Cancer Chemother Pharmacol (1991) 28: 319–330
034457049100111L

Cancer Chemotherapy and Pharmacology

Review

Chemotherapy in malignant mesothelioma: a review

Anders Krarup-Hansen and Heine H. Hansen

Dept. of Oncology, The Finsen Institute, Rigshospitalet, DK-2100 Copenhagen, Denmark

Received 2 February 1990/Accepted 14 April 1991

Summary. This review of malignant mesothelioma focuses on the activity of single-agent and combination chemotherapy, a field in which research has thus far been rather unsystematic and sparse. Available results neither accede to any substantial drug activity nor justify the use of standard therapy. Furthermore, even when pooled most findings do not fulfil the basic criteria for a phase II trial. Prospective (multicenter) phase II trials are recommended for the identification of new agents that show antineoplastic activity in malignant mesothelioma. The use of computed tomography scans can assist in the prediction of the extent of disease both before and during treatment. Tumor-biological systems using mice xenografts or cell lines of human mesothelioma should be further developed so as to improve the screening of new agents exhibiting potential antineoplastic activity that is especially directed against mesothelioma.

Introduction

Malignant mesothelioma accounts for 0.16% (geographical range, 0.07%–0.17%) of all malignancies but for approximately 0.38% of all cancer deaths [8, 36, 77, 131, 147]. A history of asbestos exposure can be elicited in 0–90% of the patients [10, 12, 27]. Asbestos is oviously the principal etiologic agent and the development of malignant pleural mesothelioma requires less exposure to asbestos than does asbestosis. The peak incidence of the disease occurs at 20–40 years following the initial exposure, but it may occasionally develop within the first 5 years. Malignant mesotheliomas derive from the mesothelium covering the body cavities. The first symptoms are most frequently dyspnoea, weight loss, and chest pain. The chest X-ray film usually reveals a unilateral pleural effusion, and a visible pleural tumor is only seen in 20% of cases. The ratio of peritoneal to pleural mesotheliomas in exposed asbestos workers has been reported to be 2:5 [130].

Law et al. [91] have reported the natural history of malignant mesothelioma based on data from 64 untreated patients. The median survival from the onset of symptoms was 18 months; survival exceeded 4 years in 7 of the subjects and 5 years in 4, whereas 1 patient lived for 16 years. Subdivision into epithelial, fibrosarcomatous, and mixed cell types revealed no difference in survival between the various histological subtypes [4]. Other studies have reported a better relative survival for the epithelial subtype [1, 16, 76, 90], but definitive conclusions cannot be drawn

Table 1. Systems for clinicopathological staging of diffuse malignant mesothelioma

Butchart staging[a]
I. Tumor confined to the ipsilateral pleura and lung
II: Tumor involving the chest wall, mediastinum, pericardium, contralateral pleura
III: Tumor involving both the thorax and the abdomen or lymph nodes outside the chest
IV: Distant blood-borne metastases
Proposed TNM staging**[b]
Primary tumor:
T1: Limited to ipsilateral pleura only
T2: Superficial local invasion
T3: Deep local invasion
T4: Extensive direct invasion
Lymph nodes (LN):
N0: No positive LN
N1: Positive ipsilateral hilar LN
N2: Positive mediastinal LN
N3: Positive contralateral hilar LN
Metastases (M):
M0: No M
M1: Blood-borne or lymphatic M
Stage:
I: T1N0M0
II: T1+2,N0+1,M0
III: T3,Nx,M0 or T<4,N2+3
IV: T4,Nx,M0+1

[a] According to Butchart et al. [29
[b] From Chahinian [32]

Offprint requests to: Anders Krarup-Hansen

Table 2. Prognostic factors in malignant mesothelioma

Predictor	Prognosis		References
	Good	Bad	
Performance status (WHO)	0–1	2–4	[4, 16]
Duration of symptoms	>6 months	<6 months	[4, 16]
Stage (Butchart)	1	2–4	[4, 16, 29]

at this point. The most commonly accepted staging system, proposed by Butchart et al. [29], is a simply applicable tool that predicts survival (Table 1). Chaihinian [32] recently modified this system using the TNM staging system (Table 1). The significant clinical prognostic factors are listed in Table 2. Thus far, the prognosis has unfortunately been determined less by treatment than by these factors [4, 16, 61, 92]. The treatment of malignant mesothelioma has undergone some changes during the last decade, but it remains controversial. Thus, physicians resort to such modalities as surgery, radiotherapy, and chemotherapy. The objective of this review was to analyze the effect of chemotherapy on this disease and to recommend proposals for future research.

Methodology

The WHO criteria for response were [150]. For evaluable disease, a complete response (CR) was defined as the total disappearance of all measurable disease. A partial response (PR) was defined as a reduction of $\geq 50\%$ in the product of two perpendicular diameters of reproducibly measurable lesions for at least 4 weeks. The criterion for stable disease (NC) was either an increase of <25% or a decrease of <50% in tumor size and the appearance of no new lesions for at least 8 weeks. Finally, disease progression (PD) was defined as any increase of >25% in tumor size as compared with the measurement obtained at the time of initiation of chemotherapy or as the appearance of any new tumor. Similar standard definitions for the response of evaluable but nonmeasurable disease were used [54].

The end points applied were defined as described below. Response (R) was defined as the rate of CR + PR vs the number of evaluable cases. Classification of a drug that evoked an actual R of <100% as being >100% R-effective represented the false-positivity (FP) error, and the allowable size of its probability P(FP) was denoted alpha. Classification of a drug that produced an actual R of >100% as being <100% R-effective represented the false-negativity (FN) error, and the allowable size of its probability P (FN) was denoted beta.

The drug data were classified into one of three categories: (1) activity (A)>100% R if the drug data supported an R rate of $\geq 100\%$, (2) no activity (NA)<100% R if the drug data supported an R rate of <100%, and (3) potential activity [IC(100% R)] if the drug data were inconclusive for a 100% R rate. In this review a reference including R = 0.2 and alpha = beta = 0.05 was used. For analysis of response rates, we applied the methods and tabulations introduced by Lee and Wesley [92].

Evaluation procedures

Pleural metastatic adenocarcinoma may be difficult to distinguish histologically from the epithelial variant of mesothelioma. In some instances, the use of alcian blue stain – in the presence and absence of hyaluronidase predigestion – coupled with periodic acid-Schiff stain (PAS) can assist the distinction of the former from the latter [57, 109]; several studies have also suggested that immunohistochemical methods show diagnostic value [45, 121, 128]. The definitive diagnosis is best established by a histopathological examination that includes electron microscopy [48, 137, 144, 145] of surgically obtained tumor tissue. A histopathology panel review is also desirable when a finite clinical evaluation must be confirmed [61].

One of the greatest problems in the interpretation of the efficacy of a cytostatic agent in mesothelioma is the means of evaluating the treatment response. Conventional chest X-ray films often give inadequate information about disease dissemination, but the introduction of new technologies such as computed tomography (CT) scans and mag-

Table 3. Computer tomography scanning in malignant mesothelioma

Year	Number of evaluable cases	Number of serially evaluable cases	Number of False-pos. diagnoses by CT		False-neg.		Number of chest-film-neg./ CT-pos. diagnoses			References
			Pleura		Chest wall		Initial	During treatment		
			Pos.	Neg.	Pos.	Neg.		Remis.	PD	
1981	5	4	0/ 5	0/ 5	–	–	4/ 5	–	–	[6
1983	4	–	–	–	–	–	2/ 3	–	–	[117]
1983	9	9	0/ 7	–	–	–	5/ 9	2/9	4/ 9	[104]
1983	13	13	0/14	0/14	–	–	12/14	–	–	[71]
1986	1	1	–	–	–	–	0/ 1	–	–	[119]
1988	13	13	–	–	–	–	6/13	–	–	[5]
1988	20	12	0/20	0/20	2/20	7/20	16/20	–	6/ 8	[120]
Totals	65	52	0/46	0/39	2/20	7/20	45/65	2/9	10/17	
Ratio			0	0	0.1	0.35	0.69	0.22	0.59	
95% confidence limits			(0–0.08)	(0–0.09)	(0.01–0.32)	(0.15–0.59)	(0.57–0.8)	(0.03–0.6)	(0.33–0.82)	

pos., Positive; neg., negative; Remis., remission; PD, progressive disease

Table 4. Impact of CT scanning on the staging of malignant mesothelioma[a]

Stage[b]	Number of cases	
	Pre-CT	Post-CT
I	13	7
II	0	6
III	0	0
IV	1	1

[a] From Grant et al. [71]
[b] According to Butchart et al. [29]

netic resonance imaging may have solved this problem to a certain degree. To illustrate this problem, a review of 65 CT-evaluated patients with malignant pleural mesothelioma is summarized in Table 3. The pretherapeutic ratio of negative diagnoses from chest X-ray films vs positive diagnoses from CT scans was 0.69 (95% confidence limits, 0.57–0.8). CT also enabled a better assessment of disease parameters during treatment yielding a remission ratio of 0.22 (95% confidence limits, 0.03–0.6) and a progression ratio of 0.59 (95% confidence limits, 0.33–0.82). The significant impact of CT on staging is shown in Table 4 as based on a study by Grant et al. [71] that included 14 patients.

