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Systemic therapy in malignant mesothelioma: treat it or leave it

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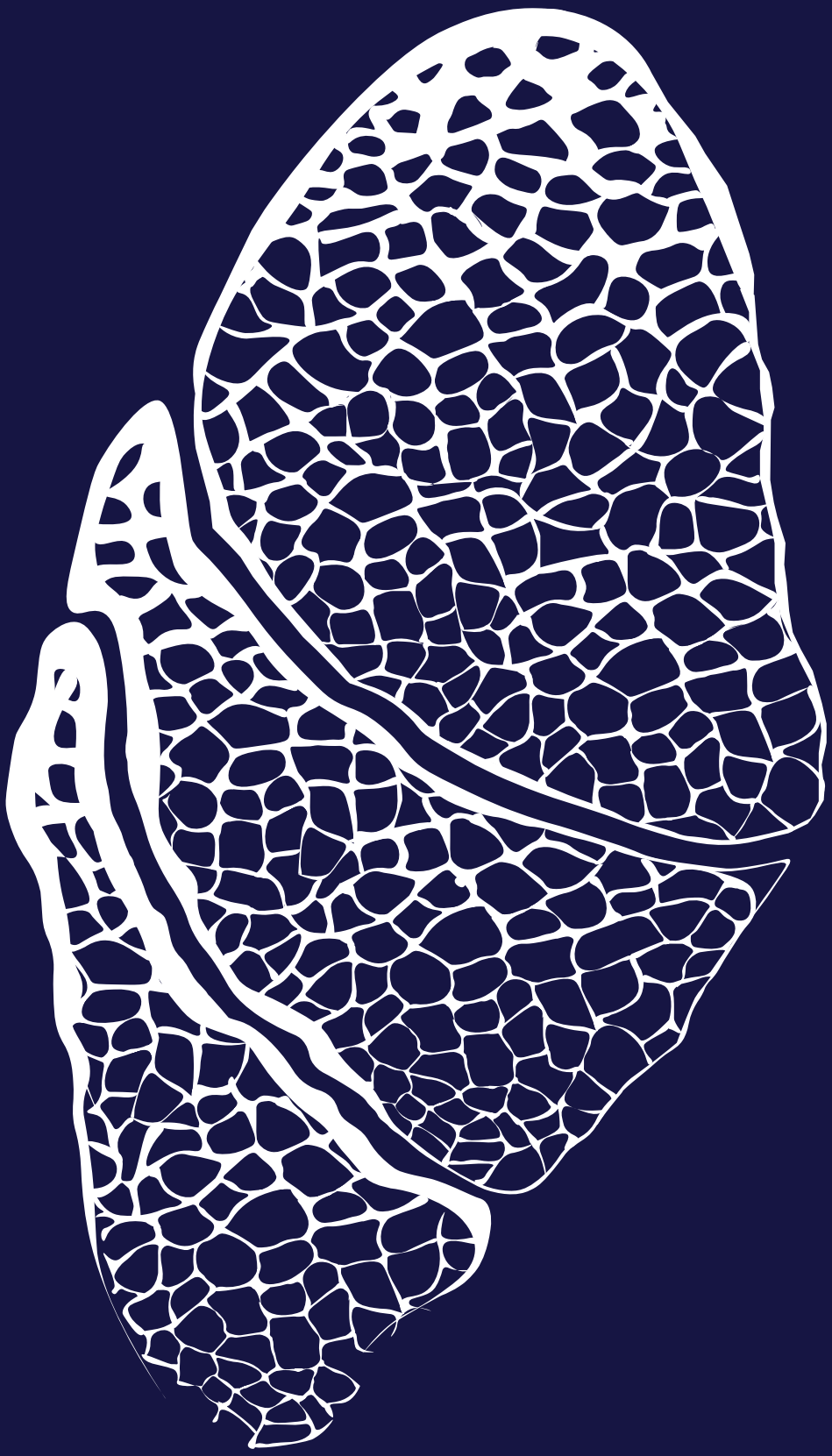
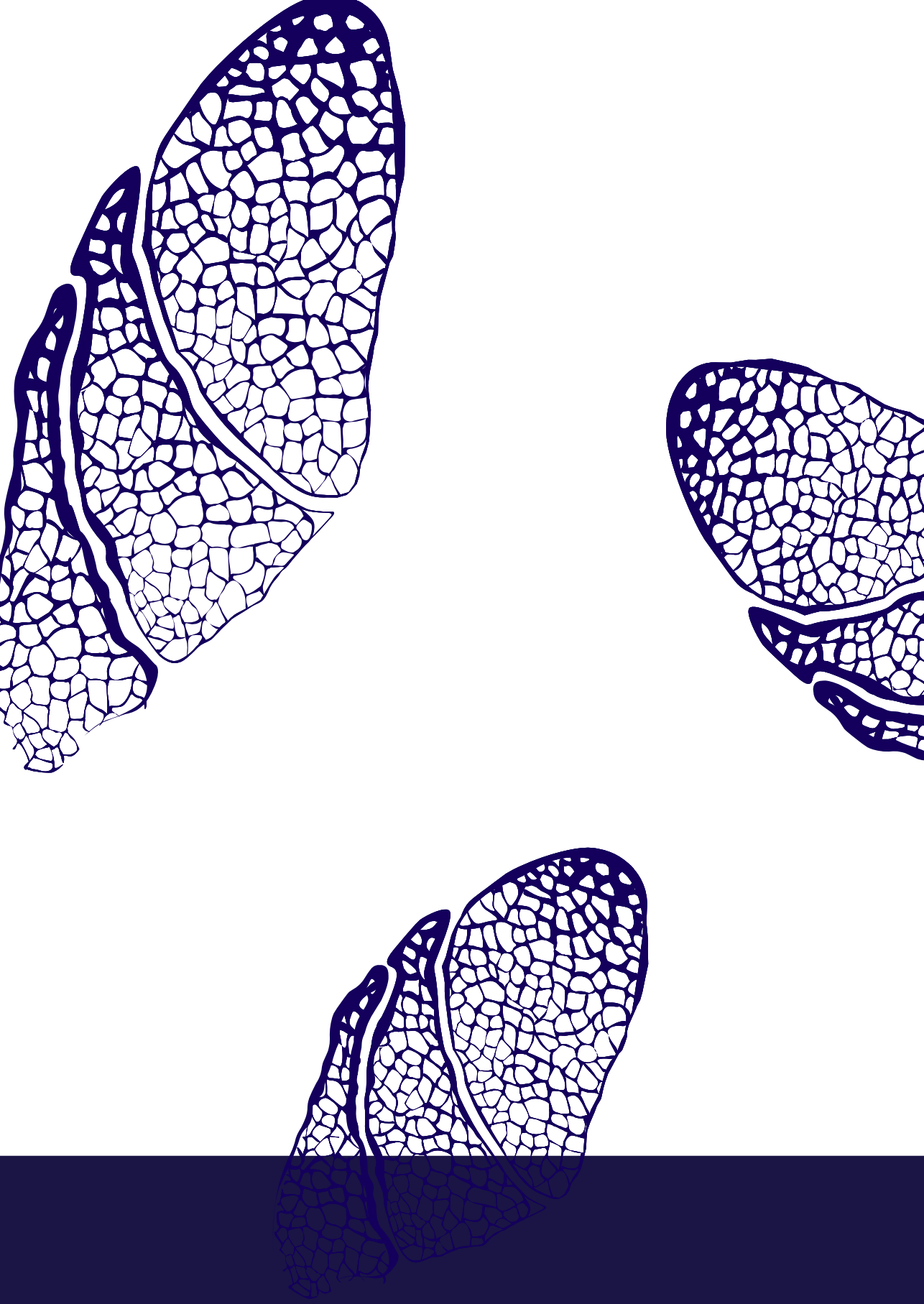


