 29%. The lowest order of activity (0) was observed by Ferrazi et al. [33]. A possible explanation for this discrepancy may be that dosage adjustments upon the initial 3 mg/m^2 i.v. were necessary in half the patients. Furthermore, one-third of the patients were pretreated, and this too may have contributed to the poor response rate.

The study by Sledge et al. [88], which also included pretreated patients, yielded a low response rate (6%). This contrasts with the response rate of 21% reported by Natale et al. [69] in a study in which 19 of 29 patients had received prior chemotherapy. Both studies use a VDS schedule of 3 mg/m^2 weekly. The distribution of other prognostic factors in this latter study was not different from that in the studies of Ferrazi et al. or Sledge et al. Hutcheon et al. [48], whose study included only untreated patients, observed a response rate of 29%.

The only study to employ a dose of 4 mg/m^2 was reported by the Copenhagen Group [75] in a trial including 22 patients. The 27% response rate was not superior to that achieved in some of the studies in which the dose given was 3 mg/m^2 [48, 64–69], but this study accounted for the only CR recorded with VDS as a single agent.

Miscellaneous agents (Table 8)

Studies on the activity of bisantrene, ICRF-187 and methyl-glyoxal bis-guanylhydrazone (MGBG) have shown no demonstrable activity in ACL as seen in Table 8.

The acridinyl anisidide (*m*-AMSA) has been extensively evaluated in three studies including 80 patients with ACL [7, 72, 83], but none of the studies reported response rates exceeding 5%.

II. Randomized trials

In total, 15 randomized trials designed for investigation of the activity of single-agent chemotherapy in ACL have been published (Table 9). Most studies have included patients with lung cancer of other cell types, and several fail to provide complete information with respect to important data such as duration of response or survival.

Table 8. Miscellaneous single agents

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
Acridinylanidiside (m-AMSA)							
90–120 mg/m^2 i.v. every 3 weeks		18	0 (0–19)	0			[7]
25–35 mg/m^2 daily × 3 every 3 weeks	15	22	5 (0–23)	0	16	16	[72]
55–120 mg/m^2 i.v. every 3 weeks	22	40	2 (1–17)	0	9		[83]
Total		80	3 (0– 9)	0			
Bisantrene							
260 mg/m^2 i.v. every 3–4 weeks		12	0 (0–26)	0			[66]
200 mg/m^2 i.v. every 3 weeks		10	0 (0–31)	0			[38]
260 mg/m^2 i.v. every 5 weeks	0	39	8 (2–21)	0			[40]
Total		61	5 (1–14)	0			
ICRF-187							
1500 mg/m^2 daily i.v. × 3 every 3 weeks		16	0 (0–21)	0			[70]
Methyl-glyoxal bisguanylhydrazone (MGBG)							
400–500 mg/m^2 i.v. weekly		36	6 (1–19)	0			[9]
500 mg/m^2 i.v. weekly	12	20	5 (0–25)	0	40		[56]
500 mg/m^2 i.v. weekly	10	20	5 (0–25)	0	5		[84]
600 mg/m^2 i.v. weekly	22	43	7 (1–19)	0			[97]
Total		119	6 (2–12)	0			
Spirogermanium							
100 mg/m^2 daily i.v. × 5 every 2 weeks		11	0 (0–28)	0			[20]