Cytostatic treatment of malignant mesothelioma

Most trials are hampered in that any single institution can accumulate only a few patients exhibiting malignant mesothelioma. Conclusions based on such insufficient data can hardly be said to be well founded; therefore, in the present review we found it necessary to summarize data across many schedules and trials. It is also recognized that case studies often emphasize responders, whereas nonresponders may not be reported, resulting in a tendency toward overestimation of pooled activity.

Single-agent cytostatic treatment

The results of single-agent chemotherapy are shown in Table 5. When the information was given in the actual reference, the following data were included: the dose, treatment schedule, number of evaluable cases, number of cases achieving a CR or PR, and median time to PD. Whenever possible, an R rate was calculated and the value was analyzed according to R = 0.2 and alpha = beta = 0.05. Only the anthracyclines detorubicin [43, 44] and doxorubicin [88, 89] have met the R criteria, and the reported R rates have not been confirmed in subsequent trials for either of these drugs. When the number of evaluable cases was pooled (n >13) for each single agent, an R rate of 0.13 (95% confidence limits, 0.1–0.15) was observed, with the vast majority being PRs. The response was generally of short duration (5–7 months). According to Table 6, only detorubicin showed activity [43, 44]. It must be borne in mind that the results obtained using detorubicin were based on the treatment of 21 patients, and new trials will therefore be needed to confirm this activity.

The data supported a conclusion in only 11% of the trials and/or schedules, with 2% showing activity and 9% displaying no activity (Table 7). In conclusion, the testing of single-agent chemotherapy was performed in a nonsystematic fashion. The available data neither confirm any substantial drug activity nor justify the use of any single agent as standard therapy.

Table 5. Single-agent chemotherapy in malignant mesothelioma

Agent	Year	Dose (mg/m^2 daily)[a]	Route	Schedule	Number of evaluable cases	Number of responses		Median time to PD (months)	Observed response rate	Comments	References
						CR	PR				
Acivicin	1987	20	i.v.	3 days q 3 weeks	21	0	0		0	NA	[60]
Aclacinomycin	1986	100	i.v.	q 3 weeks	9	–	–	–	–	IC, SM	[24]
ACNU	1978	3 mg/kg	i.v.	X 1	2	0	0		0	IC, SM	[122]
5-Azacytidine	1974	50–200	i.v.	q 4 days	3	0	0		0	IC, SM	[143]
5-Azacytidine	1982	100–150	i.v.	q 3–4 days	3	0	0		0	IC, SM	[36]
Baker's antifol	1977	250	i.v.	3 days q 3 weeks	3	0	0		0	IC, SM	[138]
BCG (immunotherapy)	1982	900,000 v.o.	i.d.	q 3–6 weeks	30	0	0		0	NA	[146]
BCNU	1966	150	i.v.	3 days q 8 weeks	1	0	0		0	IC, SM	[80]
Bleomycin	1983/1981	20	i.v.	q 1 weeks	3	0	1	–	0.33	IC, SM	[94, 96]
Bleomycin	1982	15	i.v.	5 days X 1	3	0	0		0	IC, SM	[36]
Bleomycinb	1985	20	i.v.	q 1 weeks	19	0	2	–	0.11	IC, SM	[7]
Bruceantin	1979	0.8–8	i.v.	q 1 weeks	1	0	0		0	IC, SM	[63]
Carboplatin	1986	400	i.v.	q 4 weeks	9	0	2	6	0.22	IC, SM	[31]
Carboplatin	1986	300–400	i.v.	q 4 weeks	17	1	1	13	0.12	IC, SM	[101]
Carboplatin	1987	800–1,600	i.v.	q 4 weeks	4	0	0		0	IC, SM	[66]
Carboplatin	1989	400	i.v.	q 4 weeks	37	0	2	–	0.05	NA	[142]
Chlorozotocin	1988	150	i.v.	q 6 weeks	10	0	0		0	IC, SM	[7]
Cisplatin	1977	4 mg/kg	i.v.	q 3 weeks	1	0	0		0	IC, SM	[73]
Cisplatin	1979	15	i.v.	5 days q 4 weeks	6	1	0	5	0.17	IC, SM	[124]

Agent	Year	Dose (mg/m^2 daily)[a]	Route	Schedule	Number of evaluable cases	Number of responses		Median time to PD (months)	Observed response rate	Comments	References
						CR	PR				
Cisplatin	1981	100	i.v.	q 3 weeks	9	1	0	15	0.11	IC, SM	[47]
Cisplatin+thiosulphate	1984	270	i.p.	q 3 weeks	1	0	1	4	1	IC, SM	[79]
Cisplatin+thiosulphate	1984/1985/1988	90	i.c.	q 1–3 weeks	34	5	4	7	0.26	IC, SM	[85, 111, 112]
Cisplatin	1984/1985	120	i.v.	q 4–6 weeks	24	0	3	4	0.13	IC, SM	[102,103]
Cisplatin	1986	90–100	i.c.	q 1 week	21	1	3	10	0.19	IC, SM	[99]
Cisplatin	1987	100	i.v.	q 3 weeks	35	0	5	6	0.14	IC, SM	[154]
Cycloleucin	1983/1981	300 mg/kg	i.v.	8 days q 4 weeks	7	0	2	–	0.29	IC, SM	[94, 96]
Cyclophosphamide	1963	4,000	i.v.	X 2	1	0	1	18	1	IC, SM	[52]
Cyclophosphamide	1966	100	p.o.	q 1 day	1	0	0		0	IC, SM	[118]
Cyclophosphamide	1978	500	i.v.	q 3 weeks	1	0	0		0	IC, SM	[151]
Cyclophosphamide vs	1985	1,500	i.v.	q 3 weeks	22	0	0		0	NA	[134]
Doxorubicin		60	i.v.	q 3 weeks	21	0	0		0	NA	
Cytosine arabinoside	1984	6,000	i.v.	q 2–4 days	1	0	1	3	1	IC, SM	[86]
Detorubicin	1985	40	i.v.	3 days q 3 weeks	21	2	7	8	0.43	A, ANC	[43, 44]
Diaminodichlorophenylmethyl pyrimidine+folic acid	1976	1.5–4 mg/kg	p.o.	q 1 week	2	0	0		0	IC, SM	[115]
Diazonorleucine	1986	50	i.v.	5 days q 4 weeks	6	0	0		0	IC, SM	[24]
Dibromodulcitol	1971	3.5 mg/kg	p.o.	q 1 day	1	0	0		0	IC, SM	[9]
Dibromodulcitol	1980	180	p.o.	10 days q 4 weeks	4	0	0		0	IC, SM	[23]
Dihydroazacytidine	1989	5,000	i.v.	q 4 weeks	12	0	0		0	IC, SM	[50]
Dimethyltriazeno-imidazolecarboxamide	1971	450	i.v.	2 days q 1 week	1	0	0		0	IC, SM	[67]
Diaziquone	1986	30	i.v.	q 4 weeks	20	0	0		0	NA	[55]
Doxorubicin	1975	45–75	i.v.	q 3 weeks	5	1	1	8	0.4	IC, SM	[22]
Doxorubicin	1975	50	i.v.	q 3 weeks	6	2	2	7	0.67	A, ANC	[88, 89]
Doxorubicin	1975	60	i.v.	q 3 weeks	1	0	1	9	1	IC, SM	[21]
Doxorubicin	1975	75	i.v.	q 3 weeks	5	1	1	–	0.4	IC, SM	[70
Doxorubicin	1976	60	i.v.	q 3 weeks	9	0	3	5	0.33	IC, SM	[140]
Doxorubicin	1979	50	i.v.	q 4 weeks	1	0	0		0	IC, SM	[82]
Doxorubicin	1979	35–70	i.v.	q 1 week	1	0	0		0	IC, SM	[105]
Doxorubicin	1982	15–30	i.v.	3 days q 3 weeks	14	1	2	18	0.21	IC, SM	[36]
Doxorubicin	1983/1981	70	i.v.	q 3 weeks	51	2	5	11	0.14	IC, SM	[94, 96]
Doxorubicin	1983	60	i.v.	q 3 weeks	1	0	1	9	1	IC, SM	[13]
Doxorubicin/vs	1983	70	i.v.	q 3 weeks	16	–	–	–	0.14	IC, SM	
Doxorubicin/vs		20	i.v.	3 days q 3 weeks	16	–6	–	–7	0.14	NSD IC, SM	[95]
Doxorubicin		15	i.v.	q 1 week	16	–	–	–	0.14	IC, SM	
Doxorubicin	1984	–	i.v.	–	11	0	1	–	0.09	IC, SM	[141]
Doxorubicin	1984	60	i.v.	q 4 weeks	11	0	1	26	0.09	IC, SM	[72]
Doxorubicin	1988	70	i.v.	q 3 weeks	12	0	4	7	0.33	IC, SM	[4]
4-Epidoxorubicin	1988	110–130	i.v.	q 4 weeks	54	2	6	24	0.15	IC, SM	[100]
4-Epidoxorubicin	1988	75	i.v.	q 3 weeks	12	0	1	–	0.08	IC, SM	[97]
5-Fluorouracil	1974	1–2 g	i.v./p.o.	q 1 week	2	1	0	16	0.5	IC, SM	[64]
5-Fluorouracil	1974	10 mg/kg	i.v.	q 1 week	3	2	0	18	0.67	IC, SM	[65]
5-Fluorouracil	1984	10–15 mg/kg	i.v.	5 days q 4 weeks	20	0	1	24	0.05	IC, SM	[72]
Glucosamine	1974	1,200	i.v.	2 days q 4 weeks	1	0	0		0	IC, SM	[64]
ICRF-159	1980	300	p.o.	3 days q 4 weeks	2	0	0		0	IC, SM	[23]
Ifosfamide+mesna	1986	5,000	i.v.	q 3 weeks	3	0	1	11	0.33	IC, SM	[148]
Ifosfamide+mesna	1988	1.2–1.5 g	i.v.	5 days q 3 weeks	17	0	4	7	0.24	IC, SM	[5]
JM9 (CHIP)	1986	300	i.v.	q 4 weeks	7	0	0		0	IC, SM	[31]
M-Amsacrine	1988/1983	120	i.v.	q 3 weeks	19	0	1	4	0.05	IC, SM	[4, 59]
Maytansine	1980	1.5	i.v.	q 3 weeks	4	0	0		0	IC, SM	[23]
Maytansine	1982	0.6	i.v.	q 1 week	1	0	0		0	IC, SM	[36]
Melphalan	1978	–	–	–	1	0	0		0	IC, SM	[151]
Methyl-CCNU	1976	130–170	i.v.	q 6 weeks	1	0	0		0	IC, SM	[41]
Methyl-gloxal-bis-quanyl-hydrazone	1974	4 mg/kg	i.m.	q 3 days	1	0	1	2	1	IC, SM	[64]
Mitomycin C	1985/1987	10	i.v.	q 4–6 weeks	19	0	4	5	0.21	IC, SM	[19, 84]