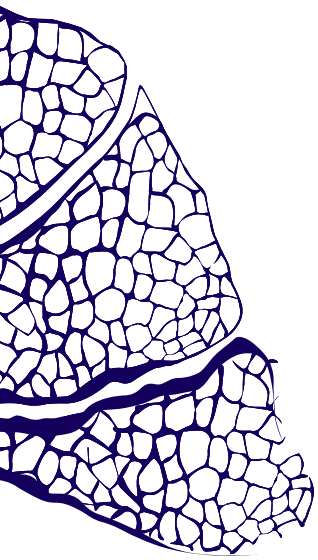
PART 1

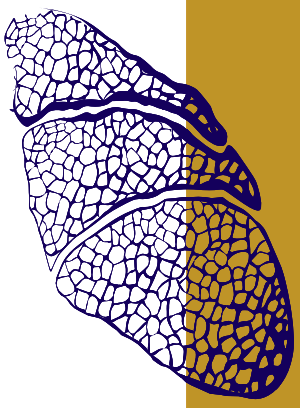
Chemotherapy in Malignant Mesothelioma



Chapter 2

Current chemotherapy strategies in malignant pleural mesothelioma





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REVIEW.

ABSTRACT

Malignant pleural mesothelioma (MPM) is an aggressive malignancy with a 5-year survival rate of ~10%. Since most patients present with irresectable disease, the vast majority is treated with chemotherapy. The only registered therapy for MPM is platinum-pemetrexed doublet therapy, although only up to half of patients have clinical benefit from this palliative treatment. Of the anti-angiogenesis agents, only bevacizumab and nintedanib have shown activity with platinum-pemetrexed doublet therapy. Other anti-angiogenesis agents like thalidomide did not prolong (progression free) survival or response rate. Eventually, all patients will get a recurrence and no active second line therapy has been identified to date. The clinical benefit of (switch) maintenance therapy after first line treatment and combination strategies
of different chemotherapies with angiogenesis inhibitors are currently under investigation. The major challenges are finding optimal treatment combinations and to select the adequate treatment for an individual patient. This review focusses on the current standard of chemotherapy and new systemic therapy strategies under investigation.

KEYWORDS Chemotherapy; Clinical Trials; Malignant Mesothelioma

INTRODUCTION

Chemotherapy is the mainstay of treatment of malignant pleural mesothelioma (MPM). The European Society for Medical Oncology (ESMO) guidelines, the National Comprehensive Cancer Network (NCCN) guidelines and the European Respiratory Society (ERS) guidelines indicate chemotherapy as an option for patients with 'irresectable MPM' who are not fit for major surgery[1-3]. Only a minority of patients is fit enough to be a surgical candidate and the indication for surgery has become stricter in the last years.

Use of targeted therapy based on genetic profiling has been successful in other solid tumor types, targeting activating oncogenes. In MPM this approach has failed to improve clinical benefit in phase II studies. This is related to the fact that MPM is mostly driven by loss of tumor suppression genes like CDKN2A, NF2 and BAP1, rather than activation of oncogenes[4]. Also, MPM is a heterogeneous tumor type (with three different subtypes) which makes it more challenging to develop effective therapies. Immunotherapy, targeting immune checkpoints (like PD-1 or its ligand PD-L1) has become standard of care in numerous solid tumors like non-small cell lung cancer (NSCLC) [5]. The first studies with immunotherapy in second and third- line mesothelioma patients seem promising, but their value in the first line setting has yet not been defined[6-9]. Therefore, chemotherapy remains a prominent treatment option in MPM.

In this review, the current available literature (*see Table 1*) and ongoing studies (*see Table 2*) with chemotherapy in the palliative setting and combination strategies in MPM are discussed. The use of chemotherapy as part of multimodality treatment and targeted therapy for MPM is covered in companion papers in this issue.

FIRST LINE CHEMOTHERAPY

For more than fifteen years, the standard first line treatment has been cisplatin- pemetrexed and it is currently the only regime approved by the Food and Drug Administration (FDA) for MPM. In the study by Vogelzang et al., 448 treatment naïve patients were 1:1 randomized to cisplatin monotherapy or cisplatin-pemetrexed doublet therapy, in which overall survival (OS) was the primary endpoint. Median OS in the cisplatin-pemetrexed arm was 12.1 vs. 9.3 months in the control arm (P=0.020, two-sided log-rank test). An updated analysis presented at the World Conference on Lung Cancer (WCLC) 2005 revealed a median OS for cisplatin alone of 9.0 and 12.8 months for the combination arm. Patients in the combination arm had a lower hazard ratio for death (0.77) compared with those in the control arm. The median time to progression was significantly longer in the cisplatin-pemetrexed arm; 5.7 vs. 3.9 months (P=0.001) and the response rates were higher (41.3%) in the cisplatin-pemetrexed arm versus 16.7% in the control arm (P<0.0001). The most common hematological toxicity in the cisplatin- pemetrexed combination arm was neutropenia (27.9% in the combination arm vs. 2.3% in the control arm). The most common non-hematological toxicities, in both groups, were nausea, vomiting and fatigue within around 90% of patients experiencing grade 3 toxicity. After 117 patients were enrolled, folic acid and vitamin B12 were added to reduce toxicity, resulting in a significant reduction in toxicities in the cisplatin-pemetrexed arm21. More recently, the French Cooperative Thoracic Intergroup performed a phase III study, in which patients were 1:1 randomized to either cisplatin-pemetrexed or cisplatin-pemetrexed + bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor. The progression free survival (PFS) and OS were longer (7.3 and 16.1 months) in the cisplatin-pemetrexed arm

compared to the study of Vogelzang. This improvement might be related to: use of rechallenge of pemetrexed, stricter inclusion criteria (like excluding patients with cardiovascular comorbidities) and the use of thoracoscopy as the diagnostic procedure which led to 90% efficient pleurodesis procedures (34). Replacement of cisplatin by carboplatin did not influence the PFS in patients with MPM, including similar 1-year survival rates (63.1% vs. 64.0%) and time to progression (7 vs. 6.9 months)[38].