* Prior chemotherapy

Table 9. Single agent chemotherapy in randomized studies

Treatment	Evaluable patients		Response rate % (Range)	Complete response (no.)	Median duration (weeks)		References
	PC*	Total			Response	Survival	
HN2 vs		38			6 months survival	19%	[42]
Inert compound		136				27%	
CTX vs		69			6 months survival	15%	[42]
Inert compound		101				24%	
CCNU vs		24	0 (0–14)	0		19	[22]
Me-CCNU		23	0 (0–15)	0			
HMM vs		37	16 (6–32)			22	[103]
DBD		45	20 (10–35)			35	
CTX sequ. with	0	79	12 (6–22)	1		17	[28]
CCNU vs	16	16	13 (2–38)		14		
CTX + CCNU	0	83	12 (6–21)	3	17	26	
ICRF 159 vs		25	8 (1–26)	0			[23]
VCR + BLM + ADR		16	13 (2–38)	0			
DAG vs	2	18	0 (0–19)				[24]
CTX + ADR + CDDP	8	22	36 (17–59)	**			
CDDP sequ. with	0	22	9 (1–29)	1	4	25	[2]
CTX + ADR vs	17	17	29 (10–56)	1	38		
CTX + ADR + CDDP	0	19	26 (9–51)	1	14	29	
					*		
CTX vs		50	8 (2–19)			19	[104]
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	9 (2–25)	0		15	[79]
MTX + ADR + CTX + CCNU vs	0	15	7 (0–32)	0		14	
DBD + ADR vs	0	32	9 (2–25)	1		24	
Ftorafur vs	0	33	3 (0–16)	0		14	
Piperazinedione vs	0	27	7 (1–24)	** 0		15	
ADR + 5-FU + CDDP	0	39	26 (13–42)	* 0		27	
TZT vs		21	5 (0–24)				[16]
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)				
ADR 50 mg/m² vs	0	47	6 (1–18)	0		20	[47]
ADR 70 mg/m² vs	0	38	18 (8–34)	0		18 *	
CTX	0	51	4 (0–13)	0		13	
VCR vs	0	6	0 (0–46)	0			[52]
VDS	0	14	7 (0–34)	0			
PALA vs		10	10 (0–45)	0			[30]
PCNU		12	0 (0–26)	0			
DHAD vs		12	0 (0–26)	0			[31]
ACM-A vs		15	≤7	0			
AZQ		16	≤6	0			
VDS vs	0	71	22 (13–34)	5	12	29	[89]
CTX + CCNU + MTX vs	0	74	23 (14–34)	2	16	29	
CTX + CCNU + MTX + VDS	0	73	27 (18–39)	2	16	34	

* $P < 0.05$

** $P < 0.01$

ACM-A, aclarubicin; ADR, doxorubicin; AZQ, aziridinylbenzoquinone; BLM, bleomycin; CCNU, lomustine; CDDP, cisplatin; CTX, cyclophosphamide; DAG, dianhydrogalactitol; DBD, dibromodulcitol; DHAD, dihydroxyanthracenedione; 5-FU, 5-fluorouracil; HMM, hexamethylmelamine; HN2, nitrogen mustard; Me-CCNU; methyl-CCNU; MTX, methotrexate; PALA, *N*-(phosphonacetyl)L-aspartic acid; PCNU, *N*-(2-chloroethyl)-*N*-(2,6 dioxo-3-piperidinyl)-*N*-nitrosourea; PCZ, procarbazine; TZT, triazinate; VCR, vincristine; VDS, vindesine

Alkylating agents

One of the first, and still most important, studies was reported in 1969 by Green et al. on behalf of the Veterans Administration Lung Cancer Study Group [42]. Patients were randomized to receive an alkylating agent, either nitrogen mustard (HN_2) or cyclophosphamide (CTX) or an inert compound after stratification for extent of disease and prior therapy. Patients were sampled over a 10-year period, and treated according to six protocols with varying doses and schedules of the cytotoxic agents. The evaluation of therapeutic effectiveness in these studies was based on survival time rather than objective tumor regression. No significant difference was observed between 38 patients treated with HN_2 and 136 patients receiving supporting care only or between 69 patients treated with CTX and 101 patients receiving supportive care only. The 1-year survival rates were in the range of 5%–8% for all groups.

Cyclophosphamide as a single agent has also been evaluated against other compounds in three studies. In the study conducted by ECOG [28] in 162 previously untreated patients, no difference was observed between CTX alone and the combination CTX + CCNU, with response rates of 12% and 13%, respectively. Even though the overall response rate for CTX was only 12%, a somewhat higher number of responses occurred in patients with the most pronounced toxicity ($P = 0.008$), with 10% and 31% responders among patients experiencing moderate and severe toxicity, respectively. This effect did not apply to the combination of CTX + CCNU. Patients treated initially with the single agent subsequently received CCNU at the time of CTX failure. The median survival was 17 weeks for patients initially treated with CTX, as against 26 weeks for patients treated with CTX + CCNU ($P = 0.07$).