Agent	Year	Dose (mg/m² daily)[a]	Route	Schedule	Number of evaluable cases	Number of responses		Median time to PD (months)	Observed response rate	Comments	References
						CR	PR				
Mitoxantrone	1986	12	i.v.	q 3–4 weeks	28	1	1	5	0.07	IC, SM	[56]
Methotrexate+rescue	1985	18–50 g	i.v.	–	9	0	4	–	0.44	IC, SM	[53]
Methotrexate+rescue	1980	–	i.v.	–	2	0	0		0	IC, SM	[12]
Nitrogen mustard +ATCH	1959	0.1 mg/kg	i.v.	5 days q 1 week	2	0	0		0	IC, SM	[149]
Nitrogen mustard	1979	4	i.c.	X 1	1	0	0		0	IC, SM	[82]
N-Propargyl-dideazafolic acid	1986	300–400	i.v.	q 3 weeks	18	0	1	7	0.06	IC, SM	[30]
Thiotepa	1974	10	i.v.	5 days q 4 weeks	1	0	0		0	IC, SM	[64]
Thiotepa	1974	20	i.c.	q 2 weeks	1	0	0		0	IC, SM	[64]
Vincristine	1989	1.3	i.v.	q 2–4 weeks	23	0	0		0	NA	[106]
Vindesine	1983	3	i.v.	q 1 week	17	0	1	5	0.06	IC, SM	[82]
Vindesine	1987	2	i.v.	2 days q 2 weeks	21	0	0		0	NA	[20]
VP-16	1972	54	i.v.	q 1 day	1	0	0		0	IC, SM	[107]
VP-16	1974	200	p.o.	5 days q 3 weeks	4	0	0		0	IC, SM	[58]
VP-16 (solution)	1976	120	p.o.	5 days q 2 weeks	2	0	0		0	IC, SM	[108]
Totals					961	27	92				
Ratio						0.03	0.1		0.12		
95% confidence limits						(0.02–0.04)	(0.08–0.12)		(0.10–0.15)		

[a] Unless indicated otherwise

CR, Complete response; PR, partial response; PD, progressive disease; A, activity; ANC, activity not confirmed; NA, no activity; IC, inconclusive data [limit of response = 20%, type I error (alpha) = 0.05, type II error (beta) = 0.05]; SM, small study; NSD, no significant difference; v.o., viable organism; –, no information; i.c., intracavitary; i.d., intradermal; i.m., intramuscular; i.p., intraperitoneal; i.v., intravenous; p.o., oral; ACNU, nimustine; BCG, bacille Calmette-Gubrin; BCNU, carmustine; CCNU, lomustine; CHIP, JM9, iproplatin; VP-16, etoposide; ATCH, adrenocorticotropic hormone

Table 6. Single-agent chemotherapy in malignant mesothelioma – pooled data (n >13)

Agent	Number of trials	Number of evaluable cases	Number of responses		Median time to PD (months)	Observed response rate (95% confidence limits)	Comments
			CR	PR			
Acivicin	1	21	0	0	–	0	NA
Bleomycin	3	25	0	3	–	0.12 (0.03–0.31)	IC, SM
BCG	1	30	0	0		0	NA
Carboplatin	4	67	1	5	10	0.09 (0.03–0.18)	NA
Cisplatin	8	131	8	16	7	0.18 (0.12–0.26)	IC, SM
Cyclophosphamide	4	25	0	1	18	0.04 (0–0.2)	NA
Detorubicin	1	21	2	7	13	0.43 (0.22–0.66)	A, ANC
Diaziquone	1	20	0	0		0	NA
Doxorubicin	15	197	7	28	9	0.18 (0.13–0.24)	IC, SM
4-Epidoxorubicin	2	66	2	7	24	0.14 (0.06–0.24)	IC, SM
5-Fluorouracil	3	25	3	1	18	0.16 (0.05–0.36)	IC, SM
Ifosfamide	2	20	0	5	9	0.25 (0.09–0.49)	IC, SM
M-Amsacrine	1	19	0	1	4	0.05 (0–0.26)	IC, SM
Mitomycin C	1	19	0	4	5	0.21 (0.06–0.46)	IC, SM
Mitoxantrone	1	28	1	1	5	0.07 (0.01–0.24)	IC, SM
N-Propargyl-dideazafolic acid	1	18	0	1	7	0.06 (0–0.27)	IC, SM
Vincristine	1	23	0	0		0	NA
Vindesine	2	38	0	1	5	0.03 (0–0.14)	NA
Totals	52	793	24	83			
Ratio			0.03	0.1		0.13	
95% confidence limits			(0.02–0.04)	(0.08–0.12)		(0.1–0.15)	

CR, Complete response; PR, partial response; PD, progressive disease; A, activity; ANC, activity not confirmed; NA, no activity; IC, inconclusive data [limit of response = 20%, type I error (alpha) = 0.05, type II error (beta) = 0.05]; SM, small study; –, no information; BCG, bacille Calmette-Guérin

Table 7. Clinical trials/pooled data (n >13) of chemotherapy in malignant mesothelioma

	Number of trials/agents	Number of trials			
		Na = 20% (%)	IC = 20% (%)	A = 20% (%)	Conclusive data (%)
Single-agent trials	87	8 (9)	77 (89)	2 (2)	10 (11)
Single-agent trials – pooled	18	7 (39)	10 (55)	1 (6)	8 (44)
Combination trials	67	1 (1)	61 (91)	5 (8)	6 (9)
Combination trials – pooled	10	1 (10)	9 (90)	0	1 (10)

NA, No activity; IC, inconclusive data; A, activity [limit of response = 20%, type I error (alpha) = 0.05, type II error (beta) = 0.05]

Combination chemotherapy

Malignant mesotheliomas have often been grouped with soft-tissue sarcomas in broad trials exploring the efficacy of combination chemotherapy, and only very few studies have focused directly on mesothelioma as a specific disease entity in a phase II design. Many studies report complex treatment plans that include combination chemotherapy, surgery, and irradiation. No trial using a multimodality approach was included in this review of 526 patients, which is summarized in Table 8. Otherwise, we applied the same evaluation procedure described above.

Of all the combinations evaluated, only three met the R criteria: cisplatin + mitomycin C [53], cisplatin + doxorubicin [74, 75, 153], and high-dose methotrexate + leucovorin rescue + vincristine [51]. For the first and third combinations, the activity has not been confirmed in other studies, and for the second, the activity could not be confirmed by pooling the results (Table 9). When the number of evaluable cases was pooled (n >13) for each combination, an R rate of 0.22 (95% confidence limits, 0.18–0.25) was observed, with the fast majority being PRs. The response was generally of short duration (6–8 months). The data supported a conclusion in only 9% of the trials and/or schedules, with 8% displaying activity and 1% showing no activity (Table 7). The results of combination chemotherapy are thus comparable with those of single-agent chemotherapy, and no major difference was detected among the various combinations.

