

Activity of chemotherapy and immunotherapy on malignant mesothelioma: a systematic review of the literature with meta-analysis

Research Article

Thierry Berghmans^{1*}, Jean-Jacques Lafitte³, Céline Mascaux¹, Anne-Pascale Meert¹, Marianne Paesmans² and Jean-Paul Sculier¹

¹Service de Médecine Interne et Laboratoire d'Investigation Clinique et d'Oncologie Expérimentale and ²Data Centre, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Belgium and ³Department of Pneumology, CHU Calmette, Lille, France

*Correspondence: Dr Thierry Berghmans, Institut Jules Bordet, Rue Héger-Bordet, 1, 1000 Bruxelles, Belgium; Tel: 322/541.31.11; Fax: 322/534.37.56; e-mail: thierry.berghmans@bordet.be

Key Words: chemotherapy, immunotherapy, mesothelioma, quality score, systematic review, meta-analysis

Abbreviations: cisplatin CDDP; vinblastine VBL; interferon INF; interleukine 2 IL-2; mitomycin C MMC; doxorubicin Doxo; ifosfamide Ifo cyclophosphamide CPA; bleomycin Bleo; hyaluronidase Hyal; global quality score QS; internal validity IV; external validity EV; response rate RR; confidence interval CI

Received: 19 September 2003; Accepted: 11 November 2003; electronically published: November 2003

Summary

Malignant mesothelioma is a tumour with increasing incidence, for which treatment remains debatable. Different chemotherapy regimens have been tested in phase II studies. The aim of the present report is to update the results of a previous meta-analysis to identify new chemotherapy regimens which could be selected for future randomised trials. Ninety-five articles corresponding to 100 treatment arms, published between 1983 and 2003, were eligible for the analysis. A qualitative evaluation was performed using the ELCWP methodological quality scale. No statistically significant difference in term of methodological score was found between the positive and potentially positive (upper limit of the 95% confidence interval (CI) for the response rate (RR) > 20%) and negative studies (median: 57.3% versus 56.7%; $p = 0.68$), allowing us to perform an aggregation of the results of the different studies. We found that the most active combination regimens, in terms of response rate are cisplatin plus doxorubicin (RR 28.5%), gemcitabine (RR 29.8%) or etoposide (RR 27.1%). When single agent therapy is considered, cisplatin seems to be the most active single agent (RR 17.0%). No other endpoints such as survival, toxicity or quality of life could be meta-analysed, due to the lack of data in the publications. Cisplatin plus doxorubicin, gemcitabine or etoposide appear as the most active regimens in the treatment of malignant mesothelioma. These results must be interpreted in the context of the recently published phase III trial demonstrating a significant survival advantage of cisplatin plus pemetrexed on cisplatin monotherapy.

I. Introduction

The incidence of malignant mesothelioma is expected to rise in the next few years, due to increased asbestos exposure during the last decades (Driscoll et al, 1993). Few treatments have demonstrated activity against this disease. The beneficial survival impact of surgery, pleurectomy or extrapleural pneumonectomy, has never been proven in randomised trial. Only a minority of the patients are eligible for these treatments (Sugarbaker et al, 1991), whose mortality and morbidity can be considerable. The efficacy of radiotherapy is not proven (Ong and Vogelzang, 1996).

A majority of the patients are medically treated. Some chemotherapeutic agents such as cisplatin or doxorubicin are considered as potentially useful. In a

previous systematic review of the literature with meta-analysis, we found that cisplatin-based or cisplatin and doxorubicin-based chemotherapy were the most active regimens with respective response rates of 23.2% and 28.3% (Berghmans et al, 2002). Some new agents have been tested the last two years in phase II studies, including gemcitabine (Nowak et al, 2002; van Haarst et al, 2002), taxans (Vorobiof et al, 2002), raltitrexed (Baas et al, 2003; Fizazi et al, 2003; Maisano et al, 2001) or oxaliplatin (Fizazi et al, 2003; Maisano et al, 2001) and the first randomised phase III trial comparing two chemotherapeutic regimens has been published (Vogelzang et al, 2003).

In the present report, we update our previous systematic review on the activity of chemotherapy and

immunotherapy in malignant mesothelioma, in order to identify new cisplatin-based chemotherapy regimens which could be selected for future randomised trials.

II. Materials and methods

The search for prospective published trials relative to the treatment of malignant mesothelioma of pleural or peritoneal origin was performed by consulting the Medline, Health Star and National Cancer Institutes electronic data bases and completed by references found in the papers, in textbooks, in reviews and those known by the investigators.

The criteria of eligibility of the articles were the following: to focus only on patients with malignant mesothelioma; to be related to the study of single or combined cytotoxic and/or immunomodulatory agents, administered by systemic or local routes; to be published in English, French or Dutch languages between 1965 and January 2003; to be a prospective single or randomised phase II or phase III trial with a minimum of 14 patients included. If less than 14 patients were included in a prospective phase II trial, the study could be considered as eligible if at least one objective response was observed when targeting a response rate of 20%, according to the Gehan's design for phase II studies (Gehan EA, 1961). Abstracts were excluded from this analysis because of insufficient data to apply the scoring system and to evaluate the methodological quality of the trial.

The methodological qualitative evaluation was performed by a team of 5 medical doctors and 1 biostatistician. Consensual agreement on the scores attributed to each item for each trial was obtained by regular meetings. The study quality was assessed according to the information provided in the publication, using the previously published ELCWP quality scale (Berghmans et al, 2002). All items were grouped in ten categories and a global quality score as well as two subscores assessing the internal and external validities of the studies were calculated.

For each article, the numbers of eligible patients were recorded by applying the criteria used in ELCWP trials (Sculier et al, 1996) considering toxic death, early death due to cancer or treatment discontinuation due to toxicity as treatment failures. We assumed that a chemotherapeutic agent had a clinical potentially useful activity in a trial if its objective response rate was at least 20%. We considered that a study was negative if the upper limit of the 95% confidence interval (CI) of the response rate was $< 20\%$. It was considered as positive if the lower limit of the 95% CI was $> 20\%$ and as not conclusive but potentially positive if the upper limit of the 95% CI was $> 20\%$ but the lower limit $< 20\%$.

Descriptive summary statistics were calculated in each category for the distributions of the scores (internal validity, external validity and global score). Normality of the distribution of continuous variables was assessed by a Kolmogorov-Smirnov test. If the distribution was normal, the distribution of these continuous variables according to the levels of a categorical variable were compared by using parametric tests (ANOVA or Student). Otherwise, non parametric tests (Wilcoxon or Kruskal-Wallis) were applied. Relationship between the scores and other continuous variables was assessed by the calculation of Pearson or Spearman correlation coefficients, according to the normality of the distributions of the continuous variables. Confidence intervals for the response rate to the chemotherapeutic regimen were, for consistency, recalculated using the exact binomial distribution. Proportions were compared with chi square tests for homogeneity. All reported p values are two-tailed.

III. Results

A. Phase II studies

1. Trials characteristics

Ninety-five articles, published between 1983 and 2003, met our selection criteria and were eligible for the analysis. Out of these 95 eligible studies, 92 were single arm phase II trials and 3 were randomised phase II trials. For the purpose of this review, each arm of the randomised studies was assessed as an independent trial. In 2 papers, 2 separate phase II trials were reported in the same publication. Thus, 100 «arms», each considered as an independent study, were analysed. They will be further called «studies».

In a first analysis, the studies were separated in 4 groups according to the treatment regimen (**Table 1**). Group 1 (n = 22) corresponded to the trials testing cisplatin but not doxorubicin. Group 2 (n = 9) was composed of the trials investigating doxorubicin without cisplatin. Seven studies, assessing a combination including both cisplatin and doxorubicin, formed Group 3. The last 62 trials, with regimens without cisplatin or doxorubicin, were included in Group 4. Sixty-two studies (62%) used a single agent regimen. The chemotherapy mainly consisted in platinum (n = 32) and/or anthracycline (n = 27) derivatives. In 20 studies, an immunomodulatory agent was used either alone (n = 8) or combined with cisplatin (n = 8) or with other agents (n = 4). Other tested agents and regimens are detailed in **Table 1** (4,12-93).

