*Review*

# Randomized Trials of Systemic Medically-treated Malignant Mesothelioma: A Systematic Review

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**Abstract.** *Malignant pleural mesothelioma (MPM) is a rare but aggressive malignancy mainly localized to the pleura. Malignant mesothelioma grows highly invasive into surrounding tissue and has a low tendency to metastasize. The median overall survival (OS) of locally advanced or metastatic disease without treatment is 4-13 months but, during recent years, improvement in survival has been achieved since treatment for patients with mesothelioma has improved with better palliative care, systemic medical treatment, surgery and improved diagnostics methods. The present review aims at describing available data from randomized trials considering systemic medical treatment for this patient category.*

Malignant pleural mesothelioma (MPM) is a rare malignancy mainly localized to the pleura. It is an aggressive tumor with poor prognosis. Malignant mesothelioma grows highly invasive into surrounding tissue although it has a low tendency to metastasize. The median overall survival (OS) of locally advanced or metastatic disease without treatment is 4-13 months (1, 2). Multimodality treatment, including chemotherapy, surgery and radiation therapy, is an option only for a small subset of patients and systemic treatment is the main therapeutic option for most patients. In recent years, prognosis for patients with mesothelioma has improved with better palliative care, systemic medical treatment, surgery and improved diagnostics methods. The present review aims at describing available randomized trials considering systemic medical treatment for this patient category.

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## Materials and Methods

We searched for randomized studies between different systemic medical treatments or between systemic medical treatments and best supportive care (BSC). We excluded studies concerning surgery and/or radiotherapy. We also excluded all non-randomized studies not written in English and studies where the majority of the patients did not suffer from mesothelioma.

Studies were identified through a systematic search of Medline and www.clinicaltrials.gov until October 2014. In addition, all guidelines and review articles published since 2006 were systematically searched in their references for further studies.

## Results

We found 12 randomized studies of mesothelioma that met our selection criteria; 10 studies on chemotherapy-naive patients, which included between 16 and 448 patients, and two second-line studies, which included 222-243 patients (Table I). We also found four abstracts containing unpublished randomized studies of medical mesothelioma treatment (Table II). In the studies concerning first-line treatment, three were randomized phase-III studies and seven were randomized phase-II studies. The studies concerning second-line treatment were randomized phase-III studies. Only one of the first-line studies and the two second-line studies compared medical treatment *versus* BSC.

Most studies allowed patients with performance status (PS) 0-2 (alternatively Karnofsky score 70 or more) to participate but in all studies there were rather few patients included with PS 2 or Karnofsky score 70. The criteria to assess response

varied between the different studies, although most studies used the two radiographic measurement systems Response Evaluation Criteria In Solid Tumors (RECIST), or modified RECIST. Only three out of the twelve studies have reported measurement of quality of life (QoL), although all but one had reported adverse reactions.

*First-line treatment*. The few randomized studies in the 80s and 90s were small and underpowered and did not present any significant conclusions. Sörensen *et al*. (3) randomized 30 patients to either doxorubicin or cyclophosphamide. No objective response in either arm was observed. Cantwell *et al*. (4) randomized 16 patients to compare carboplatin to a new platinum analogue (JM9) with no significant difference between arms in objective response. Samson *et al*. (5) evaluated 76 patients randomized to cyclophosphamide, imidazol carboxamide and adriamycin or cyclophosphamide and adriamycin. Response rate (RR) (13 % *versus* 11%), time to progressive disease (TTPD) (2.1 months *versus* 3.2 months) and overall survival (OS) (5.5 months *versus* 6.7 months) showed no significant difference between arms. Chahinian *et al*. (6) evaluated 70 patients randomized to cisplatin and mitomycin or cisplatin and doxorubicin. The RR was greater (26% *versus* 14%) for cisplatin and mitomycin but there was no significant difference between median time to treatment failure (3.6 months *versus* 4.8 months) and overall median survival (7.7 months *versus* 8.8 months).