Table 8. Combination chemotherapy in malignant mesothelioma (cont. 1)

Agents	Year	Number of evaluable cases	Number of responses		Median time to PDrate (months)	Observed response	Comments	References
			CR	PR				
ACNU + BCG (i.c., immunotherapy) + FT 207 + vincristine	1978	1	0	0		0	IC, SM	[135]
Actinomycin D + cyclophosphamide + dacarbazine + vincristine	1977	14	0	1	–	0.07	IC, SM	[93]
Actinomycin D + cyclophosphamide + doxorubicin + vincristine	1978	3	0	0		0	IC, SM	[151]
Actinomycin D + cyclophosphamide + vincristine	1976	1	0	0		0	IC, SM	[46]
Actinomycin D + dacarbazine + doxorubicin	1978	4	0	0		0	IC, SM	[151]
Actinomycin D + doxorubicin	1981	3	0	0		0	IC, SM	[26]
5-Azacytidine + doxorubicin	1978	1	0	1	24	1	IC, SM	[35]
5-Azacytidine + doxorubicin	1978	8	2	0	18	0.25	IC, SM	[34]
5-Azacytidine + doxorubicin	1982	36	3	5	–	0.22	IC, SM	[36]
BCNU + 5-fluorouracil + methotrexate + vincristine	1973	1	0	0		0	IC, SM	[110]
Bleomycin + cisplatin + vinblastine	1976	2	0	0		0	IC, SM	[123]
Bleomycin + 5-fluorouracil + methyl-CCNU	1980	1	0	0		0	IC, SM	[12]
Carboplatin + VP-16	1987	3	–	–	–	–	IC, SM	[87]
Cisplatin + cyclophosphamide + methotrexate	1982	9	0	1	3	0.11	IC, SM	[36]
Cisplatin (i.c.) + cytosine arabinoside (i.c.) + doxorubicin (i.c.)	1984	1	0	0		0	IC, SM	[98]
Cisplatin + doxorubicin	1983	6	1	3	9	0.67	A	[153]
Cisplatin + doxorubicin	1985	1	0	0		0	IC, SM	[15]
Cisplatin + doxorubicin	1986	15	2	5	5	0.47	A	[74]
Cisplatin + doxorubicin	1988	19	2	6	7	0.42	A	[75]
Cisplatin + doxorubicin	1988	16	0	4	–	0.25	IC, SM	[17]
Cisplatin (i.c.) + doxorubicin	1988	1	0	1	17	1	IC, SM	[113]
Cisplatin + doxorubicin + mitomycin C	1985	1	0	1	–	1	IC, SM	[15]
Cisplatin + 5-fluorouracil	1982	4	0	0		0	IC, SM	[36]
Cisplatin + methotrexate + rescue	1985	6	0	4	–	0.67	A, NC	[53]
Cisplatin + mitomycin C	1984/1983	12	1	2	9	0.25	IC, SM	[37,38]

Agents	Year	Number of evaluable cases	Number of responses		Median time to PDrate (months)	Observed response	Comments	Refe-rences
			CR	PR				
Cisplatin + doxorubicin/vs	1987	23	1	1	–	0.09	IC, SM	[40]
Cisplatin + mitomycin C		25	2	1	–	0.12	IC, SM	
Cyclophosphamide + dacarbazine + doxorubicin	1980	14	0	5	10	0.36	IC, SM	[12]
Cyclophosphamide + dacarbazine + doxorubicin	1983	2	1	0	22	0.5	IC, SM	[13]
Cyclophosphamide + dacarbazine + doxorubicin	1983	20	0	5	16	0.25	IC, SM	[49]
Cyclophosphamide + dacarbazine + doxorubicin	1986	1	0	1	–	1	IC, SM	[119]
Cyclophosphamide + dacarbazine + doxorubicin vs	1987/1985	40			–	0.13/	IC, SM	[125
Cyclophosphamide + doxorubicin		36	3	6	–	0.11 NSD	IC, SM	
Cyclophosphamide + dacarbazine + doxorubicin + vincristine	1977	10	0	0		0	IC, SM	[136]
Cyclophosphamide + dacarbazine + doxorubicin + vincristine	1978	5	0	1	8	0.2	IC, SM	[151]
Cyclophosphamide + dacarbazine + doxorubicin + vincristine	1979	4	0	2	–	0.5	IC, SM	[69]
Cyclophosphamide + dacarbazine + doxorubicin + vincristine	1987	5	0	1	3	0.2	IC, SM	[127]
Cyclophosphamide + doxorubicin	1980	3	0	1	–	0.33	IC, SM	[12]
Cyclophosphamide + doxorubicin	1983	9	0	2	22	0.22	IC, SM	[13]
Cyclophosphamide + doxorubicin	1983	23	–	–	–	–	IC	[114]
Cyclophosphamide + doxorubicin	1984	2	0	1	–	0.5	IC, M	[14]
Cyclophosphamide + doxorubicin	1985	4	0	1	–	0.25	IC, M	[15]
Cyclophosphamide + doxorubicin + methotrexate	1983	1	0	0		0	IC, SM	[13]
Cyclophosphamide + doxorubicin + methotrexate + + vincristine + VP-16	1982	4	0	0		0	IC, SM	[81]
Cyclophosphamide + doxorubicin + NSC 45 388 + vincristine	1975	6	0	2	–	0.33	IC, SM	[22]
Cyclophosphamide + doxorubicin + vincristine	1984	12	0	0		0	IC, SM	[91]
Cyclophosphamide + doxorubicin + vincristine	1980	8	0	2	4	0.25	IC, SM	[62]
Cyclophosphamide + doxorubicin + vincristine	1981	1	1	0	66	1	IC, SM	[28]
Cyclophosphamide + 5-fluorouracil + methotrexate + vincristine	1975	5	2	1	8	0.6	IC, SM	[88]
Cyclophosphamide + 5-fluorouracil + methotrexate + vincristine	1978	1	0	1	3	1	IC, SM	[151]
Cyclophosphamide + 5-fluorouracil + vincristine	1968	1	0	0		0	IC, SM	[139]
Cyclophosphamide + vinblastine + vincristine	1980	1	0	0		0	IC, SM	[12]
Cytarabin + 6-thioguanine + thiotepa (i.c.)	1978	1	0	0		0	IC, SM	[151]
Dacarbazine + doxorubicin	1972	7	0	3	4	0.43	IC, SM	[68]
Dacarbazine + doxorubicin	1978	6	0	1	8	0.17	IC, SM	[151]
Dacarbazine + doxorubicin	1979	1	0	1	–	1	IC, SM	[105]
Dacarbazine + doxorubicin	1983	16	–	1	7	0.06	IC, SM	[95]
Dacarbazine + doxorubicin	1986	1	0	0		0	IC, SM	[129]
Dacarbazine + doxorubicin + vincristine	1978	3	0	0		0	IC, SM	[151]
Dacarbazine + rubidazone	1983	23	0	0		0	NA	[152]
Doxorubicin + BCG (i.c., immunotherapy)	1978	1	0	1	18	1	IC, SM	[135]
Doxorubicin + ICRF-159	1979	–	0	1	–	–	IC	[42]
Doxorubicin + methotrexate + rescue + vincristine	1980	5	0	3	–	0.6	IC, SM	[12]
Doxorubicin + methotrexate + vincristine	1983	1	0	1	12	1	IC, SM	[13]
Doxorubicin + NSC 45 388	1975	9	0	4	9	0.44	IC, SM	[22]
Doxorubicin + NSC 45 388 + vincristine	1975	6	0	0		0	IC, SM	[22]
5-fluorouracil + methyl-CCNU	1982	1	0	0		0	IC, SM	[36]
Methotrexate + nitrogen mustard	1981	1	0	1	3	1	IC, SM	[28]
Methotrexate-HD + rescue + vincristine	1982	9	3	3	10	0.67	A, ANC	51]
Totals		526	24	90	9			
Ratio			0.05	0.17		0.22		
95% confidence limits			(0.03–0.07)	(0.14–0.21)		(0.18–0.25)		

CR, Complete response; PR, partial response; PD, progressive disease; NA, no activity; IC, inconclusive data; A, activity; ANC, activity not confirmed; IC, inconclusive data [limit of response = 20%, type I error (alpha) = 0.05, type II error (beta) = 0.05]; SM, small study; NSD, no significant difference; –, no information; ACNU, nimustine; BCG, bacille Calmette-Guérin; CCNU, lomustine; HD, high-dose, i.c., intracavitary

Table 9. Combination chemotherapy in malignant mesothelioma – pooled data (n >13)

Agents	Number of trials	Number of evaluable cases	Number of responses		Median time to PD (months)	Observed response rate (95% confidence limits)	Comments
			CR	PR			
Actinomycin D + cyclophosphamide + dacarbazine + vincristine	1	14	0	1	–	0.07 (0–0.23)	IC, SM
5-Azacytidine + doxorubicin	3	45	5	6	–	0.24 (0.13–0.4)	IC, SM
Cisplatin + doxorubicin	7	81	6	20	7	0.32 (0.22–0.43)	IC, SM
Cisplatin + mitomycin C	2	37	3	3	–	0.16 (0.06–0.32)	IC, SM
Cyclophosphamide + dacarbazine + doxorubicin	5	77	3	14	–	0.22 (0.13–0.33)	IC, SM
Cyclophosphamide + dacarbazine + doxorubicin + vincristine	4	24	0	4	–	0.17 (0.05–0.37)	IC, SM
Cyclophosphamide + doxorubicin	5	54	1	8	–	0.17 (0.08–0.29)	IC, SM
Cyclophosphamide + doxorubicin + vincristine	3	21	1	2	4	0.14 (0.03–0.36)	IC, SM
Dacarbazine + doxorubicin	5	31	0	6	7	0.42 (0.25–0.61)	IC, SM
Dacarbazine + rubidazone	1	23	0	0		0 (0–0.15)	NA
Totals	36	407	19	64	–		
Ratio			0.05	0.15		0.2	
95% confidence limits			(0.03–0.07)	(0.12–0.2)		(0.17–0.25)	