Among the 100 eligible studies, 37 were negative, 5 positive and 58 potentially positive in term of antitumoral response, as defined above. For the purpose of the analysis, the potentially positive trials were pooled with the true positive ones and this whole group will be further named as the «positive trials». The total number of patients assessable for response and incorporated in the 100 studies was 2727.

Other endpoints have been considered but the lack of data or their presentation precluded to perform meaningful quantitative aggregation. Survival rates were not reported in 18 of the 100 analysed arms. Thirteen studies reported on symptoms evaluation (n = 10) or quality of life (n = 3). Toxicity was only fully described in 46 arms; partial information was available in 44; it was not analysed in 10.

2. Methodological assessment

The results of the qualitative methodological evaluation for each trial are given in **Table 1**. The overall mean and median scores attributed per score subscales are described in **Table 2**. No statistically significant difference in term of methodological score was found between the positive and negative trials whatever global (median: 57.3% versus 56.7%; p = 0.68), internal (45.8% versus 43.3%; p = 0.58) or external (68.9% versus 71.5%; p = 0.87) validity scores were considered. No statistically significant difference was observed between the 4 groups according to the type of therapeutic regimen (p = 0.42) (**Table 3**). A significant difference was found according to the method of tumour response assessment (**Table 4**): studies using radiological techniques as a part or as the whole of the evaluation had better scores than the others

Table 1. Treatment regimen, quality scores and response rates with 95% confidence interval (ELCWP) according to treatment group for assessable patients

Schedule	n pts	QS (%)	IV (/50)	EV (/50)	RR (%)	95%CI
Group 1 (n = 22) Cisplatin without doxorubicin containing regimens						
CDDP (Planting et al, 1994)	14	56.5	19.2	37.3	35.7	7-64.4
CDDP (Markman et al, 1986)	21	30.9	5.0	25.9	14.3	0-31.6
CDDP (Zidar et al, 1988)	35	46.1	12.5	33.6	14.3	1.3-27.3
CDDP (Mintzer et al, 1985)	24	36.9	12.1	24.8	12.5	0-27.8
CDDP/VP16 (Planting et al, 1995)	25	51.9	15.8	36.1	24.0	5.3-42.7
CDDP/VP16 (Eisenhauer et al, 1988)	26	44.2	15.8	28.4	11.5	0-25.7
CDDP/VBL (Tsavaris et al, 1994)	20	56.7	27.1	29.6	25.0	3.5-46.5
CDDP/MMC/VBL (Middleton et al, 1998)	39	61.7	23.4	38.4	20.5	5.0-33.0
CDDP/5Fluorouracil/Leucovorin/MMC/VP16 (Kasseyet et al, 1999)	45	61.0	30.0	31.0	37.8	23.0-53.0
CDDP/MMC (Chahinian et al, 1993)	35	65.0	27.9	37.0	25.7	9.8-41.6
CDDP/MMC/INF 2a (Metintas et al, 1999)	43	70.0	30.0	40.0	23.3	9.0-37.0
CDDP/MMC/INF 2b (Tansan et al, 1994)	19	48.6	18.8	29.8	10.5	0-27
CDDP/MMC/INF /surgery (Hasturk et al, 1996)	23	48.6	18.8	29.9	0.0	-
CDDP/INF 2b/tamoxifene (Pass et al, 1995)	39	63.3	35.0	28.3	19.4	5.1-33.8
CDDP/INF (Trandafir L et al, 1997)	29	41.3	11.7	34.5	27.0	10.0-45.0
CDDP/INF 2a (Purohit et al, 1998)	12	69.0	29.2	39.9	41.7	8.0-67.0
CDDP/INF 2a (Soulie et al, 1996)	26	67.0	30.0	37.0	40.0	18.8-61.2
CDDP/5 Azacytidine (Samuels et al, 1998)	36	67.9	31.3	36.3	13.9	0.0-25.0
CDDP/Gemcitabine (Byrne et al, 1999)	21	81.3	33.8	47.5	47.6	24.0-67.0
CDDP/Gemcitabine (van Haarst et al, 2002)	30	68.2	27.5	40.7	13.3	3.8-30.7
CDDP/Gemcitabine (Nowak et al, 2002)	53	75.7	40.0	35.7	32.1	19.5-44.6
CDDP/Irinotecan (Nakano et al, 1999)	15	76.1	30.0	46.1	40.0	7.0-67.0
Group 2 (n = 9) Doxorubicin without cisplatin containing regimens						
Doxo/INF 2a (Upham et al, 1993)	25	79.5	44.2	35.4	16.0	0-32.4
Doxo/Ifo (Dirix et al, 1994)	24	59.5	19.2	40.4	31.8	10.1-53.6
Doxo/Ifo (Carmichael et al, 1989)	17	30.7	5.0	25.7	12.5	0-31.8
Doxo/CPA/Imidazole (Samson et al, 1987)	36	54.8	28.3	26.5	11.1	0-22.8
Doxo/CPA (Samson et al, 1987)	40	54.8	28.3	26.5	12.5	0.01-24
Doxo (Sorensen et al, 1985)	15	19.7	13.3	6.4	0.0	-
Liposomal doxorubicin (Caelyx) (Baas et al, 2000)	31	78.6	37.5	41.1	6.5	0.0-16.0
Liposomal doxorubicin (Doxil) (Oh et al, 2000)	24	28.3	3.4	25.0	0.0	-
Liposomal doxorubicin (Doxil) (Skubitz, 2002)	15	44.6	13.3	31.3	6.7	2.0-31.9
Group 3 (n = 7) Cisplatin plus doxorubicin containing regimens						
CDDP/Doxo/MMC (Pennucci et al, 1997)	23	73.7	30.9	42.9	21.7	0.0-39.0
CDDP/Doxo/MMC/Bleo/Hyal (Breau JL et al, 1993)	27	35.6	11.7	23.9	44.4	23.8-65
CDDP/Doxo/CPA (Shin et al, 1995)	23	75.5	33.8	41.7	30.4	9.5-51.4

