Pemetrexed in the treatment of malignant pleural mesothelioma

Malignant pleural mesothelioma is a relatively uncommon cancer, but is increasing in frequency and will pose a major clinical challenge worldwide in the coming years. It has been considered a relatively chemoinsensitive tumor, and single-agent chemotherapy studies have been disappointing. However, pemetrexed, a pyrimidine-based multitargeted antifolate agent, has shown significant activity, and in the only Phase III study comparing two chemotherapy regimes (the EMPHACIS study), it has been demonstrated that the combination of pemetrexed and cisplatin with cisplatin alone led to an overall survival benefit of almost 3 months in the combination treatment arm, with parallel improvements in quality of life, symptom scores and pulmonary function. The combination of pemetrexed with cisplatin is the only regime licensed for use in malignant pleural mesothelioma in most parts of the world. Pretreatment with folic acid and vitamin B_{12} is required to minimize toxicity, but the regimen is generally well-tolerated in patients with a good performance status. It is now considered the 'reference' regime against which future chemotherapeutic approaches should be compared.

KEYWORDS: chemotherapy ▪ malignant pleural mesothelioma ▪ pemetrexed ▪ pharmacology

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Malignant pleural mesothelioma (MPM) is a relatively uncommon tumor that is increasing in frequency in most areas of the world. For example, in the UK there has been a sharp increase in the number of cases since the late 1970s, a trend which is predicted to reach its peak by approximately 2015, when over 2000 cases per annum are likely to be diagnosed [1]. It is a tumor which is, in the vast majority of cases, attributable to asbestos exposure, and this pattern of changing incidence closely parallels the level of exposure to this substance, but with a time delay of over 40 years. Whilst this trend in incidence is likely to reverse in most of the Western world after 2020, asbestos is still being used in vast amounts in many parts of the world, including India, China, Russia and Eastern Europe, meaning that mesothelioma is a disease that will be with us for a very long time.

Malignant mesothelioma most commonly affects the pleura, and results in progressive and distressing symptoms including breathlessness, pain and debility. Although various treatment options are emerging, it is still considered an incurable tumor, with a median survival in untreated patients of 7–9 months [2].

Background to chemotherapy for mesothelioma

Malignant pleural mesothelioma has, in the past generally been considered a relatively chemoresistant tumor. However, there is no doubt that chemotherapy can be an effective treatment, and since the vast majority of patients have advanced (International Mesothelioma Interest Group [IMIG] stage III or IV) disease, it is the only realistic option for many of them. Most published studies have been Phase II trials in relatively fit patients with a WHO performance status of 0 or 1. There are a variety of known prognostic factors in mesothelioma [3,4], but they have never been used to stratify patients prospectively in clinical trials, so the patient populations studied are likely to be quite heterogeneous. Single agents studied include doxorubicin, daunorubicin, cisplatin, vinorelbine, capecitabine, irinotecan, gemcitabine and pemetrexed [5–13]. Response rates are shown in Table 1, the highest reported being 21% with vinorelbine. The few rather small-scale randomized trials published prior to the availability of pemetrexed had shown negative results. These had used a variety of agents and were essentially underpowered, and reported median survival rates varying from 6 to 8 months. The demonstration of a 14% single-agent response rate in a Phase II trial using pemetrexed [12] and Phase I studies of pemetrexed in combination with platinum compounds, where 45% and 32% response rates were seen [14,15], led to the Phase III study described below. However, even

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Table 1. Single-agent response rates to a variety of chemotherapeutic agents in malignant pleural mesothelioma.

Agent	Response rate (%)	Ref.
Capecitabine	4	[6]
Cisplatin	14	[7]
Daunorubicin	0	[8]
Doxorubicin	6	[9]
Gemcitabine	7	[10]
Irinotecan	0	[11]
Pemetrexed	14	[12]
Vinorelbine	21	[13]

before the emergence of pemetrexed, there was evidence from a meta-analysis of chemotherapy in mesothelioma that doublet regimes should be considered the standard of care [16].