The modest activity of CTX as a single agent was confirmed by Wolf et al. [104], who reported a response rate of 8%. In another randomized study CTX was compared with ADR by Hoeltgen et al. [47], who observed only two PRs among 51 CTX-treated patients, even though none of the study group had received prior chemotherapy. The survival rates observed by Edmonson et al. [28] and Wolf et al. were almost equal, being 17 and 19 weeks respectively.

Among other alkylating agents, dianhydrogalactitol (DAG) was compared with CTX + ADR + CDDP in a randomized trial by Eagan et al. [24]. No responses were noted among 18 patients treated with DAG, only 2 of whom had received prior therapy.

In another randomized study, Ettinger et al. [31] failed to observe any responses at all when comparing AZQ with dihydroxyanthracenedione (DHAD) and aclarubicin (ACM-A), suggesting that all three drugs are inactive against ACL. No data are available concerning the prior treatment of patients with ACL, but 77% of the 110 non-small cell lung cancer patients in the study had received prior chemotherapy.

Though the effect of dibromodulcitol (DBD) was minor (response rate 6%) in a non-randomized study by Eagan et al. [27], Wilson et al. [103] found a 20% response rate among 45 patients with median survival of 35 weeks in a randomized study of DBD versus HMM. DBD is thus the only alkylating agent which has shown noteworthy activity as single agent in a randomized trial. However, the most active agent in the alkylating group in non-randomized studies is IFX, which has not been evaluated in a randomized trial in ACL.

Nitrosoureas

In 1974, investigators from the Mayo Clinic compared the two nitrosourea compounds CCNU and Me-CCNU [22]. No responses were noted in a comparative study in 47 patients, although only a minority of the patients had been exposed to prior chemotherapy. The data contrast with the findings of Takita et al. [93], who reported a response rate of 28% to CCNU in a non-randomized study including 14 patients with ACL. In this last study the drug was given every 3 weeks, while the former study had a 7-week schedule with similar doses, suggesting a dose-response relationship.

The i.v.-administered nitrosourea PCNU demonstrated only minor activity in two non-randomized studies [55, 77] and also failed to show any activity in a randomized study by Ettinger et al. [30] when compared with PALA.

Antibiotics

Two randomized studies have utilized anthracyclines as single drugs. Hoeltgen et al. [47] randomized a total of 136 patients to "low"-dose ADR (50 mg/m^2 i.v. every 3 weeks; 47 pts), "high"-dose ADR (70 mg/m^2 i.v. every 3 weeks; 38 pts) and CTX (1 g/m^2 i.v. every 3 weeks; 57 pts). No significant differences were observed in duration of response or median survival (20 and 18 weeks) between the two dose levels of ADR. The median survival times for patients treated with low-dose ADR and CTX were 20 weeks and 13 weeks, respectively ($P = 0.04$). The 4% response rate to CTX was not significantly inferior to that achieved with either low-dose ADR (6%) or high-dose ADR (18%). The conclusions from this study were that low-dose ADR is less toxic than high-dose ADR and is associated with prolonged survival compared with CTX therapy. The response rate associated with ADR as single agent is modest and is comparable to that of CTX.

Among the other anthracyclines, aclarubicin (ACM-A) yielded a response rate below 7% in 15 patients in a randomized study by Ettinger et al. [31]. No other anthracyclines have been evaluated for single-drug activity in randomized trials.

Single-agent treatment with the streptomyces derivative piperazinedione (27 pts) or ftorafur (33 pts) was compared with four different combination chemotherapy regimens by Ruckdeschel et al. [79]. A response rate of 7% was observed for treatment with piperazinedione, and this was significantly lower than the 26% response rate to the combination of ADR + 5-FU + CDDP ($P < 0.05$).