CR, Complete response; PR, partial response; PD, progressive disease; NA, no activity; IC, inconclusive data [limit of response = 20%, type I error (alpha) = 0.05, type II error (beta) = 0.05]; SM, small study; –, no information

Table 10. Systems for screening of cytotoxic effects in malignant mesothelioma

Donor	Screening systems	Agents	Observed activity	Year	References
H, MC	In vitro (cell lines)	Carminomycin	A	1981	[116]
		Dibromodulcitol	MA		
		Carminomycin + dibromodulcitol	A		
H, MC	Microculture tetrazolium (cell lines)	Actinomycin D	A	1989	[25]
		Cisplatin	VA		
		Doxorubicin	VA		
		5-Fluorouracil	VA		
		Methotrexate	VA		
		Mitomycin C	VA		
		Vinblastine	VA		
MC	Hamster (peritoneal transplantation)	Actinomycin D	NA	1981	[78]
		Azacitidine	MA		
		Aziridinyl-benzoguinone	MA		
		Cisplatin	MA		
		Dianhydroxyanthracenedione	NA		
		DTIC	NA		
		PCNU	MA		
MC	Hamster (peritoneal transplantation)	Cyclophosphamide	A	1981	[133]
		Doxorubicin	MA		
		5-Fluorouracil	MA		
H, MC	Nude mice (xenografts)	Carminomycin	NA	1980	[18]
		Cyclophosphamide	NA		
		Daunomycin	A		
H, MC	Nude mice (xenografts)	Cisplatin	VA	1984	[38]
		Mitomycin C	VA		
		Cisplatin + mitomycin C	A		
H, MC	Nude mice (xenografts)	Carboplatin	VA	1985	[39]
		Cisplatin	VA		
		Iproplatin	VA		
H, MC	Nude mice	Actinomycin D + cisplatin + interferon	A	1988	[132]

H, Human; MC, mesothelioma cells; A, activity; VA, variable activity; MA, moderate activity; NA, no activity, DTIC, dacarbazin; PCNU, piperidylchloroethyl-nitroso-urea

Randomized trials

Few centers have had the opportunity of allocating large numbers of patients into prospective randomized trials (Tables 5, 8) [40, 95, 125, 126, 134]. The R rates never reached >20%; on the basis of these results, randomized trials should not be instituted.

Conclusions

Little systematic testing of single-agent or combination chemotherapy has taken place. Even the majority of pooled results do not fit the basic criteria for phase II studies, and most of the trials are inconclusive. This review also indicates that the results of combination chemotherapy (pooled R rate, 0.2; 95% confidence limits, 0.17–0.25) are comparable with those obtained using single-agent chemotherapy (pooled R rate, 0.13; 95% confidence limits, 0.1–0.15), but there seems to be a marginal trend in favour of the former.

We accepted an R level of 20%, as have many other, less extensive reviews [4, 11, 94, 96, 141]. At this level, drug activity in malignant mesothelioma was not identified for any of the drugs investigated. This finding contrasts with the majority of conclusions drawn in other comprehensive reviews [2, 3, 12, 28, 33, 38, 61, 161] or trials [35, 51, 75, 81, 88, 89]. The available results do not confirm substantial drug activity or justify the use of a standard therapy. Phase II clinical trials are therefore needed to identify new single-agent cytostatics. Obviously, these trials must provide relevant details on prognostic factors such as the duration of symptoms, performance status, staging, and, probably, also histopathological subtyping. Furthermore, repeated CT scans are mandatory in evaluations of response. For the rapid achievement of new treatment results, cooperative studies must be conducted on a national or an international scale.

In the selection of new drugs for phase II trials, the question arises as to whether any of the existing preclinical screening systems are useful for the prediction of potential efficacy using either cell lines or xenografts. To illustrate this problem, a review of experimental screening systems is summarized in Table 10. Clinical data based on these quite new experimental results have thus far not been published. Chahinian et al. [38] found that cisplatin was the most active single agent in one human mesothelioma line of xenografted nude mice, as was mitomycin C in another. However, the combination of mitomycin C and cisplatin was the most effective regimen for both lines (Table 10). These experimental data have not yet been confirmed in clinical trials, in which the results thus far reported have been inconclusive [37, 38, 40]. The application of other tumor-biological models may spur the development and selection/identification of new cytostatic drugs.

References

1. Adams VI, Krishnan UK, Muhm JR, Jett JR, Ilstrup DM, Bernats PE (1986) Diffuse malignant mesothelioma of pleura. Cancer 58: 1540–1551
2. Aisner J, Sigman LM (1986) The role of chemotherapy in the treatment of malignant mesothelioma. In: Antman K, Eisner J (eds) Asbestos-related malignancy. Grune & Stratton, Orlando, Florida, pp 385–401
3. Aisner J, Wiernik PH (1978) Malignant mesothelioma. Current status and future prospects. Chest 74: 438–444
4. Alberts AS, Falkson G, Gaedhals L, Vorobiof DA, Van Der Merwe CA (1988) Malignant pleural mesothelioma: a disease unaffected by current therapeutic maneuvers. J Clin Oncol 6: 527–535
5. Alberts AS, Falkson G, Zyl L van (1988) Malignant pleural mesothelioma: phase II pilot study of ifosfamide and mesna. J Natl Cancer Inst 80: 698–700
6. Alexander E, Clark RA, Colley DP, Mitchell SA (1981) CT of malignant pleural mesothelioma. AJR 137: 287–291
7. Amato DA, Borden EC, Shiraki M, Enterline HT, Rosenbaum C, Davis HL, Paul AR, Stevens CM, Lerner HJ (1985) Evaluation of bleomycin, chlorozotocin, MGBG, and bruceantin in patients with advanced soft tissue sarcoma, bone sarcoma, or mesothelioma. Invest New Drugs 3: 397–401
8. Andersson M, Olsen JH (1985) Trend and distribution of mesothelioma in Denmark. Br J Cancer 51: 699–705
9. Andrews NC, Weiss AJ, Ansfield FJ, Rochlin DB, Mason JH (1971) Phase I study of dibromodulcitol. Cancer Chemother Rep 55: 61–65
10. Antman KH (1981) Clinical presentation and natural history of benign and malignant mesothelioma. Semin Oncol 8: 313–320
11. Antman KH, Corson JM (1985) Benign and malignant pleural mesothelioma. Clin Chest Med 6: 127–140
12. Antman KH, Blum RH, Greenberger JS, Flowerdew G, Skarin AT, Canellos GP (1980) Multimodality therapy for malignant mesothelioma based on a study of natural history. Am J Med 68: 356–362
13. Antman KH, Pomfret EA, Aisner J, MacIntyre J, Osteen RT, Greenberger JS (1983) Peritoneal mesothelioma: natural history and response to chemotherapy. J Clin Oncol 1: 386–391
14. Antman KH, Cohen S, Dimitrov NV, Green M, Muggia F (1984) Malignant mesothelioma of the tunica vaginalis testis. J Clin Oncol 2: 447–451
15. Antman KH, Klegar KL, Pomfret EA, Osteen RT, Amato DA, Larson DA (1985) Early peritoneal mesothelioma: a treatable malignancy. Lancet II: 977–981
16. Antman KH, Shemin R, Ryan L, Klegar KL, Osteen RT, Herman T, Lederman G, Corson JM (1988) Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over 2 decades, 1965–1985. J Clin Oncol 6: 147–153
17. Ardizzoni A, Rosso R, Palma M, Soresi E, Borghini U, Chario Sileni V, Castagneto B, Scagliotti G, Brunetti I, Fusco V, Santi L (1988) Cisplatin and Adriamycin in the treatment of malignant pleural mesothelioma. A phase II trial. Lung Cancer 4 [Suppl]: A136
18. Arnold W, Tanneberger S, Nowak C, Naundorff H (1980) Recent results with clinically used antineoplastic drugs and drug combinations in vivo. Oncology 37 S: 34–41
19. Bajorin D, Kelsen D, Mintzer DM (1987) Phase II trial of mitomycin in malignant mesothelioma. Cancer Treat Rep 71: 857–858
20. Bautin C, Irisson M, Guerin JC, Roegel E, Paramelle B, Brambilla C, Jeannin L, Dabouis G, Le Caer H, Viallat JR (1987) Phase II trial of vindesine in malignant pleural mesothelioma. Cancer Treat Rep 71: 205–206
21. Benjamin RS, Wiernik PH, Bachur NR (1975) Adriamycin: a new effective agent in the therapy of disseminated sarcomas. Med Pediatr Oncol 1: 63–76
22. Bonadonna G, Beretta G, Tancini G, Brambilla C, Bajetta E, De Palo GM, De Lena M, Fossati Bellani F, Gasparini M, Valagussa P, Veronesi U (1975) Adriamycin studies at the Instituto Nazionale Tumori, Milan. Cancer Chemother Rep 6: 231–245
23. Borden E, Ash A, Rosenbaum C, Lerner H (1980) Phase II evaluation of dibromodulcitol and maytansine in sarcomas and mesotheliomas. Proc Am Soc Clin Oncol 21: 479
24. Borden E, Amato D, Earhart R, Chang A (1986) Phase II evaluation of diazonorleucine and aclaicinomycin A for soft tissue or bone sarcomas and mesothelioma. Proc Am Soc Clin Oncol 5: 131
25. Bowman RV, Manning LS, Davis M, Musk AW, Robinson BWS (1989) Susceptibility of cultured human malignant mesothelioma cells to cytotoxic drugs, cytokines, and immune effector cells: in vitro assessment. Proc Am Assoc Cancer Res 30: 611
26. Brenner DE, Chang P, Wirnik PH (1981) Adriamycin and actinomycin-D therapy for advanced sarcomas. Cancer Treat Rep 65: 231–236
27. Brenner J, Sordillo PP, Magill GB (1981) Malignant peritoneal mesothelioma: review of 25 patients. Am J Gastroenterol 75: 311–313
28. Brenner J, Sordillo PP, Magill GB (1982) Malignant mesothelioma in children: report of seven cases and review of the literature. Med Pediatr Oncol 9: 367–373
29. Butchart EG, Ashcroft T, Barnsley WA, Holden MP (1976) Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Thorax 31: 15–24
30. Cantwell BMJ, Earnshaw M, Harris AL (1986) Phase II study of a novel antifolate, *N*-10-propargyl-5,8-dideazafolic, in malignant mesothelioma. Cancer Treat Rep 70: 1335–1336
31. Cantwell BMJ, Franks CR, Harris AL (1986) A phase II study of the platinum analogues JM8 and JM9 in malignant pleural mesothelioma. Cancer Chemother Pharmacol 18: 286–288
32. Chahinian AP (1982) Malignant mesothelioma. In: Greenspan E (ed) Clinical interpretation and practice of cancer chemotherapy. Raven, New York, pp 599–606
33. Chahinian AP, Holland JF (1978) Treatment of diffuse malignant mesothelioma: a review. Mt Sinai J Med (NY) 45: 54–67
34. Chahinian AP, Holland JF, Mandel EM (1978) Chemotherapy for malignant mesothelioma with Adriamycin and continuous infusion of 5-azacytidine. Cancer Treat Rep 62: 1108–1109
35. Chahinian AP, Suzuki Y, Mandel EM, Holland JF (1978) Diffuse pulmonary malignant mesothelioma response to doxorubicin and 5-azacytidine. Cancer 42: 1687–1691
36. Chahinian AP, Pajak TF, Holland JF, Norton L, Ambinder RM, Mandel EM (1982) Diffuse malignant mesothelioma: prospective evaluation of 69 patients. Ann Intern Med 96: 746–755
37. Chahinian AP, Norton L, Szrajer L, Holland JF (1983) Mitomycin C and cisplatin in human malignant mesothelioma xenografts in nude mice: clinical correlation. Proc Am Assoc Cancer Res 24: 151