Pharmacodynamics of pemetrexed

Pemetrexed is a pyrimidine-based antifolate agent that, in contrast to other available antifolates that inhibit single enzymes (e.g., methotrexate and ralitrexed), targets several folate-dependent enzymes. Its primary action is thought to be inhibition of thymidine synthase (TS), but it is also a weak inhibitor of glycinamide ribonucleotide formyl transferase (GARFT), dihydrofolate reductase (DHFR) and 5-aminoimidazole-4-carboxamide ribonucleotide formyl transferase (AICARFT) [17]. The inhibition of these enzymes limits DNA and RNA synthesis by blocking the synthesis of thymidylate and a range of purines.

After entering the cell via the reduced folate transporter and (to a lesser extent) the α-folate receptor (which is overexpressed in mesothelioma), pemetrexed is glutamated by folylpolyglutamate synthetase to pemetrexed-pentaglutamate. The polyglutamated forms are retained for long periods within the cell, and have significantly greater affinity for the folate-dependent enzymes (except DHFR) than pemetrexed monoglutamate itself. One important characteristic resulting from its capacity to inhibit multiple enzymes is its propensity to retain cytotoxicity against some cell lines that are resistant to other agents, such as ralitrexed. This property may also explain why pemetrexed is able to inhibit the formation of tumor colonies in a number of human cancers, including mesothelioma. Pemetrexed also has the effect of synchronization of the cell cycle, and the resulting accumulation of tumor cells in the S phase has the potential to sensitize cells to the cytotoxic effects of other agents, particularly gemcitabine [18,19]. Pemetrexed may also be a radiosensitizer [20].

Antifolates in general have deleterious effects on bone marrow and the mucosa of the gastrointestinal tract, both tissues that depend on very high cell turnover for normal function. Tissue sensitivity to pemetrexed is highly affected by the availability of folate, and the coadministration of folate supplements significantly improves the therapeutic window of the agent (as discussed later).

Pharmacokinetics of pemetrexed

After intravenous infusion, there is a broadly linear relationship between dose and maximum plasma concentration. The major published pharmacokinetic variables are shown in Table 2. Pemetrexed is thought to be largely protein bound, and there is no evidence of drug accumulation after multiple dosing in most clinical situations. However, there is the potential for accumulation of the drug in 'third spaces', such as pleural effusions and ascites, and there is one reported case of acute renal failure attributed to the accumulation of pemetrexed in a patient with advanced mesothelioma and ascites [21]. In this case, dialysis was unsuccessful in removing pemetrexed.

Pemetrexed is excreted almost entirely unmetabolized via the renal route in humans, with clearance being dependent upon the glomerular filtration rate. It is therefore recommended that patients with a creatinine clearance of less than 45 ml/min should not be prescribed pemetrexed. There are few drug interactions that are considered to be of major clinical significance, although coadministration with cisplatin may increase clearance via an unknown, nonrenal pathway [17]. There is some evidence that concomitant use of nonsteroidal anti-inflammatory drugs may also decrease the renal clearance of pemetrexed, and should be avoided around the time of pemetrexed administration [22]. Pemetrexed is poorly distributed to the CNS, the reasons for which are unclear [23].

Table 2. Main pharmacokinetic variables for pemetrexed.

Variable	Clearance (ml/min/m²)	V_{ss}* (l/m²)	$t_{½}$‡ (h)
Range	59–91	9.2–13	2.8–3.6