In 2003, Vogelzang *et al*. (7) published a study which evaluated 448 patients randomized to either cisplatin and pemetrexed or to cisplatin alone (EMPHACIS trial). The median OS in the pemetrexed/cisplatin arm was 12.1 months *versus* 9.3 months in the control arm ($p$=0.02). The median time to progression was significantly longer in the pemetrexed/cisplatin arm (5.7 months *versus* 3.9 months; $p$=0.001). RR was 41.3% in the pemetrexed/cisplatin arm *versus* 16.7% in the cisplatin arm ($p$<0.0001). After 117 patients had been enrolled, the trial design was modified to let patients in the pemetrexed arm receive folic acid and vitamin B12 to reduce toxicity. Differences in survival were most striking in patients who received supplementation with folic acid and vitamin B12 (13.2 months *versus* 9.4 months). Out of 574 patients who signed an informed consent, only 456 were randomized. The reasons to the disappearance of 118 patients between consent and randomization is unclear. There is no report of QoL in the study but the Lung Cancer symptom Scale was used and data were presented at the American Society of Clinical Oncology meeting 2002 (8, 9). Dyspnea and pain was significantly improved for patients in the pemetrexed arm.

In a phase-III trial, Van Meerbeek *et al*. (10) randomized 250 patients to cisplatin and ralitrexed or to cisplatin alone. Median survival in the cisplatin/raltitrexed arm was 11.4 months *versus* 8.8 months in the cisplatin arm ($p$=0.048). RR (24% *versus* 14%, $p$=0.056) and progression-free survival (PFS) (5.3 months *versus* 4.0 months; $p$=0.058) was better for the cisplatin/raltitrexed arm but not statistically significant. No difference in QoL was observed on any of the scales.

Muers *et al*. (11) evaluated 409 patients randomized to active symptom control (ASC) only or ASC plus mitomycin, vinblastine and low dose cisplatin (50 mg/m$^2$) (MVP) or ASC plus vinorelbine. The patients were enrolled between 2001 and 2006 and, according to the study plan, a total of 840 patients were needed (280 in each group). Because of slow accrual the study design was altered in 2004 and both chemotherapy arms were combined for analysis. The RR was not systematically formally assessed and the clinicians were asked whether, in their opinion, the tumor had improved. By that measurement, 14% of the ASC patients had improved, 29% of the MVP patients had improved and 31% of the vinorelbine patients had improved 15 weeks after randomization. No significant survival benefit was seen between the overall chemotherapy arms and the ASC arm. Median survival was 7.6 months in the ASC arm and 9.5 months in the vinorelbine arm and exploratory analyses suggested a survival advantage for vinorelbine compared to ASC, with a 2-month survival benefit (hazard ratio (HR)=0.80; (0.63-1.02); $p$=0.08), although this benefit was not seen in the MVP arm. There was no significant benefit in QoL between the arms.

Kindler *et al*. (12) evaluated 108 patients randomized to either cisplatin/gemcitabine and bevacizumab or cisplatin/gemcitabine and placebo. The median PFS was 6.9 months for the bevacizumab arm and 6.0 months for the placebo arm. Median overall survival time was 15.6 and 14.7 months in the bevacizumab and placebo arms, respectively ($p$=0.91), and bevacizumab could not significantly improve OS.

Habib *et al*. (13) randomized 40 patients to compare cisplatin/gemcitabine to carboplatin/pemetrexed. There was no significant difference in OS between arms but RR was superior in the carboplatin/pemetrexed arm ($p$=0.041).

Krug *et al*. (14) evaluated 63 patients randomized to cisplatin/pemetrexed with or without CBP501. CBP501 is a synthetic dodecapeptide, which increases cisplatin influx into tumor cells. There was no significant benefit in RR or OS between the arms. Median OS was 13.3 months in the CBP501 arm and 12.8 months in the placebo arm.

In an unpublished study, Millenson *et al*. (15) evaluated 29 patients randomized to pemetrexed plus carboplatin or pemetrexed and gemcitabine. In the pemetrexed/carboplatine arm, median OS was 13 months (95% confidence interval (CI)=5.6-21.9 months) and RR 18.8%, while, in the pemetrexed/gemcitabine arm, the median OS was 6 months (95% CI=3.9-14.0 months) and RR 0%; the authors concluded that there is no evidence to support further investigation of the combination pemetrexed/gemcitabine in the first-line treatment of MPM.