CDDP/Doxo (Henss et al, 1988)	19	45.1	12.9	32.1	42.1	17.3-66.9
CDDP/Doxo (Ardizzoni et al, 1991)	24	44.0	17.9	26.1	25.0	5.6-44.4
CDDP/Doxo (Chahinian et al, 1993)	35	65.0	27.9	37.0	14.3	1.3-27.3
CDDP/Doxo/INF 2b (Parra et al, 2001)	35	88.6	45.0	43.4	28.6	13.6-43.5
<u>Group 4 (n = 62) Regimens without cisplatin and doxorubicin</u>						
Carboplatin (Mbidde et al, 1986)	17	31.25	12.5	18.8	11.8	0-30
Carboplatin (Cantwell et al, 1986b)	9	27.5	5.0	22.5	22.2	0-54.9
Carboplatin (Raghavan et al, 1990)	31	48.0	15.8	32.1	16.1	1.6-30.7
Carboplatin (Vogelzang et al, 1990)	40	52.5	16.2	36.3	7.5	0-16.9
Carboplatin/INF 2a (O'Reilly et al, 1999)	15	72.0	29.2	42.9	6.7	0.0-20.0
Detorubicin (Colbert et al, 1985)	21	44.8	15.8	28.9	42.9	19.3-66.4
Epirubicin (Mattson et al, 1992)	51	56.4	22.9	33.5	14.6	3.6-25.6
Epirubicin/Ifo (Magri et al, 1992)	17	38.6	16.7	22.0	5.9	0-20
Epirubicin/IL-2 (Bretti et al, 1998)	21	76.5	36.7	38.3	4.8	0.0-14.0
Epirubicin (Magri et al, 1991)	21	51.5	20.0	31.5	4.8	0-16.3
Liposomal Daunorubicin (Steele et al, 2001)	14	57.9	21.7	36.3	0.0	-
Pirarubicin (Kaukel et al, 1990)	35	53.8	21.7	32.1	8.6	0-19.3
Mitoxantrone (Eisenhauer et al, 1986)	29	37.9	14.2	23.8	7.1	0-18.5
Mitoxantrone (van Breukelen et al, 1991)	40	56.3	21.3	35.0	2.5	0-8.6
Menogaril (Hudis and Kelsen, 1992)	22	39.2	14.2	25.0	4.5	0-15.5
MMC (Bajorin et al, 1987)	19	28.0	12.5	15.5	21.1	0.1-42
Mitoxantrone/Methotrexate/MMC (Pinto et al, 2001)	22	68.6	25.0	43.6	31.8	9.0-50.0
Methotrexate/INF 1b (Halme et al, 1999)	26	72.3	30.9	41.5	26.9	8.0-46.0
Methotrexate (Solheim et al, 1992)	62	47.5	17.5	30.0	36.7	23.6-49.7
Edatrexate (Kindler et al, 1999)	20	71.5	34.2	37.3	25.0	5.0-45.0
Edatrexate/Leucovorin (Kindler et al, 1999)	38	71.5	34.2	37.3	15.8	3.0-29.0
Trimetrexate (Vogelzang et al, 1994)	51	73.6	32.1	41.5	8.2	0-16.9
Ifo (Andersen et al, 1999)	26	69.0	30.0	39.0	3.8	0.0-12.0
Ifo (Icli et al, 1996)	30	44.0	18.3	25.7	20.7	4.2-37.2
Ifo (Falkson et al, 1992)	39	75.6	35.0	40.6	2.6	0-8.8
Ifo (Zidar et al, 1992)	26	57.3	22.5	34.8	7.7	0-19.9
CPA (Sorensen et al, 1985)	16	19.7	13.3	6.4	0.0	-
5 Azacytidine (Yogelzang et al, 1997)	41	73.2	29.6	43.6	17.1	4.3-29.8
5 Azacytidine (Dhingra et al, 1991)	15	55.8	20.0	35.8	0.0	-
Amsacrine (Falkson et al, 1983)	20	31.4	7.0	24.4	5.3	0-17.9
Diaziquone (Eagan et al, 1986)	20	44.8	11.7	33.1	0.0	-
CB 3717 (Cantwell et al, 1986a)	18	21.3	2.5	18.8	5.6	0-18.9
Vinorelbine (Steele et al, 2000)	29	67.3	31.3	36.1	24.1	7.0-41.0
Vindesine (Boutin et al, 1987)	21	26.8	5.0	21.8	0.0	-
Vindesine (Kelsen et al, 1983)	20	42.1	13.8	28.3	5.9	0-20
Vincristine (Martensson and Sorenson, 1989)	23	38.0	13.8	24.3	0.0	-
Acivicin (Falkson et al, 1987)	23	33.9	6.7	27.3	0.0	-

5 Fluorouracil (Harvey et al, 1984)	20	25.8	3.8	21.1	5.0	0-17.1
Etoposide (intravenously) (Sahmoud et al, 1997)	47	83.7	38.4	45.4	4.3	0.0-11.0
Etoposide (orally) (Sahmoud et al, 1997)	41	83.7	38.4	45.4	7.3	0.0-16.0
Etoposide (Tammilehto et al, 1994)	22	45.2	14.6	30.6	5.3	0-17.9
Gemcitabine (Kindler et al, 2001)	15	79.6	38.4	41.3	0.0	-
Gemcitabine (van Meerbeeck et al, 1999)	27	84.8	36.3	48.6	7.4	0.0-19.0
Topotecan (Maksymiuk et al, 1998)	22	29.0	18.8	39.3	0.0	-
Docetaxel/Irinotecan (Knuutila et al, 2000)	15	68.3	28.4	40.0	0.0	-
Taxol (Vogelzang et al, 1999)	33	37.4	10.9	26.6	9.1	0.0-21.0
Taxol (van Meerbeeck et al, 1996)	23	76.9	37.5	39.4	0.0	-
Docetaxel (Vorobiof et al, 2002)	31	56.1	25.0	31.1	9.7	0.0-20.1
IL-2 (Astoul et al, 1998)	22	59.5	25.0	34.5	54.5	27.0-73.0
IL-2 (Castagneto et al, 2001)	31	57.3	22.5	38.8	22.6	7.0-39.0
IL-2 (Mulatero et al, 2001)	29	65.5	28.4	37.2	6.9	0.0-17.0
rINF 2b (Ardizzoni et al, 1994)	13	48.3	20.0	28.3	7.7	0-26
INF 2a (Christmas et al, 1993)	25	66.1	34.2	32.0	12.0	0-26.7
INF (Boutin et al, 1991)	19	59.2	23.3	35.9	31.6	8-55.1
INF (Von Hoff et al, 1990)	15	60.2	23.3	36.9	0.0	-
INF (Monnet et al, 2002)	17	74.4	36.7	37.7	11.8	1.5-36.4
Temozolomide (van Meerbeeck et al, 2002)	27	76.8	30.0	46.8	3.7	0.1-19.0
Oxaliplatin/raltitrexed (Fizazi et al, 2003)	70	62.1	18.4	43.6	20.0	10.6-29.4
Oxaliplatin/raltitrexed (Maisano et al, 2001)	11	49.4	18.4	31.1	45.4	16.7-76.6
Raltitrexed (Baas et al, 2003)	24	66.3	23.4	42.9	20.8	7.1-42.2
Ranpirnase (Mikulski et al, 2002)	81	68.4	28.4	40.1	4.9	0.2-9.6
Mycobacterium vaccae (Mendes et al, 2002)	16	38.4	10.0	28.4	37.5	15.2-64.6

CDDP=cisplatin; VBL=vinblastine; INF= interferon; IL-2= interleukine 2; MMC= mitomycin C; Doxo= doxorubicin; Ifo=ifosfamide; CPA=cyclophosphamide; Bleo=bleomycin; Hyal=hyaluronidase; QS= global quality score; IV=internal validity; EV=external validity; RR=response rate; CI=confidence interval

Table 2. Mean and median scores by categories for all the studies pooled

<u>Category (/100)</u>	<u>Mean</u>	<u>Median</u>	<u>Range</u>
I. Description of the selection criteria for the study	72.2	83.3	0-100
II. Registration modality description	16.3	0.0	0-100
III. Description of work-ups for disease evaluation	43.2	50.0	0-100
IV. Criteria of evaluation description	56.6	50.0	0-100
V. Statistical methods description	33.5	16.7	0-100
<u>Internal validity (/100)</u>	44.4	43.3	5-90
VI. Treatment description	67.1	75	25-100
VII. Patients characteristics data and analysis	80.0	87.5	22.2-100
VIII. Survival data and analysis	50.3	50.0	0-100
IX. Antitumoral response data and analysis	76.1	78.6	16.7-100
X. Toxicity	62.6	75.0	0-100
<u>External validity (/100)</u>	67.2	69.6	12.8-97.1
<u>Global score (/100)</u>	55.8	57.2	20.1-88.6

Table 3. Median quality scores according to 4 treatment groups

	<u>n studies</u>	<u>Global score (%)</u>	<u>Range (%)</u>
Group 1	22	61.4	30.9-81.3
Group 2	9	54.8	20.1-78.1
Group 3	7	63.7	34.8-88.6
Group 4	62	57.3	20.1-84.8
		p = 0.42	

Group 1 = trials testing cisplatin but not doxorubicin; Group 2 = trials testing doxorubicin but not cisplatin; Group 3 = trials testing cisplatin and doxorubicin; Group 4 = trials without cisplatin and doxorubicin

Table 4. Median scores according to the method of response assessment

<u>Method used (n studies)</u>	<u>Global score (%)</u>	<u>Range (%)</u>
A (n = 32)	44.2	21.3-75.6
B (n = 8)	61.7	31.4-79.6
C (n = 60)	63.3	20.1-88.6
	p < 0.00003	

A = not mentioned; B = standard X-ray; C = Ct scan or presence of a measurable metastasis

Table 5. Response rates according to treatment groups.