**Apparent volume of distribution at steady state.*
‡Terminal half-life.
Data taken from [16].

Clinical efficacy of pemetrexed in malignant pleural mesothelioma

As stated above, the Phase I and II studies with pemetrexed were encouraging in terms of response rates, and this led to the first large-scale Phase III randomized trial of pemetrexed plus cisplatin versus cisplatin alone in MPM, the Evaluation of Mesothelioma in a Phase III Trial of Pemetrexed with Cisplatin (EMPHACIS) study, published by Vogelzang *et al.* [24]. This pivotal study is the largest ever published in mesothelioma, with 226 patients randomized to the pemetrexed/cisplatin arm, and 222 to the cisplatin arm. The median age was around 61 years, and all patients had a Karnofsky performance status (PS) of greater than or equal to 70 (equivalent to an ECOG/WHO PS of 0 or 1). Previously untreated patients were randomized to receive either pemetrexed at a dose of 500 mg/m^2 plus cisplatin 75 mg/m^2 on day 1, or cisplatin 75 mg/m^2 on day 1 alone. Both treatments were administered intravenously every 21 days, continuing until a maximum of three dose reductions were required, or there was evidence of progressive disease. The median number of cycles administered was six (range: 1–12) in those receiving vitamin supplementation (see below). Survival was significantly better in the pemetrexed/cisplatin arm, compared with those patients treated with cisplatin alone, with the median survival being 12.1 versus 9.3 months (hazard ratio [HR]: 0.77, long rank p = 0.02) (Figure 1). Tumor response rates were also higher, being 41% in the pemetrexed/cisplatin group versus 17% in those treated with cisplatin alone (p < 0.001). The toxicities are described below, but despite these there was evidence of improvement in symptoms and quality-of-life scores in the pemetrexed/cisplatin arm, even when the patients with and without vitamin supplementation were analyzed as a single group [25]. Dyspnoea worsened with cisplatin alone, and remained unchanged in the patients treated with pemetrexed/cisplatin. Pain also worsened in the cisplatin arm and had improved by cycle 3 in the pemetrexed/cisplatin-treated group (p < 0.05 for cycles 3–6). Anorexia and fatigue worsened over the course of the study in both arms, but fatigue scores were superior in the pemetrexed/cisplatin arm by cycle 6. Global quality-of-life and activity scores also worsened during the study in both arms, but had stabilized in the pemetrexed/cisplatin arm by cycle 6, when they were better in comparison with patients receiving cisplatin alone (p = 0.037).

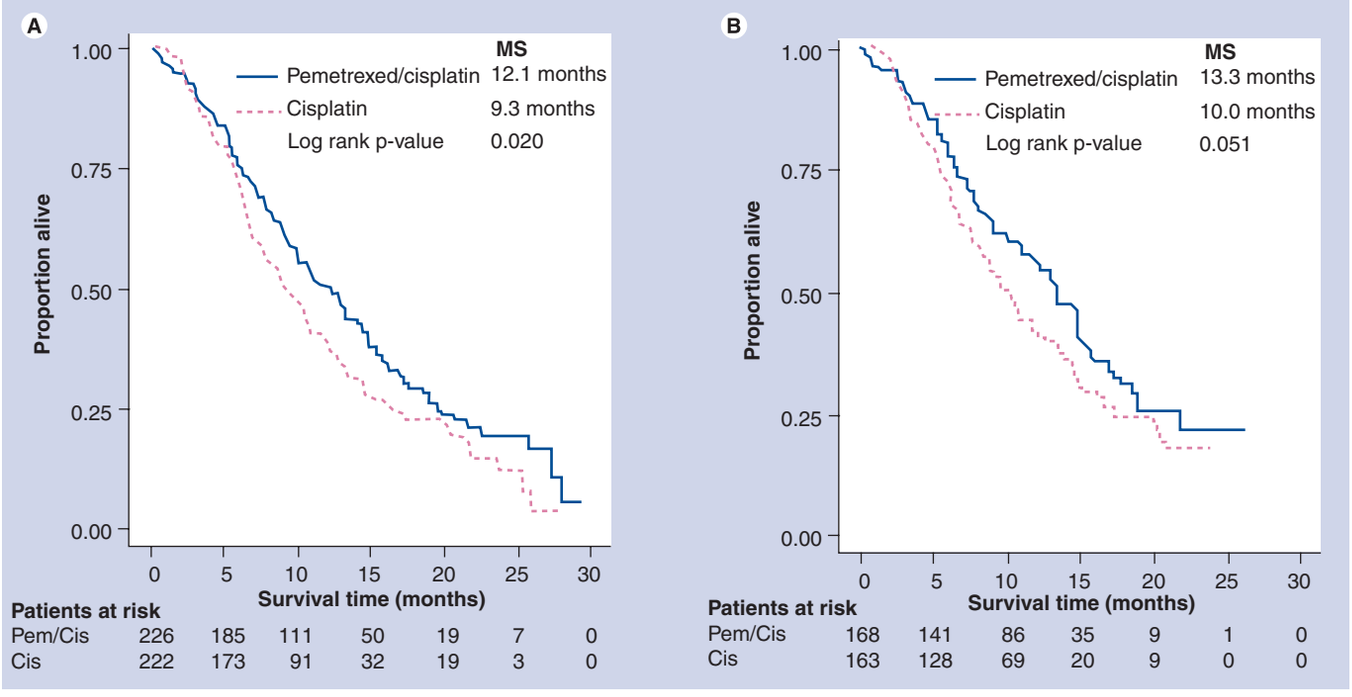

Figure 1. Kaplan–Meier estimates of overall survival time for all patients (A) and for fully supplemented patients (B).
Overall survival was significantly longer for the pemetrexed/cisplatin (Pem/Cis) treated patients in the all patients group (p = 0.020) and approached significance for the group of fully supplemented patients (p = 0.051).
Cis: Cisplatin alone; MS: Median survival; Pem/Cis: Pemetrexed/cisplatin.