In another unpublished study, Szlosarek *et al*. (16) screened 214 patients with MPM, approximately half of whom were chemotherapy-naive and half of whom were previously treated

with platinum-based combination chemotherapy. Out of these, 68 patients had tumors with negative or low argininosuccinate synthase 1 (ASS1) expression by immunohistochemistry. The 68 patients were randomized (2:1) to either the arginine-lowering agent pegylated arginine deiminase (ADI-PEG20) or to best supportive care (BSC). Mean OS was 12.8 months for patients assigned to BSC and 14.5 months for those who were also given ADI-PEG 20 ($p$=0.53). Median PFS improved from 1.9 months with BSC to 3.2 months with the addition of ADI-PEG 20 (HR=0.51; $p$=0.012).

*Second-line treatment*. Jassem *et al*. (17) enrolled 243 patients randomized to either pemetrexed or BSC. The patients had relapsed after first-line chemotherapy (excluding pemetrexed). Median OS time was not significantly different between arms, 8.4 months for pemetrexed and 9.7 months for BSC. Partial response was achieved in 18.7% and 1.7% in the pemetrexed and BSC arms, respectively. Pemetrexed significantly increased the median PFS (3.6 months *vs*. 1.5 months). Use of post-discontinuation chemotherapy was significantly greater among BSC patients compared to pemetrexed patients (51.7% *vs*. 28.5%, respectively). There was no statistically significant difference between arms in QoL.

Buikhusen *et al*. (18) randomized 222 patients to thalidomide or active supporting care (ASC). The patients had previously received a minimum of four cycles of first-line treatment containing at least pemetrexed. There was no significant difference in PFS or OS between arms (OS=10.6 months for thalidomide and 12.9 months for ASC, respectively). No analysis of QoL was reported.

Reck *et al*. (19) randomized 413 patients in an unpublished study to doxorubicin with or without ranpimase (Onconase). One chemotherapy line prior to therapy was permitted. In the intent-to-treat population, there was no significant advantage in survival, while, in a pre-planned sub-group analysis, including 130 pre-treated patients, a significant advantage in survival in favor of the doxorubicine/ranpimase arm was found (10.5 months *vs*. 9.0 months).

In the so far largest randomized but unpublished study, Krug *et al*. (20) randomized 661 patients to either vorinostat or placebo. The patients had previously progressed after 1-2 systemic therapies, including pemetrexed and either cisplatin or carboplatin. There was no significant difference in median OS between the vorinostat and placebo arms (30.7 weeks *vs*. 27.1 weeks). Median PFS was slightly better in the vorinostat arm (6.3 *vs*. 6.1 weeks; $p$<0.001). There was no difference between arms in RR.

## Discussion

Malignant pleural mesothelioma (MPM) is a rare malignancy that is mainly localized to the pleura and, despite being a highly aggressive tumor entity, survival rates has improved to 9-17 months during recent years (7, 21-23). Through large phase-III studies reported in the mid-2000s, a new standard for the frontline chemotherapy for MPM was established, a combination therapy of a platinum and an antifolate. However, due to the relative rarity of this tumor, difficulties in developing novel therapeutic strategies that must be validated in well-powered randomized trials has been an issue.

The background for the development of this malignancy was linked to asbestos in 1965. The development of mesothelioma and most new cases of mesothelioma are considered to be caused by asbestos with a latency period of around 30-40 years (24). The incidence of MPM is significantly higher in men, possibly because of occupational asbestosis exposure (25). The World Health Organization (WHO) has recognized that asbestos is one of the most important occupational carcinogens and that the burden of asbestos-related disease is rising. Consequently, WHO has declared that asbestos-related diseases should be eliminated throughout the world (26). Asbestos have been banned in most countries the last decades, in Sweden between 1976-1982, in the European Union between 1999-2005 and in the USA from 1989 but reports of an increase in the incidence of mesothelioma have been published in a wide range of countries worldwide(27-31). Globally, there is still a large use of asbestos and a long way to go to eliminate asbestos-related diseases throughout the world.