	<u>R/E patients</u>	<u>Response rate (%)</u>	<u>95% confidence interval</u>
Group 1	148/630	23.5	20.2-26.8
Group 2	25/227	11.0	6.9-15.1
Group 3	53/186	28.5	22.0-35.0
Group 4	204/1684	12.1	10.5-13.7
			p < 0.001

Group 1 = trials testing cisplatin but not doxorubicin; Group 2 = trials testing doxorubicin but not cisplatin; Group 3 = trials testing cisplatin and doxorubicin; Group 4 = trials without cisplatin and doxorubicin

R/E = number of patients responding to the allowed treatment between the number of evaluable patients according to ELCWP criteria

(p < 0.0003) but were also significantly more recent (p < 0.001).

There was a significant quality difference between single and combined agents therapies, with respective median values of 53.8% and 63.5% (p = 0.007) for the global score. Nevertheless, studies assessing polychemotherapy were also more recently published than single agent ones (respective median dates of publication of 1997 and 1992; p = 0.09). A significant correlation with the year of publication, in favour of the most recent trials, was noted as well for the global score ($r_s = 0.63$; p < 0.001) as for internal ($r_s = 0.57$; p < 0.001) and external ($r_s = 0.63$; p < 0.001) validities. A weak but statistically significant correlation was found between the number of patients included in the trial and the methodological assessment, as well for the global ($r_s = 0.34$; p = 0.0009), the internal validity ($r_s = 0.36$; p = 0.0003) and the external validity scores ($r_s = 0.26$; p = 0.01). The repartition of the different methods of response assessment (standard Rx, CT scan or not specified) were similarly distributed among the different treatment groups (p = 0.60). No quality difference was observed between studies reporting on

some quality of life/symptoms assessment and the others (p = 0.10).

3. Meta-analysis

3.1. Analysis according to the inclusion of cisplatin and/or doxorubicin

The absence of methodological quality difference between the positive and negative studies allowed us to compare the response rates between the 4 groups of trials (**Table 5**). A significant difference was noted between the 4 types of regimens defined by the presence or not of cisplatin and/or doxorubicin (p < 0.001). Group 3 (with cisplatin and doxorubicin) had a better overall response rate than group 1 (with cisplatin) (28.5% versus 23.5%; p = 0.16), and group 2 (with doxorubicin) (28.5% versus 11.0%; p < 0.0001). Group 1 had a significantly better response rate than group 4 (without cisplatin and without doxorubicin) (23.5% versus 12.1%; p < 0.0001). The difference was statistically significant between groups 1 and 2 (23.5% versus 11.0%; p < 0.0001). No difference was observed between groups 2 and 4 (11.0% versus 12.1%; p = 0.63). Results between cisplatin and carboplatin-containing regimens were significantly

different (24.6% versus 11.6%; $p = 0.002$). The comparison between doxorubicin and 4-epidoxorubicin showed a significant difference in favour of doxorubicin (18.9% versus 9.1%; $p = 0.01$) but when studies containing cisplatin were withdrawn from the comparison, the difference was no more significant (11.0% versus 9.1%; $p = 0.59$). Doxorubicin administered in a liposomal form demonstrated no meaningful activity (between 0% and 6.7% response rate). The combined agent regimens had a significantly better response rate than the single agent ones (22.9% versus 11.2%; $p < 0.00001$). It should be noted that a majority of single agent trials were incorporated in group 4, the group with the lowest response rate. Studies incorporating immunomodulatory agents, alone or in combinations, showed a response rate of 20.2%. Nevertheless, trials including both cisplatin and interferon showed higher response rates (23.0%) than for interferon alone (13.5%). Interleukin-2 alone seemed more active than interferon alone with a response rate of 25.6%. Other chemotherapeutic agents were generally considered inactive at the exception of raltitrexed and methotrexate. Ifosfamide containing regimens demonstrated a poor activity with response rate of 11.2% as well as taxanes (5.9%) or vinca alkaloids (8.6%), although vinorelbine demonstrated potential usefulness in one study. A response rate of 15.5% was associated with etoposide administration but when cisplatin containing studies were withdrawn from the analysis, VP16 had to be considered

inactive with a response rate of 5.5%. Raltitrexed had some activity with a response rate of 22.9%. Lastly, methotrexate seemed a promising drug with a response rate of 32.7%, needing confirmatory studies (**Table 6**).

3.2. Comparison of cisplatin-containing regimen among phase II studies

In our previous study, we found that cisplatin plus doxorubicin containing regimens had the higher response rate. In the present study, we observed that cisplatin/doxorubicin combination (response rate 28.5%) had the same activity than cisplatin/gemcitabine with respective response rates of 29.8% and 28.5% ($p = 0.81$). The same observation was made when cisplatin/doxorubicin was compared to the cisplatin/etoposide regimen (27.1%; $p = 0.80$). No comparison was feasible between cisplatin/doxorubicin and cisplatin/interferon because 2 among the available studies included both doxorubicin and interferon.

We compared cisplatin monotherapy with other chemotherapy used as single agent. We found that cisplatin monotherapy was statistically superior in term of response rate (17.0%) to ifosfamide (8.3%; $p = 0.05$), taxanes (5.9%; $p = 0.01$), etoposide (5.5%; $p = 0.008$) and vinca alkaloids, essentially when vinorelbine was not taken into account (1.5%; $p = 0.002$).

Table 6. Response rates of the principal chemotherapeutic agents and/or combinations used in malignant mesothelioma.

Regimen	R/E patients	Response rate (%)	95% confidence interval
Cisplatin	201/816	24.6%	21.7-27.6
Cisplatin (SA)	16/94	17.0%	9.4-24.6
Carboplatin	13/112	11.6%	5.7-17.5
Cisplatin/doxorubicin	53/186	28.5%	22.0-35.0
Cisplatin/gemcitabine	31/104	29.8%	20.0-38.6
Cisplatin/etoposide	26/96	27.1%	18.2-36.0
Cisplatin/interferon	52/226	23.0%	17.5-28.5
Doxorubicin (all studies)	78/413	18.9%	15.1-22.7
4 Epidoxorubicin	10/110	9.1%	3.7-14.5
4 Epidoxorubicin (SA)	8/72	11.1%	3.9-18.4
Ifosfamide	20/179	11.2%	6.6-15.8
Ifosfamide (SA)	10/121	8.3%	3.4-13.2
Raltitrexed (all studies)	24/105	22.9%	14.9-30.9
Etoposide (SA)	6/110	5.5%	1.3-9.7
Methotrexate	36/110	32.7%	23.9-41.5
Vincalcaloids	8/93	8.6%	2.9-14.3
Taxanes	6/102	5.9%	1.3-10.5
Interferon/interleukin2	98/484	20.2%	16.7-23.8
Interferon (SA)	12/89	13.5%	6.4-20.6
Interleukin-2 (SA)	21/82	25.6%	16.2-35.0

SA = single agent; R/E = number of patients responding to the allowed treatment between the number of evaluable patients according to ELCWP criteria

No statistically significant difference was observed between cisplatin monotherapy and epirubicin (11.1%; $p = 0.28$), interferon (13.5%; $p = 0.16$) or interleukin-2 (25.6%; $p = 0.51$).