Table 3. Grade III and IV toxicities associated with single-agent pemetrexed in patients with advanced non-small-cell lung cancer, with (+ vit) and without supplementation with folic acid and vitamin B_{12}.

Regimen	Median number of cycles	No. of patients	Incidence of grade III and IV toxicities (%)							Ref.
			Anemia	*Neutropenia*	*Thrombocytopenia*	*Nausea*	*Vomiting*	*Diarrhea*	*Fatigue*	*Stomatitis*	*Rash*	
Pemetrexed 500 mg three-times a week	2	81	16	35	15	1	2	0	5	0	5	[23]
Pemetrexed 500 mg three-times a week + vit	4	265	4	5	2	3	2	<1	5	1	<1	[24]

Pulmonary function was also assessed in this trial, with forced expiratory volume in the first second of forced expiration (FEV_1), forced vital capacity (FVC) and slow vital capacity (SVC) being measured [26]. Patients in the pemetrexed/cisplatin arm showed improvements in FEV_1, FVC and SVC of 40, 110 and 110 ml, respectively. In contrast, pulmonary function deteriorated in the cisplatin arm with falls of 60, 50 and 3 ml in FEV_1, FVC and SVC (p-values for differences were 0.054, 0.001 and 0.007, respectively).

Pemetrexed has also been studied in combination with carboplatin. In a Phase II study of 102 patients, this combination resulted in a response rate of 18%, with a further 50% having stable disease [27]. The median survival was 12.7 months and the combination was well-tolerated, with nearly 100% planned dose intensity delivered. In a large, expanded access program where over 1700 chemonaive patients were treated either in a nonrandomized way with a combination of pemetrexed and cisplatin or pemetrexed and carboplatin, there was very little difference seen in terms of efficacy or toxicity [28]. It would therefore seem reasonable to consider the use of pemetrexed with carboplatin, particularly in patients where there is any contraindication to cisplatin.

Second-line & maintenance therapy

At least two studies have addressed the issue of second-line pemetrexed in mesothelioma, one comparing pemetrexed alone with the combination of pemetrexed and cisplatin after relapse [29], and the second comparing it with best supportive care alone [30]. This second-line treatment was generally well-tolerated with partial response rates of 18–21%, although no overall survival benefit was demonstrated against best supportive care. There is also interest in maintenance pemetrexed therapy, and a small Phase II study has shown that it is a feasible, well-tolerated approach with 'promising' effects on time-to-progression and overall survival. Further studies are clearly needed before such treatments can be considered standard.

Safety & tolerability

As monotherapy, the principal adverse effect of pemetrexed is myelosuppression, particularly in the absence of vitamin supplementation as described below. In one study in non-small-cell lung cancer (NSCLC) the hematological toxicities of all grades by pemetrexed-treated patients were: anemia (86%), neutropenia (65%), leukopenia (76%) and thrombocytopenia (43%) [31]. Skin rash can be a significant problem, although the incidence and severity of this can be attenuated by pretreatment with dexamethasone. However, even with such prophylactic treatment, severe (grade III and IV) skin toxicity was reported in this study in non-vitamin-supplemented patients [32]. Other toxicities include nausea and vomiting, diarrhea, fatigue and stomatitis. Severe toxicities in single-agent studies are shown in Table 3. In the EMPHACIS study using a combination of pemetrexed and cisplatin [24], grade III and IV hematological toxicity was greater in the pemetrexed/cisplatin arm (anemia 5 vs 0%, neutropenia 28 vs 2%, thrombocytopenia 6 vs 0%). Nonhematological toxicities were also higher in the pemetrexed/cisplatin arm (nausea 15 vs 6%, vomiting 13 vs 4% and fatigue 10 vs 9%).