There are several ways to assess clinical benefit by treatment; RR, disease control rate (CDR), PFS and OS. OS has been the primary end-point in contemporary randomized trials (32). The unique growth pattern of MPM makes it difficult to assess tumor response to treatment. Different criteria have been used for tumor assessment in mesothelioma; however, there is variability between these criteria. Both the objective RRe and PFS have been used as surrogates for efficacy in older studies (33). In MPM studies, there are two radiographic measurement systems that are employed using thoracic computed tomography (CT) scans: RECIST and modified RECIST (34, 35). Modified RECIST measures the pleural rind or tumor thickness in a perpendicular manner to the chest wall in two positions at three separate levels on a chest CT scan (36). The sum of these six measurements is used to define response using the RECIST criteria. Because of the difficulties to assess response in mesothelioma, there is a need to be extra cautious when comparing non-randomized mesothelioma studies.

In first-line treatment of malignant mesothelioma, there is only one study comparing medical systemic treatment *versus* BSC and that study failed to demonstrate a statistically significant improvement in OS or QoL. Thus, there is no evidence that medical treatment is superior to BSC in terms of OS and QoL. However, provided that single-agent cisplatin does not reduce survival in the patient population, which seems very unlikely, there is significant evidence that the combination therapy with cisplatin and an antifolate

Table I. *Randomized trials of systemic medically treated malignant mesothelioma.*

| Authors | No of patients | Regime | Histology Epi/Sar/Mixed/ Other % | PS 2 (%) /KS | Median age | ORR (%) | PFS/ Time to PD | Overall Survival | Hematox, Grade 3/4 (%) | Dominating non-hematox Grad 3/4 (%) | QoL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Krug *et al.*, 2014 (14) | 63 | Pem 500 mg/m$^2$+Cis 75 mg/m$^2$+ CBP50 125 mg/m$^2$ | 75/15/10/0 | PS2=3% | 64 years | 31% | 5.1 months | 13.3 months | Anemia 8% Leukopenia 6% | Fatigue 18% Dehydration10% | Not reported |
| | | *vs.* Pem 500 mg/m$^2$+Cis 75 mg/m$^2$ | 70/22/9/0 | PS2=0% | 66 years | 10% | 3.4 months | 12.8 months | Anemia 4% Leukopenia 4% | Fatigue 13% Dehydration17% | |
| Habib *et al.*, 2013 (13) | 40 | Pem 500 mg/m$^2$+ Carbo AUC 5mg/mL 7min, bothq3wk | 79/0/21/0 | PS2=11% | 52 years | 79% | Not reported | Cumulative survival after 18 months was 57.8% *vs.* 41% | Leukopenia 10% Thrombocytopenia 5% | None | Not reported |
| | | *vs.* Cis 80 mg/m$^2$+ Gem 1000 mg/m$^2$ (d.1,8,15), bothq4wk | 62/0/38/0 | PS2=24% | 62 years | 48% | | | Leukopenia 38% Thrombocytopenia 14% | Nausea 33% Hearingloss 5% | |
| Kindler *et al.*, 2012 (12) | 108 | Cis 75 mg/m$^2$+ Gem 1250 mg/m$^2$ (d.1+8)+ Bev 15 mg/kgq3wk | 74/0/0/26 | PS2=0% | 62 years | 24% | 6.9 months | 15.6 months | Neutropenia 41% Thrombocytopenia 38% | Hypertension23% Venous thrombosis 17% | Not reported |
| | | *vs.* Cis 75 mg/m$^2$+Gem 1250 mg/m$^2$ | 67/0/0/33 | PS2=0% | 65 years | 21% | 6.0 months | 14.7 months | Neutropenia 40% Thrombocytopenia 25% | Hypertension 9% Venous thrombosis 9% | |
| Muers *et al.*, 2008 (11) | 409 | Active Symptom Control (ASC) | 74/0/8/18 | PS2=13% | 65 years | 14% | 5.1 months | 7.6 months | Not reported | Dyspnea 34% Chest pain27% | No significant difference between arms |
| | | *vs.* ASC+MVP(6/6/50 mg/m$^2$ q3W x4cycle) Or | 74/0/10/16 | PS2=14% | 65 years | 29% | 5.1 months | NS from ASC 9.5 months | Not reported | Dyspnea 31% Lethargy 27% | |
| | | ASC+vinorelbin | 73/0/13/14 | PS2=15% | 65 years | 31% | 6.2 months | | Neutropenia 41% | Dyspnea 29% Lethargy24% | |
| Van Meerbeek *et al.*, 2005 (10) | 250 | Ral 3 mg/m$^2$+Cis 80 mg/m$^2$, bothd1 q3wk | 75/14/4/7 | PS2=13% | 58 years | 24% | 5.3 months | 11.4 months | Anemia (3%) Neutropenia 16% | Nausea (14%), Fatigue (12%) | No significant difference between arms |
| | | *vs.* Cis 80 mg/m$^2$ d1q3wk | 60/24/6/1 | | 59 years | 14% | 4.0 months | 8.8 months | Anemia (2%) Neutropenia (8%) | Nausea (10%), Fatigue (6%) | |
| Vogelzang *et al.*, 2003 (7) | 448 | Pem 500 mg/m$^2$+Cis 75 mg/m$^2$, bothd1 q3wk | 69/8/16/7 | KS<80:37% | 61 years | 41% | 5.7 months | 12.1 months | Thrombocytopenenia 6% | Nausea (15%), Fatigue (10%) | Not reported (Less pain and dyspnea in the Pem+Cis arm) |
| | | *vs.* Cis 75 mg/m$^2$ d1q3wk | 69/11/16/4 | KS<80:31% | 60 years | 17% | 3.9 months | 9.3 months | Neutropenia 28% Neutropenia 2% | Nausea (6%), Fatigue (9%) | |