The additional value of adding a (multitargeted) antifolate to cisplatin monotherapy was confirmed by a phase III study in 250 treatment naïve patients with MPM, comparing cisplatin vs cisplatin-raltitrexed. The combination therapy was superior to single agent therapy with a median survival of 11.4 months in de cisplatin-raltitrexed arm vs. 8.8 months for cisplatin alone, and the 1-year survival was 46% vs. 40% (P=0.048). There was a trend for a higher response rate in the combination arm (24% vs. 14%, P=0.06). Again, more patients experienced hematologic adverse events in the combination arm (neutropenia 16% vs. 8% in the combination and single agent arm respectively). Toxicity was the reason for holding back treatment in 23% of patients in the cisplatin-only arm and in 30% of patients in the combined arm. No toxic deaths were reported [25]. The health-related quality of life was measured, and despite the toxicity of the treatment the quality of life was not affected and was equal in both treatment arms. Also, in both arms the dyspnea improved [39]. Unfortunately, raltitrexed is not registered in many European countries for this indication.

Gemcitabine combined with a platinum compound, including cisplatin, carboplatin, and oxaliplatin has been tested in several phase II studies (see Table 1)[17,23,24,27,31,40]. Response rates for these combinations have ranged from 12% to 50%, with acceptable levels of toxicity. However, it is generally accepted that mesothelioma patients should receive pemetrexed-based therapy in the first-line setting. Because gemcitabine is given on day 1 and 8 of a 3-week cycle and pemetrexed is given only on day 1 of a 3-week cycle, pemetrexed involves a lower frequency of hospital visits which benefits patients.

Despite the previous mentioned studies showing an improved (progression free) survival for combination strategies compared with single agent therapy, it was not compared with best supportive care (BSC). In the UK a study was conducted in the nineties to compare a BSC arm with two chemotherapy strategies, combining mitomycin, vinblastine, cisplatin and single-agent vinorelbine. Because of slow accrual, the two chemotherapy groups were combined. OS was compared as a primary outcome between both groups. This showed a trend towards better survival in the combination chemotherapy arms, even though chemotherapy schedules were used that are currently viewed as inferior[30].

Addition of angiogenesis inhibitors

Although platinum-pemetrexed are active agents in the first line treatment, only a minority of patients has clinical benefit. VEGF signaling is an important concept in mesothelioma cell pathophysiology[41]. The addition of anti-angiogenesis agents to chemotherapy has been tested in several clinical studies. A phase II study by Ceresoli in 76 chemo-naïve MPM patients, receiving carboplatin-pemetrexed plus bevacizumab resulted in a response rate of 34.2%, a PFS 6.9 months and an OS of 15.3 months[35]. The largest study was the phase III MAPS trial. The value of addition of maintenance bevacizumab, a VEGF antibody, was evaluated to first line cisplatin-pemetrexed therapy in 448 treatment naïve patients. PFS was significantly increased in the bevacizumab combination arm compared with patients who

Table 1. Phase II and III studies with chemotherapy in first line Malignant Mesothelioma patients.