B. Phase III randomised trial

Pemetrexed (Alimta) is a novel multitargeted antifolate which demonstrates promising activity against malignant mesothelioma. The role of Alimta was assessed in a randomised phase III trial, the only one published at this time (Vogelzang et al, 2003). Survival was the primary endpoint. Four hundred fifty-six patients were randomised between cisplatin monotherapy (75 mg/m²) and cisplatin at the same dosage plus pemetrexed (Alimta; 500 mg/m²), given every 3 weeks. Higher response rate was observed in the combined regimen (41.3% versus 16.7%; $p < 0.001$). This resulted in longer time to progression ($p = 0.001$) and better survival rates. The median survival times for the cisplatin plus Alimta and cisplatin alone regimens were respectively 12.1 months and 9.3 months ($p = 0.02$). More toxicity was associated with the combination, including grades 3/4 neutropenia, nausea and vomiting, diarrhea and stomatitis. However, among patients taking folate and vitamin B12 supplementation, toxicity was clearly reduced without adversely affecting the efficacy. Some improvements in quality of life and pulmonary function tests were also observed.

IV. Discussion

This update of our previous systematic review confirms that the combination of cisplatin and doxorubicin is suggested as one of the most active regimens, in terms of response rate, for the treatment of malignant mesothelioma. Nevertheless, gemcitabine and etoposide, when administered with cisplatin demonstrate similar activity to cisplatin and doxorubicin. When single agent therapy is considered, cisplatin remains the most active agent. Due to lack of data, no other meaningful analysis could be performed on important endpoints such as survival, toxicity or quality of life.

The treatment of malignant mesothelioma remains debatable. The role of surgery and radiotherapy is not clear and their impact on survival is not yet proven. Only well selected groups of patients with limited tumour size have been reported, principally in retrospective studies (van Ruth S et al, 2003). Chemotherapy has demonstrated its effectiveness and limitations in phase II studies. No randomised phase III trial has assessed the impact on survival of a chemotherapy regimen versus no active treatment. A recently published phase III trial (Vogelzang et al, 2003) has demonstrated that a combined regimen including pemetrexed and cisplatin is better in terms of response rate and survival than cisplatin alone, which is found the most active monotherapeutic agent in our meta-analysis. Further, the response rate in the cisplatin monotherapy arm (16.7%) of this phase III trial is similar to those found in our meta-analysis (17.0%). In the near

future, cisplatin plus pemetrexed will probably be considered as the treatment of reference in malignant mesothelioma. Nevertheless, in our meta-analysis, we observed that the combinations of cisplatin and doxorubicin, gemcitabine or etoposide are equally active in terms of response rate which is similar to those obtained with cisplatin plus pemetrexed. As the results of a meta-analysis have only exploratory value, they require confirmation by well conducted prospective trials, comparing these 3 regimens to this new combination in order to determine their possible equivalence on survival.

The use of immunomodulatory agents either alone or in combination seems promising. We found in our meta-analysis that cisplatin plus interferon or interleukine-2 have high objective response rates. Nevertheless, the type of immunotherapy (interferon or interleukin), the dosage and the route of administration are heterogeneous. New studies are needed to delineate the exact role of immunotherapy in malignant mesothelioma. Other chemotherapies such as raltitrexed or methotrexate demonstrate some efficacy but these first results need confirmation in further studies.

Our results were obtained by aggregation of data obtained in multiple individual phase II trials, including 3 randomised phase II studies. This type of quantitative overview can be the subject of biases related to differences in quality and methodology between the selected studies, namely in patients selection. These biases have been discussed in details in our previous publication (Berghmans et al, 2002). Principally, we compared methodological quality among studies by using the ELCWP methodological assessment scale, specifically designed for phase II studies. We did not find any methodological differences between positive and negative studies, allowing us to compare response rates between groups of studies. Another potential source of biases is the method used to assess tumour response. However, no statistically significant difference in the distribution of the methods of response assessment was observed among the 4 principal groups of studies.

In conclusion, this systematic qualitative and quantitative overview of the literature suggests that the most active chemotherapeutic regimen, in term of antitumoral response rate, is the combination of cisplatin and doxorubicin although cisplatin plus gemcitabine or etoposide appears to be equally effective. When single agent therapy is considered, cisplatin seems the best single-agent. These results need to be evaluated in randomised phase III trials, in comparison with the combination of cisplatin and pemetrexed. This regimen is the only combination chemotherapy which has proven its superiority on single agent cisplatin in a randomised comparison.

References

- Andersen MK, Krarup-Hansen A, Martensson G, Winther-Nielsen H, Thylen A, Damgaard K, Olling S, Wallin J (1999) Ifosfamide in malignant mesothelioma, a phase II study. *Lung Cancer* 24, 39-43