Table I. *Continued*

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| Authors | No of patients | Regime | Histology Epi/Sar/Mixed/ Other % | PS 2 (%) /KS | Median age | ORR (%) | PFS/ Time to PD | Overall survival | Hematox, Grade 3/4 (%) | Dominating non-hematox Grad 3/4 (%) | QoL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chahinian *et al*., 1993 (6) | 70 | Cis 75 mg/m$^2$+ Mit 10 mg/m$^2$q4wk | 69/0/0/31 | PS2=26% | 37% >60 years | 26% | 3.6 months | 7.7 months | Thrombocytopenia 43% | Nausea 23% Weight Loss26% | Not reported |
| | | *vs.* | | | | *vs.* | *vs.* | *vs.* | | | |
| | | Cis 75mg/m$^2$+ Dx 60 mg/m$^2$q4wk | 69/0/0/31 | PS2=14% | 62% >60 years | 14% | 4.8 months | 8.8 months | Anemia 29% Leukopenia 46% Anemia 40% | Nausea 26% Weight Loss20% | |
| Samson *et al*., 1987 (5) | 76 | Cy 500 mg/m$^2$+ Dx 50 mg/m$^2$d1q3wk | 45/17/19/19 | PS2=16% | 56 years | 11% | 3.2 months | 6.7 months | Leukopenia 38% | Not reported | Not reported |
| | | *vs.* | | | | | | | | | |
| | | Cy+Dxasabove+ IC 250mg/m$^2$d1-5 | 52/8/12/28 | PS2=22% | 62 years | 13% | 2.1 months | 5.5 months | Leukopenia 46% | | |
| Cantwell *et al*., 1986 (4) | 16 | Carbo: 400 mg/m$^2$monthly | Not reported | Median PS=2 | 58 years | 22% | Not reported | Not reported | None | Nausea 16% | Not reported |
| | | *vs.* | | | | | | | | | |
| | | JM9: 300 mg/m$^2$monthly | | Median PS=2 | 58 years | 0% | | | Anemia 6% | Nausea 31% | |
| Sorensen *et al*., 1985 (3) | 30 | Dx 60 mg/m$^2$q3wk | Overall 28/22/50/0 | PS2=0% | Not reported | 0% resp. 0% | Not reported | Not reported | Not reported | Not reported | Not reported |
| | | *vs.* | | | | | | | | | |
| | | Cy 1500 mg/m$^2$q3wk All pts received the n alternate drug at disease progressio | | | | | | | | | |
| Second-line treatment | | | | | | | | | | | |
| Buikhuisen *et al*., 2013 (18) | 222 | Thalid 200 mg daily+BSC | 86/0/0/14 | PS2=4% | 64 years | Not reported | 3.6 months | 10.6 months | Neutropenia 13% Thrombocytopenia 6% | Fatigue 4% Thrombembolism. 3% | Not reported |
| | | *vs.* | | | | | | | | | |
| | | BSC | 85/0/0/15 | PS2=2% | 64 years | | 3.5 months | 12.9 months | Neutropenia 9% Thrombocytopenia 10% | Cardiac event 3% Fatigue 1% | |
| Jassem *et al*., 2008 (17) | 243 | Pem 500 mg/m$^2$q3wk+BSC | 73/0/0/27 | KS50-80:50% | 60 years | 19% | 3.6 months | 8.4 months | Anemia 6% Neutropenia 7% | Dyspnea 17% Fatigue 16% | No significant difference between arms |
| | | *vs.* | | | | | | | *vs.* | *vs.* | |
| | | BSC | 72/0/0/28 | KS50-80:43% | 61 years | 2% | 1.5 months Fatigue 11% | 9.7 months | 0% | Dyspnea 16% | |