Reference	Number of patients	Treatment	Study type	Response rate (%)	Median progression free survival (months)	Median overall survival (months)
Samson et all[10]	76	Cyclophosphamide + Doxoruxamide +/-Imidaz-ole carboxamide	Phase II	CIA 13% CA 11	CIA 2 CA 3	CIA 5 CA 6
Henss et all.[11]	19	Cisplatin+ Doxorubicine	Phase II	46	-	12
Ardizzoni et all.[12]	26	Cisplatin + Doxorubicine	Phase II	25	-	10
Solheim[13]	63	Methotrexate	Phase II	3	-	11
Chahinian et all.[14]	79	Cisplatin+Mitomycin or Doxorubicin	Phase II	26%	CM 3.6 CD 4.8	CM 7.7 CD 8.8
Hunt et all.[15]	17	Cisplatin + Methotrexate + Vinblastine	Phase II	53%	8	14
Middleton et all [16]	39	Cisplatin + Vinblastine + Mitocyn-C	Phase II	20	-	-
Byrne et all. [17]	21	Cisplatin + Gemcitabine	Phase II	47.6	6	9
Kindler [18]	20	Edatrexate or Edatrexate + leucovorin rescue	Phase II	E 25 EL 16	E 5.2 EL 3.4	E 9.6 EL 6.6
Nowak et all. [19]	53	Cisplatin + Gemcitabine	Phase II	33%	6.4	17.3
Skubitz [20]	15	Pegylated-liposomal doxorubicin	Phase II	7%	-	-
Vogelzang et all et al [21]	456	Cisplatin +/- pemetrexed	Phase III	CP 41.3 Cisplatin 16.7	CP 5.7 Cisplatin 3.9	CP 12.1 Cisplatin 9.3
Baas[22]	24	Raltitrexed	Phase II	20.8	-	7
Schutte et all [23]	25	Oxoplatin + Gemcitabine	Phase II	40	7	13
Favaretto et all [24]	50	Carboplatin+ Gemcit-abine	Phase II	52	9	15
Meerbeeck et all [25]	250	Cisplatin +/- raltitrexed	Phase III	RC 23.6 Cisplatin 13.6	RC 5.3 Cisplatin 4	RC 11.4 Cisplatin 8.8
Berghmans et all [26]	69	Cisplatin + Epicubicin	Phase II	19.0	-	13.3
Castagneto et all [27]	35	Cisplatin + gemcitabine	Phase II	26	8	13
Cersesoli et all [28]	102	Carboplatin+ pemetrexed	Phase II	19	6.5	12.7
Catagneto et all [29]	76	Carboplatin+ pemetrexed	Phase II	25	8	14
Muers et all [30]	409	BSC+ Mitomycin+ vin-blastine+ cisplatin¥ or BSC + Vinorelbine¥ or BSC	Phase III	Chemo+B-SC 12	BSC+ che-mo 5.6 BSC 5.1	BSC+ chemo 8.5 BSC 7.6
Janne et all [31]	108	Pemetrexed + Gemcit-abine*	Phase II	17	4.34-7.3	10.08-10.12
Kalmadi [32]	50	Cisplatin + Gemcitabine	Phase II	12	6	10
Kovac et all [33]	78	Cisplatin + Gemcitabine	Phase II	54	8.0	17.0
Kindler et all [34]	115	Gemcitabine + Cisplatin + bev. or placebo	Phase II	GC+ Bev. 24.5 GC+ Place-bo 21.8	GC+ Bev. 6.9 GC+ Place-bo 6.0	GC+ Bev. 15.6 GC+ Placebo 14.7
Ceresoli [35]	76	Cisplatin-pemetrexed + bevacizumab	Phase II	34.2%	6.9	15.3

Zalcman et all [36]	448	Cisplatin+ Pemetrexed +bevacizumab or placebo	Phase III	-	CP+ Bevacizumab 9.2 CP+ Placebo 7.3	CP+ Bevacizumab 18.8 Placebo 16.1
Grosso et al et all [37]	87	Cisplatin +Pemetrexed + Nintedanib or placebo	Phase II	CP+ Nin 26 CP+ Placebo 20	CP+ Nin 7.8 CP+ Placebo 5.3 months	CP+ Nin 18.3 CP+ Placebo 14.2

¥ Two cohort were combined do to slow accrual. * Two cohorts: Both gemcitabine day one, pemetrexed day on 1 or day 8 of the 21 day cycle. - Outcome not reported. Abbreviations: BSC; Best Supportive Care, CA; cyclophosphamide Adriamycin CIA; cyclophosphamide, Imidazole Carboxamide, Adriamycin, CM; Cisplatin Pemetrexed, E; Edatrexate, EL; Edatrexate leucovorin, GC; Gemcitabine Cisplatin, RC: Cisplatin Raltitrexed,

Table 2. Ongoing studies in malignant mesothelioma

Study drug	Clinical Trail title	Clinical trial number	Phase	Date open	Estimated enrolment	Estimated completion date	Status
Cisplatin-Pemetrexed + Nintedanib or placebo	Nintedanib (BIBF 1120) in Mesothelioma	NCT01907100	III	September 2013	458	October 2019	Active, not recruiting
Cisplatin-Pemetrexed Or Nivolumab- Ipilimumab	Study of Nivolumab Combined With Ipilimumab Versus Pemetrexed and Cisplatin or Carboplatin as First Line Therapy in Unresectable Pleural Mesothelioma Patients (CheckMate743)	NCT02899299	III	October 2016	600	September 2021	Recruiting
Cisplatin-Pemetrexed + adi-PEG 20 or placbo	Ph 2/3 Study in Subjects With MPM w/Low ASS 1 Expression to Assess ADI-PEG 20 With Pemetrexed and Cisplatin (ATOMIC)	NCT02709512	II/III	October 2016	386	June 2019	Recruiting
Pemetrexed or BSC	Pemetrexed Disodium/ Observation in Treating Patients W/ Malignant Pleural Mesothelioma w/ Out Progressive Disease After 1st Line Chemotherapy	NCT01085630	II	April 2010	68	July 2017	Active, not recruiting
Gemcitabine or BSC	Switch maintenance treatment with gemcitabine for patients with malignant mesothelioma who do not progress after 1st line therapy with a pemetrexed-platinum combination. A randomized open label phase II study.	-	II	March 2014	124	January 2019	Recruiting
Pembrolizumab or gemcitabine-inorelbine	PembROlizuMab Immunotherapy Versus Standard Chemotherapy for Advanced prE-treated Malignant Pleural Mesothelioma (PROMISE-meso)	NCT02991482	III	September 2017	142	December 2020	Recruiting
Vinorelbine or BSC	Vinorelbine in Mesothelioma (VIM)	NCT02139904	II	March 2016	200	March 2018	Recruiting