38. Chahinian AP, Norton L, Holland JF, Szrajer L, Hart RD (1984) Experimental and clinical activity of mitomycin C and *cis*-diamminedichloroplatinum in malignant mesothelioma. Cancer Res 44: 1688–1692
39. Chahinian AP, Szrajer L, Malamud S, Schwartz PH, Holland JF (1985) Comparative activity of three platinum analogs against human malignant mesothelioma xenografts in nude mice. Proc Am Assoc Cancer Res 26: 261
40. Chahinian AP, Antman KH, Aisner J, Propert K, Modeas C, Elison RR, Stoll DB, Green M (1987) Cisplatin with Adriamycin or mytomycin for malignant mesothelioma: a randomized phase II trial. Proc Am Soc Clin Oncol 6: 183
41. Chang P, Levine MA, Wirnik PH, Walker MD (1976) A phase II trial of intravenously administered methyl CCNU in the treatment of advanced sarcomas. Cancer 37: 615–619
42. Chlebowski R, Pugh R, McCraken J, Glass A, Bateman JR (1979) A phase I–II trial of combination therapy with Adriamycin and ICRF. Proc Am Assoc Cancer Res 20: 199
43. Colbert N, Izrael V, Vannetzel JM, Schlienger M, Laugier A (1985) A prospective study of detorubicin in malignant mesothelioma. Proc Am Soc Clin Oncol 4: 127
44. Colbert N, Vannetzel JM, Izrael V, Schlienger M, Milleron B, Blanchon F, Herman D, Akoun G, Roland J, Chatelet F, Laugier A (1985) A prospective study of detorubicin in malignant mesothelioma. Cancer 56: 2170–2174
45. Corson JM, Pinkus GS (1982) Mesothelioma: profile of keratin proteins and carcinoembryonic antigen. An immunoperoxidase study of 20 cases and comparison with pulmonary adenocarcinomas. Am J Pathol 108: 80–88
46. Creagan ET, Hahn RG, Ahmann DL, Edmonson JH, Bisel HF, Eagan RT (1976) A comparative clinical trial evaluating the combination of Adriamycin, DTIC and vincristine, the combination of actinomycin D, cyclophosphamide and vincristine and a single agent, methyl-CCNU, in advanced sarcomas. Cancer Treat Rep 60: 1385–1387
47. Dabouis G, LeMevel B, Conoller J (1981) Treatment of diffuse pleural malignant mesothelioma by *cis*-dichlorodiammineplatinum in nine patients. Cancer Chemother Pharmacol 5: 209–210
48. Davis J (1974) Ultrastructure of human mesotheliomas. J Natl Cancer Inst 52: 1715–1719
49. Dhingra H, Valdivieso M, Tannir N, Booser DJ, Frazier OH, Benjamin RS (1983) Combined modality treatment for mesothelioma with cytoxan and Adriamycin, and DTIC and adjuvant surgery. Proc Am Soc Clin Oncol 2: 205
50. Dhingra H, Umsawasdi T, Holoye P, Murphy W, Greenburg A, Roach R, Chun H, Raber M, Hong W (1989) Phase II trial of 5,6-dihydroazacytidine in pleural malignant mesothelioma. Proc Am Assoc Cancer Res 30: 274
51. Dimitrov NV, Egner J, Balcueva E, Suhrland LG (1982) High-dose methotrexate with citrovorum factor and vincristine in the treatment of malignant mesothelioma. Cancer 50: 1245–1247
52. DiPietro, Gennari L (1963) Successful cyclophosphamide treatment in a case of diffuse pleural mesothelioma. Tumori 49: 69–73
53. Djerassi I, Kim JS, Kasserov L, Reggev A (1985) Response of mesothelioma to large doses of methotrexate with CF rescue used alone or with cisplatinum. Proc Am Soc Clin Oncol 4: 191
54. Egan RT, Flemming TR, Schonover V (1979) Evaluation of response criteria in advanced lung cancer. Cancer 44: 1125–1128
55. Eagan RT, Frytak S, Richardson RL, Creagan ET, Nichols WC (1986) Phase II trial of diaziquone in malignant mesothelioma. Cancer Treat Rep 70: 429
56. Eisenhauer EA, Evans WK, Raghaven D, Desmeules MJ, Murray NR, Stuart-Harris R, Wilson KS (1986) Phase II study of mitoxantrone in patients with mesothelioma. A National Cancer Institute of Canada Clinical Trials Group study. Cancer Treat Rep 70: 1029–1030
57. Enzinger FM, Weiss SW (1988) Classification of soft tissue tumors. In: Enzinger FM, Weiss SW (eds) Soft tissue tumors. C. V. Mosby, Washington, D. C.
58. Falkson G, Falkson HC (1974) Clinical trial of the oral form of 4′-dimethylepipodophyllotoxin-*p*-D-ethylidene glucoside. Proc Am Assoc Cancer Res 15: 160
59. Falkson G, Vorobiof DA, Lerner JH (1983) A phase II study of m-AMSA in patients with malignant mesothelioma. Cancer Chemother Pharmacol 11: 94–97
60. Falkson G, Vorobiof DA, Simon IW, Borden E (1987) Phase II trial of acivicin in malignant mesothelioma. Cancer Treat Rep 71: 545–546
61. Falkson G, Alberts AS, Falkson HC (1988) Malignant pleural mesothelioma treatment: the current state of the art. Cancer Treat Rev 15: 231–242
62. Fer MF, Beatty PG, Richardson RL, Greco FA (1980) Combination chemotherapy of malignant mesothelioma with cyclophosphamide, Adriamycin and vincristine. Cancer Chemother Pharmacol 4: 135
63. Garnick MB, Blum RH, Canellos GP, Mayer J, Parker L, Skarin AT, Li FP, Henderson C, Frei E (1979) Phase I trial of brucceantin. Cancer Treat Rep 63: 1929–1932
64. Gerner RE, Moore GE (1973) Multiple drug therapy for malignant solid tumors in adults. Cancer Chemother Rep 57: 237–239
65. Gerner RE, Moore GE (1974) Chemotherapy of malignant mesothelioma. Oncology 30: 152–155
66. Gore ME, Calvert AH, Smith IE (1987) High dose carboplatin in the treatment of lung cancer and mesothelioma: a phase I dose escalation study. Eur J Cancer Clin Oncol 23: 1391–1397
67. Gottlieb JA, Serpick AA (1971) Clinical evaluation of 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide in malignant melanoma and other neoplasma: comparison of twice-weekly and daily administration schedules. Oncology 25: 225–233
68. Gottlieb JA, Baker LH, Quagliana JM, Luce JK, Whitecar JP, Sinkovics JG, Rikvin SE, Brownlee R, Frei E (1972) Chemotherapy of sarcomas with a combination of Adriamycin and dimethyltriazeno-imidazole carboxamide. Cancer 30: 1632–1638
69. Gottlieb JA, Bodey GP, Sinkovics JG, Rodriguez VT, Burgess MA (1974) An effective new drug combination (CYVADIC) for metastatic sarcomas. Proc Am Assoc Cancer Res 15: 162
70. Gottlieb JA, Baker LH, O'Bryan RM, Sinkovics JG, Hoogstraten B, Quagliana JM, Rivkin SE, Bodey GP, Rodriguez VT, Blumenschein GR, Saiki JH, Coltman C, Burgess MA, Sullivan P, Thigpen T, Bottomley R, Balcerzak S, Moon TE (1975) Adriamycin used alone and in combination for soft tissue and bone sarcomas. Cancer Chemother Rep 6: 271–282
71. Grant DC, Seltzer SE, Antman KH, Finnberg HJ, Koster K (1983) Computed tomography of malignant pleural mesothelioma. J Comput Assist Tumogr 7: 626–632
72. Harvey VJ, Slevin ML, Ponder BAJ, Blackshaw AJ, Wrigley PFM (1984) Chemotherapy of diffuse malignant mesothelioma. Cancer 54: 961–964
73. Hayes DM, Cvitkovic E, Golbey RB, Scheiner E, Helson L, Krakoff JH (1977) High dose cisplatinum diammine dichloride. Cancer 39: 1372–1381
74. Henss H, Fiebig HH, Schildge J, Schuchhardt C, Arnold H (1986) Behandlung des fortgeschrittenen Pleuramesothelioms mit Cis-Platin und Doxorubicin. Cancer Res Clin Oncol 111 [Suppl]: 67
75. Henss H, Fiebig H, Schildge J, Arnold H, Hasse J (1988) Phase-II study with the combination of cisplatin and doxorubicin in advanced malignant mesothelioma of the pleura. Onkologie 11: 118–120
76. Hillerdal G (1983) Malignant mesothelioma 1982: review of 4710 published cases. Br J Dis Chest 77: 321–343
77. Hinds MW (1978) Mesothelioma in the United States. Incidence in the 1970s. J Occup Med 20: 469–471
78. Holiat SM, Smith WE, Hubert DD, Dacis S (1981) Chemotherapeutic trials with hamster mesothelioma 10–24: responses to azacitidine, aziridinylbenzoquinone, cisplatin, and PCNU. Cancer Treat Rep 65: 1113–1115
79. Howell SB, Pfeifle CL, Wung WE, Ohlsen RA, Lucas WE, Yon JL, Green M (1982) Intraperitoneal cisplatin with systemic thiosulfate protection. Ann Intern Med 97: 845–851