- Ardizzoni A, Pennucci MC, Castagneto B, Mariani GL, Cinquegrana A, Magri D, Verna A, Salvati F, Rosso R (1994) Recombinant interferon alpha-2b in the treatment of diffuse malignant pleural mesothelioma. **Am J Clin Oncol** 17, 80-82
- Ardizzoni A, Rosso R, Salvati F, Fusco V, Cinquegrana A, De Palma M, Serrano J, Pennucci MC, Soresi E, Crippa M, (1991) Activity of doxorubicin and cisplatin combination chemotherapy in patients with diffuse malignant pleural mesothelioma. An Italian Lung Cancer Task Force (FONICAP) Phase II study. **Cancer** 67, 2984-2987
- Astoul P, Picat-Joossen D, Viallat JR, Boutin C (1998) Intrapleural administration of interleukin-2 for the treatment of patients with malignant pleural mesothelioma, a Phase II study. **Cancer** 83, 2099-2104
- Baas P, Ardizzoni A, Grossi F, Nackaerts K, Numico G, van Marck E, van d, V, Monetti F, Smid-Geirnaerd MJ, van Zandwijk N, Debryne C, Legrand C, Giaccone G (2003) The activity of raltitrexed (Tomudex) in malignant pleural mesothelioma, an EORTC phase II study (08992). **Eur J Cancer** 39, 353-357
- Baas P, van Meerbeeck J, Groen H, Schouwink H, Burgers S, Daamen S, Giaccone G (2000) Caelyx in malignant mesothelioma, a phase II EORTC study. **Ann Oncol** 11, 697-700
- Bajorin D, Kelsen D, Mintzer DM (1987) Phase II trial of mitomycin in malignant mesothelioma. **Cancer Treat Rep** 71, 857-858
- Berghmans T, Paesmans M, Lalami Y, Louviaux I, Luce S, Mascaux C, Meert AP, Sculier JP (2002) Activity of chemotherapy and immunotherapy on malignant mesothelioma, a systematic review of the literature with meta-analysis. **Lung Cancer** 38, 111-121
- Boutin C, Irissou 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
- Boutin C, Viallat JR, van Zandwijk N, Douillard JT, Paillard JC, Guerin JC, Mignot P, Miguieres J, Varlet F, Jehan A, . (1991) Activity of intrapleural recombinant gamma-interferon in malignant mesothelioma. **Cancer** 67, 2033-2037
- Breau JL, Boaziz C, Morère JF, et al (1993) Chemotherapy with cisplatin, adriamycin, bleomycin and mitomycin C, combined with systemic and intrapleural hyaluronidase in stage II and III pleural mesothelioma. **Eur Respir Rev** 3, 223-225
- Bretti S, Berruti A, Dogliotti L, Castagneto B, Bertulli R, Spadaro P, Toscano G, Astorre P, Verusio C, Lionetto R, Bruzzi P, Santoro A (1998) Combined epirubicin and interleukin-2 regimen in the treatment of malignant mesothelioma, a multicenter phase II study of the Italian Group on Rare Tumors. **Tumori** 84, 558-561
- Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, de Klerk NH, Robinson BW (1999) Cisplatin and gemcitabine treatment for malignant mesothelioma, a phase II study. **J Clin Oncol** 17, 25-30
- Cantwell BM, Earnshaw M, Harris AL (1986a) Phase II study of a novel antifolate, N10-propargyl-5,8 dideazafolic acid (CB3717), in malignant mesothelioma. **Cancer Treat Rep** 70, 1335-1336
- Cantwell BM, Franks CR, Harris AL (1986b) A phase II study of the platinum analogues JM8 and JM9 in malignant pleural mesothelioma. **Cancer Chemother Pharmacol** 18, 286-288
- Carmichael J, Cantwell BM, Harris AL (1989) A phase II trial of ifosfamide/mesna with doxorubicin for malignant mesothelioma. **Eur J Cancer Clin Oncol** 25, 911-912
- Castagneto B, Zai S, Mutti L, Lazzaro A, Ridolfi R, Piccolini E, Ardizzoni A, Fumagalli L, Valsuani G, Botta M (2001) Palliative and therapeutic activity of IL-2 immunotherapy in unresectable malignant pleural mesothelioma with pleural effusion, Results of a phase II study on 31 consecutive patients. **Lung Cancer** 31, 303-310
- Chahinian AP, Antman K, Goutsou M, Corson JM, Suzuki Y, Modeas C, Herndon JE, Aisner J, Ellison RR, Leone L, . (1993) Randomized phase II trial of cisplatin with mitomycin or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group B. **J Clin Oncol** 11, 1559-1565
- Christmas TI, Manning LS, Garlepp MJ, Musk AW, Robinson BW (1993) Effect of interferon-alpha 2a on malignant mesothelioma. **J Interferon Res** 13, 9-12
- Colbert N, Vannetzel JM, Izrael V, Schlienger M, Milleron B, Blanchon F, Herman D, Akoun G, Roland J, Chatelet F, . (1985) A prospective study of detorubicin in malignant mesothelioma. **Cancer** 56, 2170-2174
- Dhingra HM, Murphy WK, Winn RJ, Raber MN, Hong WK (1991) Phase II trial of 5,6-dihydro-5-azacytidine in pleural malignant mesothelioma. **Invest New Drugs** 9, 69-72
- Dirix LY, van Meerbeeck J, Schrijvers D, Corthouts B, Prove A, van Marck E, Vermeire P, van Oosterom AT (1994) A phase II trial of dose-escalated doxorubicin and ifosfamide/mesna in patients with malignant mesothelioma. **Ann Oncol** 5, 653-655
- Driscoll TR, Baker GJ, Daniels S, Lee J, Thompson R, Ferguson DA, Leigh J (1993) Clinical aspects of malignant mesothelioma in Australia. **Aust N Z J Med** 23, 19-25
- Eagan RT, Frytak S, Richardson RL, Creagan ET, Nichols WC (1986) Phase II trial of diaziquone in malignant mesothelioma. **Cancer Treat Rep** 70, 429
- Eisenhauer EA, Evans WK, Murray N, Kocha W, Wierzbicki R, Wilson K (1988) A phase II study of VP-16 and cisplatin in patients with unresectable malignant mesothelioma. An NCI Canada Clinical Trials Group Study. **Invest New Drugs** 6, 327-329
- Eisenhauer EA, Evans WK, Raghavan 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
- Falkson G, Hunt M, Borden EC, Hayes JA, Falkson CI, Smith TJ (1992) An extended phase II trial of ifosfamide plus mesna in malignant mesothelioma. **Invest New Drugs** 10, 337-343
- Falkson G, Vorobiof DA, Lerner HJ (1983) A phase II study of m-AMSA in patients with malignant mesothelioma. **Cancer Chemother Pharmacol** 11, 94-97
- Falkson G, Vorobiof DA, Simson IW, Borden EC (1987) Phase II trial of acivicin in malignant mesothelioma. **Cancer Treat Rep** 71, 545-546
- Fizazi K, Doubre H, Le Chevalier T, Riviere A, Viala J, Daniel C, Robert L, Barthelemy P, Fandi A, Ruffie P (2003) Combination of raltitrexed and oxaliplatin is an active regimen in malignant mesothelioma, results of a phase II study. **J Clin Oncol** 21, 349-354
- Gehan EA (1961) The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. **J Chron Dis** 13, 346-353
- Halme M, Knuutila A, Vehmas T, Tammilehto L, Mantyla M, Salo J, Mattson K (1999) High-dose methotrexate in combination with interferons in the treatment of malignant pleural mesothelioma. **Br J Cancer** 80, 1781-1785
- Harvey VJ, Slevin ML, Ponder BA, Blackshaw AJ, Wrigley PF (1984) Chemotherapy of diffuse malignant mesothelioma. Phase II trials of single-agent 5-fluorouracil and adriamycin. **Cancer** 54, 961-964
- Hasturk S, Tastepe I, Unlu M, Cetin G, Baris YI (1996) Combined chemotherapy in pleurectomized malignant pleural mesothelioma patients. **J Chemother** 8, 159-164