Vitamin supplementation

In a study comparing single-agent pemetrexed supplemented with folic acid and cyanacobalamin in NSCLC, the neutropenia and neutropenic fever rates were significantly lower than with single-agent docetaxel [32]. In the EMPHACIS study, there was a 7% rate of treatment-related deaths in the first 43 patients randomized to the pemetrexed/cisplatin arm. Previous studies with pemetrexed had revealed high rates of grade 4 neutropenia and diarrhea, which were linked to high blood levels of homocysteine and methylmalonic acid, suggesting that toxicity such as this, and the treatment-related deaths, may have been related to low levels of folic acid and vitamin B_{12} stores. Thus, part way into the study, folic acid and B_{12} supplementation was instigated for all patients subsequently randomized to either arm of the trial. The toxicity was significantly less in the supplemented group, and the median survival was 13.3 months in this subgroup as compared with 12.1 months in the whole group on an intention-to-treat basis. Thus, all patients should receive oral folic acid and intramuscular injection of vitamin B_{12} 1–3 weeks prior to the start of chemotherapy, and continually during treatment [101].

Chemotherapy vs 'active supportive care'

The only study that has compared chemotherapy with supportive care alone in MPM was published after the EMPHACIS study referred to above. This UK-based study, MSO1, was jointly managed by the Medical research Council and the British Thoracic Society [33]. Patients were randomized to either 'active supportive care' (ASC) alone (in which treatment could include steroids, analgesics, bronchodilators, palliative radiotherapy, etc,); ASC plus MVP (4 ×

3-weekly cycles of mitomycin 6 mg/m^2, vinblastine 6 mg/m^2 and cisplatin 50 mg/m^2); or ASC plus vinorelbine (V) (12 weekly injections of vinorelbine 30 mg/m^2). Recruitment failed to meet the predetermined target, and thus the two chemotherapy arms were combined (ASC plus chemotherapy [CT]) and compared with ASC alone for the primary outcome, which was overall survival. A total of 409 patients were randomized (136 ASC, 137 ASC plus MVP, 136 ASC plus V), and a small nonstatistically survival benefit was seen for ASC plus CT (349 deaths; HR: 0.89; 95% CI: 0.72–1.12; p = 0.32). The median age of subjects was 65 years, and 91% were of WHO PS 0 or 1. The median survival in the ASC arm was 7.6 months and 8.5 months in the ASC plus CT arm, both significantly shorter than those reported in the pemetrexed study (12.1 vs 9.3 months). This may have been because of a longer period between diagnosis and trial entry in the UK study. Exploratory analyses suggested there may be a survival advantage for vinorelbine compared with ASC (235 deaths; HR: 0.81; 95% CI: 0.63–1.05; p = 0.11), with a median survival for ASC plus V of 9.4 months. However, there was no evidence of a survival benefit with ASC plus MVP (231 deaths; HR: 0.98, 95% CI: 0.76–1.28; p = 0.91). All three treatment groups resulted in good symptom control, and no between-group differences were observed in four predefined quality-of-life subscales.

On the basis of the pemetrexed/cisplatin Phase III study [24], this combination has become the internationally standard treatment for MPM, and is licensed as such in most parts of the world. Some have expressed concern that there was no 'supportive care only' arm to the trial, but it would probably now be unethical to carry out a trial without active treatment, at least in the first-line setting. In addition, MSO1 failed to show any benefit of MVP (a regime containing cisplatin), and thus the cisplatin-alone arm of the EMPHACIS study can perhaps be considered a 'control' against which the combination of pemetrexed and cisplatin could be reasonably compared, albeit in an indirect manner. The efficacy of this combination was recognized in the Cochrane review in 2007 [34].

It is, however, important to note that the two major chemotherapy studies referred to above were carried out in patients with a median age of 61 and 65 years with good performance status – almost entirely PS 0 and 1. The median age of patients in the UK is around 74 years, and many are of poor PS. The benefit of chemotherapy in older, less fit patients has yet to be determined.