80. Iriarte PV, Hananian J, Cortner JA (1986) Central nervous system leukemia and solid tumors of childhood: treatment with 1,3-bis(2-chlorethyl)-1-nitrosourea. Cancer 19: 1187–1194
81. Jett JR, Eagan RT (1982) Chemotherapy for malignant mesothelioma. Am J Clin Oncol 5: 429–431
82. Jones DEC, Silver D (1979) Peritoneal mesotheliomas. Surgery 86: 556–560
83. Kelsen D, Gralla R, Cheng E, Martin N (1983) Vindesine in the treatment of malignant mesothelioma: a phase II study. Cancer Treat Rep 67: 821–822
84. Kelsen DP, Bajorin D, Mintzer D (1985) Phase II trial of mitomycin in malignant mesothelioma. Proc Am Soc Clin Oncol 4: 146
85. Kirmani S, Cleary SM, Mowry J, Howell SB (1988) Intracavitary cisplatin for malignant mesothelioma; an update. Proc Am Soc Clin Oncol 7: 273
86. Kirschner J, Delosantos R, Ziegler P, Canty R, Lawrence W, Spaulding M (1984) Phase I/II study of high dose ara-C in solid tumors. Proc Am Soc Clin Oncol 3: 44
87. Klastersky J, Sculier JP, Tueni E (1987) A phase I study of a carboplatin and etoposide chemotherapy in patients with advanced thoracic cancer. Proc Am Soc Clin Oncol 6: 184
88. Kucuksu N, Ezdinli E, Cehreli C (1975) Chemotherapy of mesotheliomas. Proc Am Assoc Cancer Res 22: 527
89. Kucuksu N, Thomas W, Ezdinli E (1976) Chemotherapy of malignant diffuse mesothelioma. Cancer 37: 1265–1274
90. Law MR, Hodson ME, Heard BE (1982) Malignant mesothelioma of the pleura: relation between histological type and clinical behaviour. Thorax 37: 810–815
91. Law MR, Gregor A, Hodson ME, Bloom HJG, Turner-Warwick M (1984) Malignant mesothelioma of the pleura: a study of 52 treated and 64 untreated patients. Thorax 39: 255–259
92. Lee YL, Wesley RA (1981) Statistical contributions to phase II trials in cancer: interpretation, analysis and design. Semin Oncol 8: 403–416
93. Legha SS, Muggia FM (1977) Therapeutic approaches in malignant mesothelioma. Cancer Treat Rev 4: 13–23
94. Lerner JH, Schoenfeld D, Martin A, Falkson G, Borden E (1981) Malignant mesothelioma. Proc Am Assoc Cancer Res 22: 527
95. Lerner H, Amato D, Shiraki M, Borden E (1983) A prospective study of Adriamycin in malignant mesothelioma. Proc Am Soc Clin Oncol 2: 230
96. Lerner HJ, Schoenfeld DA, Martin A, Falkson G, Borden E (1983) Malignant mesothelioma. Cancer 52: 1981–1985
97. Magri MD, De Giovanni D, Serra C, Crismanich F, Della Valentina M, Nicotra M, Tomasi M, Morassut S, Carbonne A, Grandi G, Monfardini S, Bianchi C (1988) Epirubicin treatment of mesothelioma: a phase II study. Proc Am Soc Clin Oncol 7: 207
98. Markman M, Howell SB, Lucas WE, Pfeifle CE, Green MR (1984) Combination intraperitoneal chemotherapy with cisplatin, cytarabine and doxorubicin for refractory ovarian cancer and other malignancies principally confined to the peritoneal cavity. J Clin Oncol 2: 1321–1326
99. Markman M, Cleary S, Pfeifle CE, Howell SB (1986) Cisplatin administered by the intracavitary route as treatment for malignant mesothelioma. Cancer 58: 18–21
100. Mattson K, Breukelen FJM van, Tammilehto L, Kirkpatrick A, McVie JG (1988) 4-Epidoxorubicin in mesothelioma: a phase II study for the EORTC Lung Cancer Cooperative Group. Lung Cancer 4 [Suppl]: A138
101. Mbidde EK, Harland SJ, Calvert AH, Smith IE (1986) Phase II trial of carboplatin (JM8) in treatment of patients with malignant mesothelioma. Cancer Chemother Pharmacol 18: 284–285
102. Mintzer D, Kelsen D, Frimmer D, Heelan R, Gralla R, Ochoa M (1984) Phase II trial of high dose cisplatin in patients with malignant mesothelioma. Proc Am Soc Clin Oncol 3: 258
103. Mintzer DM, Kelsen D, Frimmer D, Heelan R, Gralla R (1985) Phase II trial of high-dose cisplatin in patients with malignant mesothelioma. Cancer Treat Rep 69: 711–712
104. Mirvis S, Dutcher JP, Haney PJ, Whitley NO, Aisner J (1983) CT of malignant pleural mesothelioma. AJR 140: 665–670
105. Mischler NE, Chuprevich T, Johnson RO, Tormey DC (1979) Malignant mesothelioma presenting in the pleura and peritoneum. J Surg Oncol 11: 185–191
106. Mårtensson G, Sörenson S (1989) A phase II study of vincristine in malignant mesothelioma – a negative report. Cancer Chemother Pharmacol 24: 133–134
107. Nissen NI, Larsen V, Pedersen H, Thomsen K (1972) Phase I clinical trial of a new antitumor agent, 4′dimethylepipodophyllotoxin-9-4(4,6-*O*-ethylidene-beta-D-glucopyranoside). Cancer Chemother Rep 56: 769–777
108. Nissen NI, Dombernowsky P, Hansen HH, Larsen V (1976) Phase I clinical trial of an oral solution of VP16-213. Cancer Treat Rep 60: 943–945
109. Oels HC, Harrison EG, Carr DT, Bernatz PE (1971) Diffuse malignant mesothelioma of the pleura: a review of 37 cases. Chest 60: 564–570
110. Omura GA, Roberts GA (1973) Combination therapy of solid tumors using 1,3-bis(2-chlorethyl)-1-nitrosourea, vincristine, methotrexate and 5-fluorouracil. Cancer 31: 1374–1381
111. Pfeifle CE, Howell SB, Markman M (1984) Intracavitary cisplatin for mesothelioma. Proc Am Soc Clin Oncol 3: 258
112. Pfeifle CE, Howell SB, Markman M (1985) Intracavitary cisplatin chemotherapy for mesothelioma. Cancer Treat Rep 69: 205–207
113. Plaus WJ (1988) Peritoneal mesothelioma. Arch Surg 123: 763–766
114. Pomfret E, Antman KH, Corson J, MacIntyre J, Price K, Greenberger J, Osteen R, Collins J (1983) Intensive treatment of patients with malignant mesothelioma. Proc Am Assoc Cancer Res 24: 156
115. Price LA, Hill BT (1976) Clinical use of DDMP (2,4-diamino)-6-(3′5′-dichlorophenyl)-6-methyl pyrimidine. Proc Am Assoc Cancer Res 17: 15
116. Projan A, Nissen E, Tanneberger S (1981) Die Wirksamkeit von Carminomycin in Kombination mit Dibromodulcitol auf Tumorzellen des Menschen in vitro. Arch Geschwulstforsch 51: 497–502
117. Reuter K, Raptopoulos V, Reale F, Krolikowski FJ, D'Orsi C, Graham S, Smith EH (1983) Diagnosis of peritoneal mesothelioma: computed tomography, sonography, and fine-needle aspiration biopsy. AJR 140: 1189–1194
118. Ridell RJ (1966) Three cases of mesothelioma. Med J Aust 2: 554–559
119. Rivera FJ (1986) Malignant peritoneal mesothelioma: a difficult diagnosis. Iowa Med 76: 222–224
120. Rusch VW, Godwin JD, Shuman WP (1988) The role of computed tomography scanning in the initial assessment and the follow-up of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 96: 171–177
121. Said JW, Nash G, Lee M (1982) Immunoperoxidase localization of keratin, proteins, carcinoembryonic antigen, and factor VIII in adenomatoid tumors: evidence for a mesothelial derivation. Hum Pathol 13: 1106–1108
122. Saijo N, Nishiwaki Y, Kawase I, Kobayashi T, Suzuki A, Niitani H (1978) Effect of ACNU on primary lung cancer, mesothelioma and metastatic pulmonary tumors. Cancer Treat Rep 62: 139–141
123. Samson MK, Baker LH, Devos JM, Buroker TR, Izbicki RM, Vaitkevicius VK (1976) Phase I trial of combined therapy with vinblastine, bleomycin, and *cis*-dichlorodiammine-platinum. Cancer Treat Rep 60: 91–97
124. Samson MK, Baker LH, Benjamin RS, Lane M, Piager C (1979) *cis*-Dichlorodiammineplatinum in advanced soft tissue and bony sarcomas. Cancer Treat Rep 63: 11–12
125. Samson MK, Baker LH, Wasser LP, Borden E, Wanebo HJ (1985) Randomized comparison of cyclophosphamide, DTIC, and Adriamycin versus cyclophosphamide and Adriamycin in patients with advanced malignant mesothelioma. Proc Am Soc Clin Oncol 4: 128
126. Samson MK, Wasser LP, Borden E, Wanebo HJ, Creech RH, Phillips M, Baker LH (1987) Randomized comparison of cyclophosphamide, imidazole carboxamide, and Adriamycin versus cyclophosphamide and Adriamycin in patients with advanced stage malignant mesothelioma: a Sarcoma Intergroup study. J Clin Oncol 5: 86–91