ASC, Active symptom control; Bev, bevacizumab; BSC, best supprtive care; Carbo, carboplatin; Cis, cisplatin; Cy, cyclophosphamide; Dx, doxorubicin; Epi, epithelial; Gem, gemcitabin , Hematox, haematological toxicty; IS, imidazole carboxamide; JM9, platinum analogue; KS, Karnofsky score; Mit, mitomycin; MVP, mitomycin+vinblastine+cisplatin; NS, non significant; ORR, overall response rate; PFS, progression-free survival; PD, progressive disease; Pem, pemetrexed; PS, performance status; pts, patients; q, every; QoL, quality of life; Ral, raltitrexed; Sar, sarcomatous; Thalid, thalidomide; *vs.*, *versus*.

Table II. *Randomized abstracts of unpublished trials of systemic medically treated malignant mesothelioma.*

| Authors | No of patients | Regime | Histology Epi/Sar/Mixed/ Other % | PS 2 (%) /KS | Median age | ORR (%) | PFS/ Time to PD | Overall survival | Hematox, Grade 3/4 (%) | Dominating non-hematox Grad 3/4 (%) | QoL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Krug *et al.*, 2011 (13) | 660 | BSC+vorinostat 3dq3wk | 83/0/0/17 | Median KS= 90% | 64 years resp. | No significant | 6.3 weeks | 30.7 weeks | No significant | No significant | Not reported |
| | | *vs.* | | | | | | | | | |
| | | BSC | 81/0/0/19 | Median KS= 85% | 65 years | diff between arms | 6.1 weeks | 27.1 weeks | diff between arms | diff between arms | |
| Millenson *et al.*, 2010 (15) | 29 | Pem 500mg/m$^2$+ Carbo AUC5 bothq3wk | Not reported | PS2=0% | 71 years | 19% | 4.1 months | 13.0 months | Neutropenia 19% Anemia 19% | Fatigue 13% | Not reported |
| | | *vs.* | | | | | | | Neutropenia 77% | Fatigue 23% | |
| | | Pem 500mg/m$^2$+ Gem 1000mg/m$^2$ (d.1,8), bothq3wk | | PS2=0% | | 0% | 3.3 months | 6.0 months | Anemia 15% | | |
| Szlosarek *et al.*, 2014 (16) | 68 | ADI-PEG20 (36.8mg/m$^2$weekly)+BSC | Not reported | PS2=0% | Not reported | 0% | 3.3 months | 13.0 months | Neutropenia 11% | Fatigue 7% | Not reported |
| | | *vs.* | | | | | | | Thrombocytopenia | Anaphylactoid | |
| | | BSC | | PS2=0% | | 0% | 2.0 months | 10.6 months | 5% | reactions 7% | |
| Reck *et al.*, 2009 (19) | 413 | Dx60 mg/m$^2$q3wk+ Ran240-480µg/m$^2$weekly | Not reported | PS2=0% | 62 years | Not reported | Not reported | 11.1 months | Not reported | No significant diff | Not reported |
| | | *vs.* | | | | | | | | | |
| | | Dx60mg/m$^2$q3wk | | PS2=0% | 62 years | | | 10.7months | | between arms | |