Abbreviations: BSC; Best Supportive Care

received cisplatin-pemetrexed alone [median 9.2 vs. 7.3 months; hazard ratio (HR) 0.61, 95% CI: 0.50–0.75]. Besides PFS, OS was also significantly increased with the combination (median 18.8 vs. 16.1 months; HR 0.77, 95% CI: 0.62–0.95). In the bevacizumab combination arm more grade 3 toxicity occurred, like hypertension (23% vs. 0%) and thrombotic events (6% vs. 1%) [36]. A longer PFS and OS were seen in the MAPS trial compared to the phase II study of Ceresoli. It is unlikely that this is related to cisplatin-carboplatin switching. The selection of patients and the single arm set up might be responsible.

Addition of bevacizumab to cisplatin-gemcitabine in patients with MPM resulted in a similar response rate of 24.5% in the bevacizumab arm and 21.8% in the placebo arm. The median PFS and OS did not improve in the bevacizumab arm compared with the placebo arm (PFS 6.9 vs. 6.0 months, OS 15.6 vs. 14.7 months). There were no statistically significant differences in the rates of grade 3 or greater toxicity between treatment groups. Venous thrombosis developed in 17% of patients treated with the active agent and 9% on placebo (P=0.26) [34]. It is still not clear why bevacizumab resulted in a survival benefit in combination with cisplatinum-pemetrexed and not with cisplatin-gemcitabine.

Nintedanib is a targeted therapy agent against i.e., the VEGF receptor. In the phase II LUME-Meso trial with chemo naïve patients with MPM, PFS was higher in the combination arm (cisplatin-pemetrexed-nintedanib median 9.4 months), compared to the cisplatin-pemetrexed-placebo arm median 5.7 months. Patients with a sarcomatoid type MPM were excluded in the trial. There was no survival benefit of nintedanib addition (30 vs. 32 months, P=0.319). There was an increased frequency of grade ≥3 toxicity linked neutropenia (43.2% vs. 12.2%), hypertension (9.1% vs. 2.4%) and diarrhea (6.8% vs. 0%) in the active agent arm. Three patients (6.8%) in the nintedanib arm and 7 patients (17.1%) in the placebo arm experienced AEs leading to permanent discontinuation of last study medication. No treatment related deaths were reported [37].

Both the LUME-Meso trial and the MAPS trial show an additional value of angiogenesis inhibition to platinum-pemetrexed. Despite the incoherent results of studies with the addition of angiogenesis inhibitors, the NCCN Panel now recommends adding bevacizumab to cisplatinum-pemetrexed as new first-line therapy option [1].

Addition of angiogenesis inhibitors

Up to 63% of the MPM cells lack the argininosuccinate synthase 1 (ASS1), resulting in dependency on systemic arginine. Without arginine, cells will undergo apoptosis. In 82 MPM patients low ASS1 expression was found most frequently in the sarcomatoid type (7 out of 7) and less frequent in the mixed type (17 out of 25) and epithelial type (28 out of 50). A (possible) strategy to improve the survival in the first line treatment in MPM is the depletion of systemic arginine by using pegylated arginine deiminase (ADI-PEG)[42]. To assess the clinical relevance of this mechanism in MPM, a phase 1 study of ADI-PEG with cisplatin-pemetrexed in patients in ASS1 deficient MPM patients (1 epithelioid, 2 biphasic, 2 sarcomatoid) was conducted. It showed a response in the two patients with the biphasic MM, in the epithelioid type and in 1 patient with a sarcomatoid type[43]. A randomized phase II study investigated single agent ADI-PEG. Patients with in ASS1-deficient MPM (both treatment naïve and pre-treated) were 2:1 randomized between ADI-PEG + BSC or BSC alone. Screening of 201 MPM patients identified 68 patients with low ASS1 expression (2 sarcomatoid, 66 non-sarcomatoid). The other patients were excluded because ASS1 was positive [83], ASS1 status could not be determined [21] or ASS1 was negative but other inclusion criteria were not met [29]. The median PFS was longer in the active agent arm compared to BSC alone (3.2 vs. 2.0 months,

P=0.03). Half of the patients in the active agent arm experienced progression at the first 8-week tumor evaluation. The survival was equal between the two arms (11.1 BSC vs. 11.5 ADI-PEG). The toxicity profile was mild with 30% in the treatment arm experiencing a grade 3–4 event and 17% in the BSC arm (P=0.43) [44]. So single agent ADI-PEG has a limited effect, and the efficiency of combination strategies with platinum-pemetrexed needs to be revealed.