Miscellaneous alkylator-like agents

Only one randomized study has focused on CDDP applied as a single agent. Britell et al. [2] randomized 22 patients to CDDP and 19 patients to a combination of CTX + ADR + CDDP (CAP). None of these patients had received prior chemotherapy. The response rate to CDDP alone was only 9%, while a 26% response rate was obtained with the CAP treatment ($P < 0.05$). The duration of responses was brief, being 4 weeks for CDDP and 14 weeks for CAP. Survival times were also similar, being 25 and 29 weeks, respectively.

As mentioned above, conflicting results for the alkylator-like agent hexamethylmelamine (HMM) were observed in two non-randomized studies [91, 102] with response rates of zero and 30% and an overall response rate of 14%.

Virtually the same order of activity was found by Wilson et al. [103] in a randomized study comparing HMM with dibromodulcitol (DBD). HMM yielded a response rate of 16% in 37 patients and a median survival of 22 weeks. Results were similar for DBD ($P > 0.05$).

Antimetabolites

Three antimetabolites have been evaluated in randomized trials. Triazinate (TZT) was tested in a study of ECOG [16] and compared with four different combination chemotherapy regimens (Table 9). Only one response was noted among 21 patients treated with TZT, but the single agent was not significantly inferior to the combination regimens.

PALA, another antimetabolite, yielded a 10% response rate among 10 patients in a randomized trial reported by Ettinger et al. [30]. Ftorafur was significantly inferior to a combination of ADR + 5-FU + CDDP (3% versus 26% responders) in a study by the ECOG [79].

Vinca alkaloids

With respect to vinca alkaloids, VDS as single agent was compared with CCNU + CTX + MTX and with the combination of all four drugs in a randomized study by the Copenhagen group [89]. There were 218 patients evaluable for response. The VDS dose was 4 mg/m^2 i.v. weekly for the first 8 weeks, then biweekly. The response rate was 22% among 71 previously untreated patients, the median duration of response, 12 weeks, and the median survival, 29 weeks. This was equal to the activity obtained with both the three- and the four-drug regimens.

A trial comparing VCR with VDS was published by Jewkes et al. [52]. Only minor activity was observed, as there were no responders among 6 VCR-treated patients and only 1 PR occurred among 14 patients treated with VDS. However, the relative activity of the two vinca alkaloids in ACL cannot be judged from this study, as it included only a total of 20 patients with this tumor type.

Discussion

Interpretation of treatment results for inoperable ACL requires accurate knowledge of the natural course of the disease entity. The largest studies dealing with this topic have been performed by The Veterans Administration Lung Cancer Study Group, USA [42, 49, 50]. Green et al. [42] reported data from six of their studies with a total of 136 untreated ACL patients. All were classified as having extensive disease and randomized to receive an inert compound. The 6-month survival rate was 27%, 8% of patients were alive at 12 months, and the median survival was approximately 3 months.

The impact of disease stage was analyzed by Hyde et al. [50], who found a median survival of 13 weeks in 93 patients with extensive ACL receiving only symptomatic care. In a previous study [49] including both limited and extensive disease, the median survival was 27 weeks among 68 patients. These figures emphasize the poor overall prognosis for patients with inoperable ACL.

When considering the overall results for single-agent chemotherapy in ACL, it is apparent that major methodological problems exist in assessing the activity of the various drugs. First, differences in dose and/or schedule may result in major variations in the results obtained. For some drugs, such as CDDP, the existing data suggest a dose-response relationship or schedule dependency, stressing the importance of considering this aspect in the planning of future trials.

Secondly, differences in patients' characteristics and thereby prognostic factors may give widely varying results with regard to response rate or survival, as emphasized by Lad and McGuire [61]. Commonly accepted positive prognostic factors in non-small cell lung cancer are high performance status, limited disease, absence of weight loss, female sex and no prior therapy [53]. Many studies fail to report these characteristics, so that attempts to compare treatment results are fraught with difficulty.

The validity of the therapeutic results is also critically dependent upon study design. Because the principal goal of a phase II trial is to determine whether a drug is active or not, it is important, in relation to the size of the trial, to choose the relevant threshold for a clinically useful response rate. When the probabilities of the false-positive error, alpha, and the false-negative error, beta, are known, it is possible to calculate the actual number of patients needed for such studies [62]. This information is regularly omitted from published reports.