127. Sauer H, Kremer G, Wilmanns W (1987) Zur Toxizität einer CYVADIC-Modifikation bei Patienten mit Weichteilsarkomen oder malignen Mesotheliomen. Onkologie 10: 294–300
128. Schlegel R, Banks-Schlegel S, McLeod JA (1980) Immunoperoxidase localization of keratin in human neoplasms. Am J Pathol 101: 41–50
129. Schroeter NJ, Rushing DA, Parker JP, Beltaos E (1986) Minimal-change nephrotic syndrome with malignant mesothelioma. Arch Intern Med 146: 1834–1836
130. Selikoff IJ (1977) Cancer risk of asbestos exposure: origins of human cancer. Cold Spring Harbor Laboratory, New York, pp 1765–1784
131. Silverberg E (1985) Cancer statistics, 1985. CA 35: 19–35
132. Sklarin NT, Chahinian AP, Feuer EJ, Lahman LA, Szrajer L, Holland JF (1988) Augmentation of activity of *cis*-diamminedichloroplatinum(II) and mitomycin C by interferon in human mesothelioma xenografts in nude mice. Cancer Res 48: 64–67
133. Smith WE, Hubert DP, Holiat SM, Sobel HJ, Davis S (1981) An experimental model for treatment of mesothelioma. Cancer 47: 658–663
134. Sørensen PG, Bach F, Bork E, Hansen HH (1985) Randomized trial of doxorubicin versus cyclophosphamide in diffuse malignant mesothelioma. Cancer Treat Rep 69: 1431–1432
135. Sone S, Tsubura E (1978) Mesothelioma and local immunotherapy. Ann Intern Med 88: 575
136. Spremulli E, Wampler G, Becelson W, Borochowitz D, Hapdy T (1977) Chemotherapy of malignant mesothelioma. Cancer 40: 2038–2045
137. Suzuki V, Churg J, Kannerstein M (1976) Ultrastructure of human malignant diffuse mesothelioma. Am J Pathol 85: 241–262
138. Thigpen JT, O'Bryan RM, Benjamin RS, Coltman CA (1977) Phase II trial of Baker's antifol in metastatic sarcoma. Cancer Treat Rep 61: 1485–1487
139. Tucker WG, Talley RW, Brownlee RW, Burrows JH, Stott PB, Moorhead EL, San Diego EL (1968) Preliminary trials with combination therapy of cyclophosphamide, vincristine and 5-fluorouracil. Cancer Chemother Rep 52: 593–596
140. Van Dyk JJ, Van Der Merve AM, Falkson HC, Falkson G (1976) Adriamycin in the treatment of cancer. S Afr Med J 50: 61–66
141. Vogelzang NJ, Schultz SM, Iannucci AM, Kennedy BJ (1983) Malignant mesothelioma – the University of Minnesota experience. Cancer 52: 1788–1791
142. Vogelzang NJ, Goutsou M, Graziano S (1989) Carboplatin in malignant mesothelioma: a phase II study of CALGB. Proc Am Soc Clin Oncol 8: 321
143. Vogler WR, Arkun S, Velez-Garcia E (1974) Phase I study of twice weekly 5-azacytidine. Cancer Chemother Rep 58: 895–899
144. Wang NS (1973) Electron microscopy in the diagnosis of pleural mesotheliomas. Cancer 31: 1046–1054
145. Warhol MJ, Hickey WF, Corson JM (1982) Malignant mesothelioma: ultrastructural distinction from adenocarcinoma. Am J Surg Pathol 6: 307–314
146. Webster I, Cochrane JWC, Burkhardt KR (1982) Immunotherapy with BCG vaccine in 30 cases of mesothelioma. S Afr Med J 62: 277–278
147. Weiss RB, Muggia FM (1979) Working conference on mesothelioma treatment trials. Cancer Res 33: 3799–3800
148. Wiltshaw E, Westbury G, Harmer C, McKinna A, Fisher C (1986) Ifosfamide plus mesna with and without Adriamycin in soft tissue sarcoma. Cancer Chemother Pharmacol 18 [Suppl 2]: 10–12
149. Wolcott MW, Shaver WA, Walkup HE, Peasley ED (1959) Mesotheliomas of the pleura. Dis Chest 36: 119–126
150. World Health Organisation (1979) WHO handbook for reporting results of cancer treatment. Offset publication 48. WHO, Geneva
151. Yap B, Benjamin RS, Burgess MA, Bodey GP (1978) The value of Adriamycin in the treatment of diffuse malignant pleural mesothelioma. Cancer 42: 1692–1696
152. Zidar BL, Benjamin RS, Frank J, Lane M, Baker LH (1983) Combination chemotherapy for advanced sarcomas of bone and mesothelioma utilizing rubidazone and DTIC. Am J Clin Oncol 6: 71–74
153. Zidar BL, Pugh RP, Schiffer LM, Raju RN, Vaidya KA, Bloom RL, Horne D, Baker LH (1983) Treatment of six cases of mesothelioma with doxorubicin and cisplatin. Cancer 52: 1788–1791
154. Zidar BL, Goldberg R, Guy J (1987) A phase II evaluation of cisplatinum in unresectable diffuse malignant mesothelioma. Proc Am Soc Clin Oncol 6: 125