Current studies

The PFS survival benefit of nintedanib to platinumpemetrexed in the first line setting in the LUME-Meso trial warranted confirmation and the global, prospectively randomized phase III trial, which is currently awaiting its analyses (NCT01907100).

The first small phase II studies with immunotherapy in MPM patients in the second and third line seempromising [6-9]. Based on these promising results with immunotherapy, the CheckMate743 (NCT02899299) is currently randomizing treatment naïve MPM patients to receive either platinum-pemetrexed or anti-PD1 (nivolumab) + anti-CTLA4 (ipilimumab). The estimated enrollment is 600 patients and the estimated primary completion is September 2021.

The ATOMIC phase II/III trial is currently recruiting sarcomatoid and biphasic MPM schould patients, in which patients are randomized between cisplatinum-pemetrexed plus ADI-PEG or placebo (NCT02709512) [45]. The choice of excluding the epithelial type of MPM gives food for thought. A high proportion of ASS1 loss in the sarcomatoid type MPM was expected based on the retrospective series of Szlosarek [42]. The phase II study of Szlosarek could only include two low ASS1 expression sarcomatoid MPM out of 201 screened MPM [44]. Unfortunately, they did not separate the non-sarcomatoid group, so it is unknown how many mixed type MPM were ASS1 negative. So, it may be a challenge to recruit enough patients with a low ASS1 status, and also it might be hard to see if this is a right biomarker by excluding the epithelial type. Also, in the previous mentioned phase I study with only 5 MPM patients, here were partial responses in the sarcomatoid type (1 out of 2) and the biphasic type (2 out of 2), and epithelial type (1 out of 1). By excluding the epithelial type, one might miss clinical benefit for this group.

Several other combinations of targeted therapy with chemotherapy are under investigation and will be discussed in the companion paper in this issue including: The additional value of cetuximab to platinum-pemetrexed doublet therapy in first line setting (NCT00996567); the combination of gemcitabine and imatinib mesylate in pemetrexed-pretreated patients with malignant pleural mesothelioma (MPM) (NCT02303899); amatuximab in combination with pemetrexed and cisplatin (NCT02357147) and the combination of gemcitabine with ganetespib (NCT01590160).

MAINTENANCE TREATMENT

Current options

Unlike in other solid tumors like lung cancer, there is no current evidence for maintenance chemotherapy in MPM. Maintenance pemetrexed is feasible, but studies showing a better PFS or survival benefit are lacking. Single center experience with maintenance pemetrexed without progression on carboplatin- pemetrexed induction or pemetrexed monotherapy have been described. In a cohort of 13 patients (out of 30 patients who started with platinum-pemetrexed), patients were treated with pemetrexed maintenance therapy (PMT). The median survival in the maintenance group was 8.5 vs. 3.4 months in the cohort without maintenance therapy. Grade 3 toxicity consisted of neutropenia, leucopenia and anemia. The only

non-hematological grade 3 toxicity during PMT was fatigue (15%). The reason to stop PMT was disease progression (69%), toxicity (23%) and in patient's best interest (8%) [46].

The previous mentioned studies with cisplatin-pemetrexed with bevacizumab and nintedanib provide the first evidence for maintenance therapy with an anti-VEGF agent. In both studies maintenance anti-VEGF therapy was continued until disease progression after the initial 4–6 cycles of cisplatin-pemetrexed+ anti-VEGF[36,37]. Other drugs after chemotherapy, like thalidomide (a well-known antiangiogenic agent), were tested in a large phase III study, randomizing patients to thalidomide or BSC. Unfortunately, no improvement was observed in progression free survival (3.6 months active agent arm vs. 3 in the BSC arm) [47].

Current studies

To determine the benefit of maintenance pemetrexed in MPM patients in patients without progression after first line platinum-pemetrexed doublet therapy, a randomized phase II study was designed (arm 1: pemetrexed, arm 2: BSC), with progression free survival as primary outcome. (NCT01085630). The study opened in April 2010, but no results have been presented yet. Based on the advance of switch maintenance therapy in i.e., NSCLC and the previous activity of gemcitabine in phase II studies, a multi-center phase II study (NVALT19) in The Netherlands is investigating switch maintenance therapy with gemcitabine in MPM patients without progression after platinum-pemetrexed doublet therapy and is currently open for randomization. Patients are 1:1 randomized to receive maintenance gemcitabine or BSC. The primary outcome is PFS and secondary outcomes are i.e., toxicity and OS. The first results are expected early 2019 [48].