The assessment of tumor response is another source of difficulty. Whereas some trials require shrinkage of all measurable tumors, others utilize only one indicator lesion. Other differences are found in the definitions of measurable and evaluable lesions or duration of remission. Interobserver variation in response measurements may also contribute to the varying results [46].

Although prolongation of survival is an ultimate goal, survival data are frequently not reported in the results of phase II trials. This is partly due to the fact that many studies include several cell types of non-small cell lung cancer and specific information in relation to the individual tumor types is usually omitted.

Within the limitations posed by these methodological problems, we have tried to draw some cautious conclusions cencerning the activity of single drugs in non-randomized studies of ACL. An overall response rate of 20% has been shown for 5-fluorouracil, mitomycin C, vinblastine and ifosfamide. However, both vinblastine and 5-fluorouracil have each been evaluated in only a single study. More substantial data support the activity of mitomycin C (2 trials including 31 patients) and ifosfamide (3 trials including 89 patients). Lower overall response rates in the range of 10%–19% have been obtained with cisplatin (18%), dihydroxyanthracenedione (17%), vindesine (16%), vincristine (16%), lomustine (14%), hexamethylmelamine (14%), triazinate (13%), doxorubicin (10%), epirubicin (10%) and maytansine (10%).

Some of the agents that have shown encouraging results in non-randomized single-institution studies have subsequently been evaluated in randomized trials. In several instances, randomized studies have failed to confirm previously reported activity. Overall response rates below 10% were noted for cisplatin, triazinate, lomustine and dihydroxyanthracenedione. Only vindesine, dibromodulcitol, doxorubicin and hexamethylmelamine displayed response rates above 10%, the two first agents being the most active with a 20% overall response rate. It is of some concern that several of the most promising agents in non-randomized studies, i.e. 5-fluorouracil, mitomycin C, vinblastine and ifosfamide, have not been adequately evaluated in randomized trials.

Even though information concerning the activity of cyclophosphamide is scarce in non-randomized studies, substantial data are available from randomized trials. A total of 180 patients have been treated, resulting in a 9% overall response rate, indicating that cyclophosphamide has very modest single-agent activity in ACL.

Only three studies have suggested that combination chemotherapy might be superior to treatment with single agents. The CAP regimen has shown a significantly higher response rate than dianhydrogalactitol [24], and a significantly higher response rate and longer duration of response than cisplatin [2], but the overall survival was similar. A combination of ADR + 5-FU + CDDP has been advantageous with respect to response rate when compared with both piperazinedione and ftorafur, but these two drugs have only minimal activity in ACL [79]. The majority of combinations, mostly two-drug regimens, have not proved significantly superior to single drugs. Nor has combination chemotherapy with three or four drugs yielded superior results compared with single-drug treatment.

Furthermore, only two trials, both performed in the early 1960s, have compared single-agent chemotherapy with supportive care only in a matched control group. Neither of these trials, of CTX and HN_2, yielded superior results for chemotherapy.

No survival advantage has thus been documented. The overall prognosis for patients with inoperable ACL is still dismal. Indeed, none of the 94 trials included in this review yielded a median survival in excess of 35 weeks. Because of the significant morbidity associated with chemotherapy, the poor results of treatment to date suggest that single-agent chemotherapy for inoperable adenocarcinoma is only justifiable in the context of a controlled clinical trial.

Conclusions

In summary, we conclude that in spite of numerous non-randomized and randomized studies conducted within the last 25 years, there are still no clear indications as to which of the many single available agents are the most active in ACL. Furthermore, none of these studies has suggested that single-agent chemotherapy is superior to no treatment with respect either to survival or to quality of life.

Finally, there are considerable methodological problems in the design, execution, analysis and reporting of studies. It must be hoped that these deficiencies will be rectified in future studies. Interpretation of results might be facilitated by the use of internationally accepted guidelines (e.g., WHO handbook for reporting results of cancer treatment [101], while the unnecessary duplication of studies and publication of inconclusive data should also be avoided.

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