- Henss H, Fiebig HH, 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
- Hudis CA, Kelsen DP (1992) Menogaril in the treatment of malignant mesothelioma, a phase II study. **Invest New Drugs** 10, 103-106
- Icli F, Karaoguz H, Hasturk S, Kurt B, Akbulut H, Dincol D, Demirkazik A, Cay F, Akyar S (1996) Two dose levels of ifosfamide in malignant mesothelioma. **Lung Cancer** 15, 207-213
- Kasseyet S, Astoul P, Boutin C (1999) Results of a phase II trial of combined chemotherapy for patients with diffuse malignant mesothelioma of the pleura. **Cancer** 85, 1740-1749
- Kaukel E, Koschel G, Gatzemeyer U, Salewski E (1990) A phase II study of pirarubicin in malignant pleural mesothelioma. **Cancer** 66, 651-654
- Kelsen D, Gralla R, Cheng E, Martini N (1983) Vindesine in the treatment of malignant mesothelioma, a phase II study. **Cancer Treat Rep** 67, 821-822
- Kindler HL, Belani CP, Herndon JE, Vogelzang NJ, Suzuki Y, Green MR (1999) Edatrexate (10-ethyl-deaza-aminopterin) (NSC #626715) with or without leucovorin rescue for malignant mesothelioma. Sequential phase II trials by the cancer and leukemia group B. **Cancer** 86, 1985-1991
- Kindler HL, Millard F, Herndon JE, Vogelzang NJ, Suzuki Y, Green MR (2001) Gemcitabine for malignant mesothelioma, A phase II trial by the Cancer and Leukemia Group B. **Lung Cancer** 31, 311-317
- Knuutila A, Ollikainen T, Halme M, Mali P, Kivisaari L, Linnainmaa K, Jekunen A, Mattson K (2000) Docetaxel and irinotecan (CPT-11) in the treatment of malignant pleural mesothelioma--a feasibility study. **Anticancer Drugs** 11, 257-261
- Magri MD, Foladore S, Veronesi A, Serra C, Nicotra M, Tommasi M, Grandi G, Monfardini S, Bianchi C (1992) Treatment of malignant mesothelioma with epirubicin and ifosfamide, a phase II cooperative study. **Ann Oncol** 3, 237-238
- Magri MD, Veronesi A, Foladore S, De Giovanni D, Serra C, Crismancich F, Tuveri G, Nicotra M, Tommasi M, Morassut S, . (1991) Epirubicin in the treatment of malignant mesothelioma, a phase II cooperative study. The North-Eastern Italian Oncology Group (GOCCNE)--Mesothelioma Committee. **Tumori** 77, 49-51
- Maisano R, Caristi N, Toscano G, Aragona M, Spadaro P, Amadio P, Mare M, Zavettieri M, La Torre F (2001) Oxaliplatin and raltitrexed in the treatment of inoperable malignant pleural mesothelioma, results of a pilot study. **Tumori** 87, 391-393
- Maksymiuk AW, Marschke RF, Jr., Tazelaar HD, Grill J, Nair S, Marks RS, Brooks BJ, Mailliard JA, Burton GM, Jett JR (1998) Phase II trial of topotecan for the treatment of mesothelioma. **Am J Clin Oncol** 21, 610-613
- Markman M, Cleary S, Pfeifle C, Howell SB (1986) Cisplatin administered by the intracavitary route as treatment for malignant mesothelioma. **Cancer** 58, 18-21
- Martensson G, Sorenson S (1989) A phase II study of vincristine in malignant mesothelioma--a negative report. **Cancer Chemother Pharmacol** 24, 133-134
- Mattson K, Giaccone G, Kirkpatrick A, Evrard D, Tammilehto L, van Breukelen FJ, Planteydt HT, van Zandwijk N (1992) Epirubicin in malignant mesothelioma, a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. **J Clin Oncol** 10, 824-828
- 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
- Mendes R, O'Brien ME, Mitra A, Norton A, Gregory RK, Padhani AR, Bromelow KV, Winkley AR, Ashley S, Smith IE, Souberbielle BE (2002) Clinical and immunological assessment of Mycobacterium vaccae (SRL172) with chemotherapy in patients with malignant mesothelioma. **Br J Cancer** 86, 336-341
- Metintas M, Ozdemir N, Ucgun I, Elbek O, Kolsuz M, Mutlu S, Metintas S (1999) Cisplatin, mitomycin, and interferon-alpha2a combination chemoimmunotherapy in the treatment of diffuse malignant pleural mesothelioma. **Chest** 116, 391-398
- Middleton GW, Smith IE, O'Brien ME, Norton A, Hickish T, Priest K, Spencer L, Ashley S (1998) Good symptom relief with palliative MVP (mitomycin-C, vinblastine and cisplatin) chemotherapy in malignant mesothelioma. **Ann Oncol** 9, 269-273
- Mikulski SM, Costanzi JJ, Vogelzang NJ, McCachren S, Taub RN, Chun H, Mittelman A, Panella T, Puccio C, Fine R, Shogen K (2002) Phase II trial of a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. **J Clin Oncol** 20, 274-281
- 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
- Monnet I, Breau JL, Moro D, Lena H, Eymard JC, Menard O, Vuillez JP, Chokri M, Romet-Lemonne JL, Lopez M (2002) Intrapleural infusion of activated macrophages and gamma-interferon in malignant pleural mesothelioma, a phase II study. **Chest** 121, 1921-1927
- Mulatero CW, Penson RT, Papamichael D, Gower NH, Evans M, Rudd RM (2001) A phase II study of combined intravenous and subcutaneous interleukin-2 in malignant pleural mesothelioma. **Lung Cancer** 31, 67-72
- Nakano T, Chahinian AP, Shinjo M, Togawa N, Tonomura A, Miyake M, Ninomiya K, Yamamoto T, Higashino K (1999) Cisplatin in combination with irinotecan in the treatment of patients with malignant pleural mesothelioma, a pilot phase II clinical trial and pharmacokinetic profile. **Cancer** 85, 2375-2384
- Nowak AK, Byrne MJ, Williamson R, Ryan G, Segal A, Fielding D, Mitchell P, Musk AW, Robinson BW (2002) A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. **Br J Cancer** 87, 491-496
- O'Reilly EM, Ilson DH, Saltz LB, Heelan R, Martin L, Kelsen DP (1999) A phase II trial of interferon alpha-2a and carboplatin in patients with advanced malignant mesothelioma. **Cancer Invest** 17, 195-200
- Oh Y, Perez-Soler R, Fossella FV, Glisson BS, Kurie J, Walsh GL, Truong M, Shin DM (2000) Phase II study of intravenous Doxil in malignant pleural mesothelioma. **Invest New Drugs** 18, 243-245
- Ong ST, Vogelzang NJ (1996) Chemotherapy in malignant pleural mesothelioma. A review. **J Clin Oncol** 14, 1007-1017
- Parra HS, Tixi L, Latteri F, Bretti S, Alloisio M, Gravina A, Lionetto R, Bruzzi P, Dani C, Rosso R, Cosso M, Balzarini L, Santoro A, Ardizzoni A (2001) Combined regimen of cisplatin, doxorubicin, and alpha-2b interferon in the treatment of advanced malignant pleural mesothelioma, a Phase II multicenter trial of the Italian Group on Rare Tumors (GITR) and the Italian Lung Cancer Task Force (FONICAP). **Cancer** 92, 650-656
- Pass HW, Temeck BK, Kranda K, Steinberg SM, Pass HI (1995) A phase II trial investigating primary immunochemotherapy