SECOND LINE TREATMENT

Current options

There is no standard second line treatment in MPM. The NCCN guidelines recommend consideration of rechallenge of pemetrexed (if not administrated in the first- line) if there was a good sustaining response at the time of initial chemotherapy interruption. Other options like vinorelbine, gemcitabine, and immunotherapy (pembrolizumab and nivolumab-ipilimumab) could be considered [1].

The additional value of pemetrexed in second line is doubtful. In a phase III study in 243 previous treated MPM patients (excluding pemetrexed) were patients randomized to BSC or pemetrexed. Pemetrexed prolonged the progression free survival (3.6 vs. 1.5 months, P=0.0148), although there was no effect on the primary endpoint OS (pemetrexed 8.4 vs. 9.7 in the BSC arm, P=0.7434). The authors suggested that this was due to the imbalance in post study therapies. Patients in the BSC were allowed to receive chemotherapy after discontinuation of the study. The percentage of BSC patients who received pemetrexed after discontinuation of study treatment was also much higher (18.3% vs. 3.3%, respectively; P=0.0001). Furthermore, BSC patients received chemotherapy, after discontinuation of the study, significantly earlier than P + BSC patients (median time to initiation, 4.3 vs. 15.7 months, respectively; log-rank P<0.0001) [49]. Manegold et al. analyzed whether the OS in the cisplatin pemetrexed arm of the phase III study by Vogelzang et al. was influenced by post-study chemotherapy (PSC) [21,50]. Less patients in the combination arm received PSC (37.2% vs. 47.3% in the cisplatin arm). The patients who received PSC had a survival benefit (P<0.01), but it is unknown whether this survival benefit is caused by the PSC, or that patients who lived longer received more second line treatment [50].

Predicting responses to chemotherapy would be of great value. A way to identifying the proper drug (combination) was developed by Schunselaar et al. With this technique, it is possible to perform a drug screening on primary mesothelioma cultures from pleural fluid and thereby guide treatment decisions of corresponding patients that were progressive after first or second line treatment. The in vitro prediction was adequate in seven out of the eleven drug screens. Limitation to this study was the inability to screen for pemetrexed sensitivity and the limited number of pleural fluid samples that led to a primary mesothelioma culture that was a candidate for drug screening (155 pleural fluid samples from 102 patients)[51].

Current studies

Currently, a randomized phase III study is investigating if immunotherapy (pembrolizumab) is beneficial compared to gemcitabine or vinorelbine in patients with progressive disease after at least one prior line of platinum-based chemotherapy. The estimated number of patients to be accrued is 142, with estimated completion of accrual end of 2020 (NCT02991482). Vinorelbine is currently also under investigation in a phase II study in MPM progressive patients after first line therapy. Patients will be randomized (1:2) to receive either BSC or BSC with vinorelbine (NCT02139904). The estimated enrolment is 200 patients and is expected to complete in March 2018.

THE FUTURE OF CHEMOTHERAPY

Combining therapies like chemotherapy, targeted therapy and immunotherapy will be more and more prominent. The first studies in lung cancer, combining chemotherapy (like paclitaxel/carboplatin, platinum with gemcitabine or pemetrexed and docetaxel) with immunotherapy (like nivolumab with or without ipilimumab or pembrolizumab) are promising with improvement of PFS and response rates [52]. Challenges will be to find the optimal combinations strategies in terms of timing, agents and to select the right patients for the right treatment.

CONCLUSION

Chemotherapeutic options have extensively been evaluated in the last three decades. This has resulted only in a few active chemotherapeutic regimes, which provide a limited but significant profit for the patients. A platinum pemetrexed combination remains the standard first line therapy. There is growing evidence for addition of antiangiogenesis therapy, like bevacizumab, to first line treatment. There is no standard second line treatment in which the value of single agent chemotherapy in recurrent seems limited. Combinations of active agents, including cytotoxic agents, targeted therapy and immunotherapy are currently under investigation, and first results seem promising. The next step is to reveal the optimal combination of chemotherapy with angiogenesis inhibitors or immunotherapy in the (near) future and to select the optimal treatment for the individual patient.

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None.

FOOTNOTE

Conflicts of Interest: Dr. JA Burgers: Advisory board AstraZeneca, Boehringer-Ingelheim, Roche Nederland. Prof. Dr. P Baas: Advisor/consultant BMS, MSD, AZ Pfizer and Grants of MSD and BMS. Dr. de Gooijer has no conflicts of interest to declare.

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