ADI-PEG20, Arginine-lowering agent pegylated arginine deiminase; BSC, best supprtive care; Carbo, carboplatin; Dx, doxorubicin; Epi, epithelial; Gem, gemcitabin; Hematox, haematological toxicty; KS, Karnofsky score; Mit, mitomycin; NS, non-significant; ORR, overall response rate; PFS, progression free survival; PD, progressive disease; Pem, pemetrexed; PS, performance status; pts, patients; q, every; QoL, quality of life; Ran, ranpimase; Sar, sarcomatous; *vs.*, *versus*.

(pemetrexed or raltitrexed) will extend OS. In previous non-randomized studies, single-agent cisplatin appeared as the most active and effective single-agent chemotherapy treatment compared to other single-agent treatments (37). The improvement in OS in the combination treatment arms in the EMPHACIS study was about the same as in the cisplatin/raltitrexed study (2.8 months *vs*. 2.6 months) but in the EMPHACIS study and not in the cisplatin/raltitrexed study RR, PFS and QoL -in terms of dyspnea and pain- were significantly improved. The differences between cisplatin/pemetrexed and cisplatin/raltitrexed could, perhaps, be due to differences in power between the studies; however, since 2003, the combination treatment with cisplatin and pemetrexed are in many countries used as standard chemotherapy treatment of malignant mesothelioma.

The combination carboplatin/pemetrexed is sometimes substituted for cisplatin/pemetrexed to reduce toxicity. There exists no randomized evidence to support this substitute but there exist non-randomized studies and analyses supporting that this may be an alternative regimen if cisplatin toxicity is a problem (38-41). In Habib and Fahmy's study (13), there was a significant better RR in favor of carboplatin/pemetrexed *versus* cisplatin/gemcitabine.

Kindler's *et al*. study (12) of cisplatin/gemcitabine with or without bevacizumab is interesting because the median OS was approximately 15 months on both treatment arms, a result exceeding the OS seen with cisplatin/pemetrexed. This may reflect differences in patient selection, treatment experience and impact of subsequent therapies between the studies. Patients under anti-coagulant therapy were excluded from Kindler's study, which may have introduced a selection bias. Due to high cost, pemetrexed is not available to some patients in countries with limited health care resources and there is an ongoing randomized phase II study based in Slovenia comparing cisplatin/pemetrexed *versus* cisplatin/gemcitabine.

There were rather few patients with performance status 2, alternatively Karnofsky score 70 or less, in the randomized studies and whether or not these patients benefit from medical systemic treatment is unclear.

In second-line treatment of malignant mesothelioma, there is no evidence that systemic treatment is superior to BSC in terms of OS or QoL. In the Jassem *et al*. study (17), pemetrexed significantly increased PFS but did not improve OS or QoL. Thalidomide, ranpimase/doxorubicin and vorinostat have not shown any significantly positive effects *versus* BSC. There is no current standard-of-care for second-line treatment of mesothelioma. The most commonly used second-line treatments include single-agent pemetrexed, single-agent vinorelbine or single-agent gemcitabine (42-46), but there exists insufficient evidence to recommend second-line treatment as standard treatment. Treatment of mesothelioma in the second-line setting outside clinical studies should still be an issue of debate.

In conclusion, there exists significant evidence to support treatment of malignant mesothelioma among patients with good performance status (PS 0-1) with the combination of cisplatin and an antifolate as first-line treatment. There is still a lack of high-quality studies on the role of medical systemic treatment of malignant mesothelioma and further studies are required. Many novel agents are being investigated and further progress is eagerly awaited.

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