Other treatments

A small proportion of patients with MPM have the combination of early-stage disease and are sufficiently fit to allow for the possibility of a more radical approach to therapy. There are advocates of radical surgery in the form of extra-pleural pneumonectomy (EPP) for such patients [35], although there are no published randomized studies to support such treatment out of the context of a clinical trial. The case series that have been published have usually used trimodality treatment with neoadjuvant chemotherapy prior to the EPP, followed by radical radiotherapy. The use of neoadjuvant pemetrexed plus cisplatin followed by EPP and radiotherapy has recently been shown in an uncontrolled Phase II study to be a feasible option with a reasonable long-term survival rate [36]. However, it will only be with a randomized trial of this therapeutic approach that the issue of patient selection can be overcome. An EORTC trial (08031) is studying this trimodality approach, and a feasibility study for a randomized study – the Mesothelioma and Radical Surgery (MARS) trial – has recently completed recruitment in the UK [37]. The results of these are, as yet, unpublished. Radical decortication is considered to be a reasonable alternative surgical approach to EPP [38], and seems to be gaining support in thoracic surgical circles. Palliative pleurodesis either by a surgical or a medical approach is useful in limiting the collection of pleural fluid. Superficial radiotherapy to chest drainage and biopsy sites is often used in an attempt to avoid the 'seeding' of the tumor, although there is some uncertainty regarding its efficacy [39]. Supportive care, including pain control, is an essential element of the management of MPM in all patients.

Conclusion & future perspective

Mesothelioma is increasing in frequency, and although there may be a fall in new cases in the Western world over the next 10–15 years, worldwide there will be an epidemic that will be a feature of all our lifetimes. Whilst MPM remains essentially an 'incurable' cancer, there may be a few patients whose survival can be significantly prolonged by surgery as part of trimodality therapy. For the majority, however, chemotherapy is currently the treatment of choice that is most likely to lead to symptomatic improvement and a modest improvement in survival. The current 'gold standard' is the combination of pemetrexed and cisplatin (although carboplatin would appear to be a reasonable alternative), which has been shown to confer almost 3 months additional survival with symptomatic benefit compared

with single-agent cisplatin. However, research to find better approaches to the management of this dreadful disease is urgently required. For the future, there are still issues to be resolved with regard to the potential optimum duration of treatment, of maintenance single-agent pemetrexed and the role of second-line treatments in general. There are also a variety of new agents that are currently being studied in Phase II clinical trials in MPM, particularly the VEGF inhibitors, but it is disappointing that the EGFR inhibitors gefitinib and erlotinib have shown little activity in Phase II trials [40,41]. In any studies in the foreseeable future, the combination of pemetrexed and cisplatin will remain the 'comparitor' regimen.

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The author has been in receipt of occasional lecture fees from Eli Lilly & Co, the manufacturers of pemetrexed. On all such occasions the content of the lectures has been entirely independently developed by the author and has had no direct relevance to the content of this paper. The author is also vice chairman of a charity which has received unrestricted educational grants from Eli Lilly & Co. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

- Malignant pleural mesothelioma (MPM), whilst still relatively uncommon, is increasing in frequency in the UK, and will pose a major clinical challenge worldwide for the foreseeable future.
- Single-agent chemotherapy studies have been disappointing, but pemetrexed showed promise in Phase I and II trials.
- Pemetrexed is a pyrimidine-based antifolate agent that targets several folate-dependent enzymes.
- Its primary action is thought to be inhibition of thymidine synthetase (TS), which results in the limitation of DNA and RNA synthesis by blocking the synthesis of thymidylate and a range of purines.
- Pemetrexed is administered by intravenous infusion.
- Pemetrexed is renally excreted, and its use is limited to patients with a creatinine clearance of greater than 45 ml/min.
- The only Phase III study (the Evaluation of Mesothelioma in a Phase III Trial of Pemetrexed with Cisplatin [EMPHACIS] study) compared the combination of pemetrexed and cisplatin with cisplatin alone, and showed an overall survival benefit of almost 3 months in the combination treatment arm with parallel improvements in quality of life, symptom scores and pulmonary function.
- The combination of pemetrexed with cisplatin is the only regime licensed for use in MPM in most parts of the world, although there is evidence that carboplatin is a reasonable alternative in patients in whom cisplatin is contraindicated.
- Pretreatment with folic acid and vitamin B_{12} is required to minimize toxicity.
- Pretreatment with dexamethasone is recommended to reduce the risk and severity of skin rash.
- The main toxicities are hematological, but are usually well within the tolerable range for combination chemotherapy.

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- ▪▪ of considerable interest

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