- for malignant pleural mesothelioma and the feasibility of adjuvant immunochemotherapy after maximal cytoreduction. **Ann Surg Oncol** 2, 214-220
- Pennucci MC, Ardizzoni A, Pronzato P, Fioretti M, Lanfranco C, Verna A, Giorgi G, Vignani A, Frola C, Rosso R (1997) Combined cisplatin, doxorubicin, and mitomycin for the treatment of advanced pleural mesothelioma, a phase II FONICAP trial. Italian Lung Cancer Task Force. **Cancer** 79, 1897-1902
- Pinto C, Marino A, Guaraldi M, Melotti B, Piana E, Martoni A, Pannuti F (2001) Combination chemotherapy with mitoxantrone, methotrexate, and mitomycin (MMM regimen) in malignant pleural mesothelioma, a phase II study. **Am J Clin Oncol** 24, 143-147
- Planting AS, Schellens JH, Goey SH, van der Burg ME, Boer-Dennert M, Stoter G, Verweij J (1994) Weekly high-dose cisplatin in malignant pleural mesothelioma. **Ann Oncol** 5, 373-374
- Planting AS, van der Burg ME, Goey SH, Schellens JH, van den Bent MJ, Boer-Dennert M, Stoter G, Verweij J (1995) Phase II study of a short course of weekly high-dose cisplatin combined with long-term oral etoposide in pleural mesothelioma. **Ann Oncol** 6, 613-615
- Purohit A, Moreau L, Dietemann A, Seibert R, Pauli G, Wihlm JM, Quoix E (1998) Weekly systemic combination of cisplatin and interferon alpha 2a in diffuse malignant pleural mesothelioma. **Lung Cancer** 22, 119-125
- Raghavan D, Gianoutsos P, Bishop J, Lee J, Young I, Corte P, Bye P, McCaughan B (1990) Phase II trial of carboplatin in the management of malignant mesothelioma. **J Clin Oncol** 8, 151-154
- Sahmoud T, Postmus PE, van Pottelsberghe C, Mattson K, Tammilehto L, Splinter TA, Planting AS, Sutedja T, van Pawel J, van Zandwijk N, Baas P, Rozenendaal KJ, Schrijver M, Kirkpatrick A, Van Glabbeke M, Ardizzoni A, Giaccone G (1997) Etoposide in malignant pleural mesothelioma, two phase II trials of the EORTC Lung Cancer Cooperative Group. **Eur J Cancer** 33, 2211-2215
- Samson MK, Wasser LP, Borden EC, 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
- Samuels BL, Herndon JE, Harmon DC, Carey R, Aisner J, Corson JM, Suzuki Y, Green MR, Vogelzang NJ (1998) Dihydro-5-azacytidine and cisplatin in the treatment of malignant mesothelioma, a phase II study by the Cancer and Leukemia Group B. **Cancer** 82, 1578-1584
- Sculier JP, Paesmans M, Bureau G, Giner V, Lecomte J, Michel J, Berchier MC, Van Cutsem O, Kustner U, Kroll F, Sergysels R, Mommen P, Klastersky J (1996) Randomized trial comparing induction chemotherapy versus induction chemotherapy followed by maintenance chemotherapy in small-cell lung cancer. European Lung Cancer Working Party. **J Clin Oncol** 14, 2337-2344
- Shin DM, Fossella FV, Umsawadi T, Murphy WK, Chasen MH, Walsh G, Komaki R, McMurtrey MJ, Hong WK (1995) Prospective study of combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin for unresectable or metastatic malignant pleural mesothelioma. **Cancer** 76, 2230-2236
- Skubit KM (2002) Phase II trial of pegylated-liposomal doxorubicin (Doxil) in mesothelioma. **Cancer Invest** 20, 693-699
- Solheim OP, Saeter G, Finnanger AM, Stenwig AE (1992) High-dose methotrexate in the treatment of malignant mesothelioma of the pleura. A phase II study. **Br J Cancer** 65, 956-960
- Sorensen PG, Bach F, Bork E, Hansen HH (1985) Randomized trial of doxorubicin versus cyclophosphamide in diffuse malignant pleural mesothelioma. **Cancer Treat Rep** 69, 1431-1432
- Soulie P, Ruffie P, Trandafir L, Monnet I, Tardivon A, Terrier P, Cvitkovic E, Le Chevalier T, Armand JP (1996) Combined systemic chemoimmunotherapy in advanced diffuse malignant mesothelioma. Report of a phase I-II study of weekly cisplatin/interferon alfa-2a. **J Clin Oncol** 14, 878-885
- Steele JP, O'Doherty CA, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM (2001) Phase II trial of liposomal daunorubicin in malignant pleural mesothelioma. **Ann Oncol** 12, 497-499
- Steele JP, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM (2000) Phase II study of vinorelbine in patients with malignant pleural mesothelioma. **J Clin Oncol** 18, 3912-3917
- Sugarbaker DJ, Heher EC, Lee TH, Couper G, Mentzer S, Corson JM, Collins JJ, Jr., Shemin R, Pugatch R, Weissman L, . (1991) Extrapleural pneumonectomy, chemotherapy, and radiotherapy in the treatment of diffuse malignant pleural mesothelioma. **J Thorac Cardiovasc Surg** 102, 10-14
- Tammilehto L, Maasilta P, Mantyla M, Salo J, Mattson K (1994) Oral etoposide in the treatment of malignant mesothelioma. A phase II study. **Ann Oncol** 5, 949-950
- Tansan S, Emri S, Selcuk T, Koc Y, Hesketh P, Heeren T, McCaffrey RP, Baris YI (1994) Treatment of malignant pleural mesothelioma with cisplatin, mitomycin C and alpha interferon. **Oncology** 51, 348-351
- Trandafir L, Ruffie P, Borel C, Monnet I, Soulie P, Adams D, Cvitkovic E, Armand JP (1997) Higher doses of alpha-interferon do not increase the activity of the weekly cisplatin-interferon combination in advanced malignant mesothelioma. **Eur J Cancer** 33, 1900-1902
- Tsavaris N, Mylonakis N, Karvounis N, Bacoyiannis C, Briasoulis E, Skarlos D, Pavlidis N, Stamatelos G, Kosmidis P (1994) Combination chemotherapy with cisplatin-vinblastine in malignant mesothelioma. **Lung Cancer** 11, 299-303
- Upham JW, Musk AW, van Hazel G, Byrne M, Robinson BW (1993) Interferon alpha and doxorubicin in malignant mesothelioma, a phase II study. **Aust N Z J Med** 23, 683-687
- van Breukelen FJ, Mattson K, Giaccone G, van Zandwijk N, Planteydt HT, Kirkpatrick A, Dalesio O (1991) Mitoxantrone in malignant pleural mesothelioma, a study by the EORTC Lung Cancer Cooperative Group. **Eur J Cancer** 27, 1627-1629
- van Haarst JM, Baas P, Manegold C, Schouwink JH, Burgers JA, de Bruin HG, Mooi WJ, van Klaveren RJ, de Jonge MJ, van Meerbeeck JP (2002) Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. **Br J Cancer** 86, 342-345
- van Meerbeeck J, Debruyne C, van Zandwijk N, Postmus PE, Pennucci MC, van Breukelen F, Galdermans D, Groen H, Pinson P, Van Glabbeke M, van Marck E, Giaccone G (1996) Paclitaxel for malignant pleural mesothelioma, a phase II study of the EORTC Lung Cancer Cooperative Group. **Br J Cancer** 74, 961-963
- van Meerbeeck JP, Baas P, Debruyne C, Groen HJ, Manegold C, Ardizzoni A, Gridelli C, van Marck EA, Lentz M, Giaccone G (1999) A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. **Cancer** 85, 2577-2582

- van Meerbeeck JP, Baas P, Debruyne C, Smit EF, van Klaveren RJ, Galdermans D, Lentz MA, Manegold C, Giaccone G (2002) A phase II EORTC study of temozolomide in patients with malignant pleural mesothelioma. **Eur J Cancer** 38, 779-783
- van Ruth S, Baas P, Zoetmulder FA (2003) Surgical treatment of malignant pleural mesothelioma. A review. **Chest** 123, 551-561
- Vogelzang NJ, Goutsou M, Corson JM, Suzuki Y, Graziano S, Aisner J, Cooper MR, Coughlin KM, Green MR (1990) Carboplatin in malignant mesothelioma, a phase II study of the Cancer and Leukemia Group B. **Cancer Chemother Pharmacol** 27, 239-242
- Vogelzang NJ, Herndon JE, Miller A, Strauss G, Clamon G, Stewart FM, Aisner J, Lyss A, Cooper MR, Suzuki Y, Green MR (1999) High-dose paclitaxel plus G-CSF for malignant mesothelioma, CALGB phase II study 9234. **Ann Oncol** 10, 597-600
- Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeyer U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. **J Clin Oncol** 21, 2636-2644
- Vogelzang NJ, Weissman LB, Herndon JE, Antman KH, Cooper MR, Corson JM, Green MR (1994) Trimetrexate in malignant mesothelioma, A Cancer and Leukemia Group B Phase II study. **J Clin Oncol** 12, 1436-1442
- Von Hoff DD, Metch B, Lucas JG, Balcerzak SP, Grunberg SM, Rivkin SE (1990) Phase II evaluation of recombinant interferon-beta (IFN-beta ser) in patients with diffuse mesothelioma, a Southwest Oncology Group study. **J Interferon Res** 10, 531-534
- Vorobiof DA, Rapoport BL, Chasen MR, Abratt RP, Cronje N, Fourie L, McMichael G, Hacking D (2002) Malignant pleural mesothelioma, a phase II trial with docetaxel. **Ann Oncol** 13, 412-415
- Yogelzang NJ, Herndon JE, Cirrincione C, Harmon DC, Antman KH, Corson JM, Suzuki Y, Citron ML, Green MR (1997) Dihydro-5-azacytidine in malignant mesothelioma. A phase II trial demonstrating activity accompanied by cardiac toxicity. Cancer and Leukemia Group B. **Cancer** 79, 2237-2242
- Zidar BL, Green S, Pierce HI, Roach RW, Balcerzak SP, Militello L (1988) A phase II evaluation of cisplatin in unresectable diffuse malignant mesothelioma, a Southwest Oncology Group Study. **Invest New Drugs** 6, 223-226
- Zidar BL, Metch B, Balcerzak SP, Pierce HI, Militello L, Keppen MD, Berenberg JL (1992) A phase II evaluation of ifosfamide and mesna in unresectable diffuse malignant mesothelioma. A Southwest Oncology Group study. **Cancer** 70, 2547-2551