Review

The Value of Pemetrexed for the Treatment of Malignant Pleural Mesothelioma: A Comprehensive Review

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Abstract. *This review aims to provide insight into treatment of malignant pleural mesothelioma (MPM) considering effects on survival, quality of life (QoL) and costs, in order to determine the value of pemetrexed in MPM treatment. Cisplatin in combination with pemetrexed or raltitrexed increased survival in MPM, whereas vinorelbine and gemcitabine have led to good response rates. None of these appear to have any detrimental effect with respect to symptoms and global QoL. The cost-effectiveness of pemetrexed-cisplatin was found to be acceptable in advanced MPM compared with cisplatin, but raltitrexed-cisplatin was found to be a more cost-effective treatment option. This may also apply for gemcitabine and vinorelbine, since in contrast to pemetrexed, both agents can be obtained from generic manufacturers. As yet platinum-doublet therapy is the most effective palliative treatment of MPM. To provide a more cost-effective treatment approach for advanced MPM, further research should include randomized controlled trials comparing the recommended pemetrexed-cisplatin directly with platinum doublets with raltitrexed, gemcitabine, or vinorelbine.*

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Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy of the mesothelium particularly affecting older men exposed to asbestos in the workplace, 20 to more than 50 years ago (1, 2). Except for the USA, incidence rates of MPM are increasing worldwide with an expected peak within the next 10 years (1, 2). By the time that patients experience symptoms such as shortness of breath and chest pain as the result of pleural effusion, the disease is usually at an advanced stage. Fatigue, profuse sweating, weight loss, anorexia and difficulty in swallowing are also common symptoms as the disease progresses (1, 2). The median overall survival is between four to 13 months for untreated patients and between five to 18 months for patients given palliative chemotherapy (1-4). Over the years in the Netherlands, the 1-year survival has increased from 30 to 40% but the 5-year survival rate remains less than 5% (5). Diagnosis of MPM mainly depends on histology. Epitheloid MPM, the most common histological subtype (60-75% of patients), is associated with the best prognosis. Despite advances in the treatment of MPM, no treatment, including surgery, radiotherapy and chemotherapy or a combination of those, has proven curative. For the majority of patients, treatment options are limited to palliative chemotherapy and best supportive care (BSC) (1-4).

The median overall survival after single-agent chemotherapy is similar to or only slightly better than that obtained with BSC (2-4, 6). A meta-analysis of phase II studies up to 2001 found cisplatin to be the most active agent (7). Antimetabolites such as gemcitabine and pemetrexed, and the semi-synthetic vinca-alkaloid vinorelbine have similar radiological response rates (2-4, 6). Following

developments in the treatment of advanced non-small cell lung cancer (NSCLC) (8), the combination of these agents led to the introduction of platinum doublet-based palliative chemotherapy (3, 4). On the basis of phase III trial results, the combination of cisplatin and the antifolate pemetrexed (CISPEM) is now recommended as first-line treatment for patients with non-resectable MPM and a good performance status (2, 9-11). Although not licensed for this indication, carboplatin is recommended for patients who do not tolerate cisplatin or for whom cisplatin is contraindicated (2, 10, 11). CISPEM has been licensed for the treatment of MPM since 2004 (12). In the same year, this combination was also registered for the treatment of advanced NSCLC (12). Cisplatin in combination with gemcitabine (CISGEM) or vinorelbine (CISVIN) is also used for the first-line treatment of advanced NSCLC. With respect to MPM, these platinum doublets are recommended as alternatives to CISPEM (2, 10, 11). However, the activity of both off-label combinations has only been evaluated in phase II studies (2-4).

In the Netherlands the annual costs of the use of pemetrexed in the treatment of advanced NSCLC were estimated to be between 19 and 24 million euros (13). Although the costs of pemetrexed used in the treatment of MPM are low as compared to the expenditure on pemetrexed in the treatment of NSCLC, in the coming years they are likely to grow. MPM has deep impact on the lives of patients and their relatives and strongly affects their quality of life (QoL) as the consequence of symptoms, detrimental treatment effects, poor prognosis and its effect on emotional functioning and the social consequences of having the disease (14). QoL, therefore, should also be taken into account in an assessment of the value of pemetrexed in the treatment of MPM. The current review summarizes the recent literature on the clinical effects and cost-effectiveness of MPM treatment with the aim of providing up-to-date information on the value of pemetrexed for the treatment of MPM.

Materials and Methods

A systematic literature search was performed using the MEDLINE, EMBASE and Cochrane databases through April 2013 for studies published in English. Articles on the use of pemetrexed, platinum derivatives, and other (cytotoxic) agents used in the treatment of MPM [phase II and III clinical trials, guidelines, systematic reviews, meta-analyses, and economic evaluations (cost-effectiveness and cost-utility studies)] were selected for inclusion in the review. Search terms used were combinations of 'malignant pleural mesothelioma', 'chemotherapy', 'pemetrexed', 'raltitrexed', 'gemcitabine', 'vinorelbine', 'cost' and 'cost analysis' and 'economic evaluation'. Additional hand searches were conducted using citations from the identified randomized controlled trials (RCTs), (systematic) reviews and guidelines. Data on ongoing trials were derived from the website of the US trials register (www.clinicaltrials.gov). Two authors (CB and JH) independently evaluated all titles and abstracts. Full paper manuscripts of potentially relevant titles/abstracts were obtained and assessed for inclusion. The same two reviewers, independently, also extracted relevant data, including study characteristics (participants, intervention and control, outcome measures and follow-up) and results. Risk of bias was assessed using the Cochrane Risk of Bias Tool. Because of the small number of RCTs, a formal meta-analysis was not performed. Key data have been summarized in tables. Figures of economic evaluations were recalculated to euros and corrected for 4% inflation per year from the year of publication until 2012.

Results

Study selection. The electronic search on the clinical effectiveness yielded 657 results, out of which 452 from MEDLINE, 175 from EMBASE and 30 from the Cochrane library. After removing 87 duplicates and 48 non-English publications, 522 titles and abstracts were screened for inclusion. We identified several comprehensive overviews (3, 4), including three systematic reviews underlying the current guidelines of the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) (2) and National Institute of Clinical Excellence (NICE) guidance (15, 16), in which relevant clinical trials were compared and discussed. We identified three open-label phase III RCTs on the use of platinum doublet therapy. The first study concerns a comparison of CISPEM with cisplatin monotherapy (17); the second study is a comparison of cisplatin in combination with the antifolate raltitrexed (CISRAL) with cisplatin monotherapy (18); the third study is a comparison of BSC alone with BSC in combination with vinorelbine (6). All other data were derived from phase II trials (19-31), out of which three were randomized and compared two treatment regimens (32-34). We identified a large open uncontrolled trial, the International Extended Access Program (EAP), comparing CISPEM with the combination of carboplatin and pemetrexed (CARPEM) in US (35), European (36) and German patients (37). We also identified one ongoing phase II/III RCT (IFCT-GFPC-0701) involving 445 patients comparing CISPEM with and without bevacizumab. Results of this trial are not yet available (38). Key data of selected studies are summarized in Table I.

The electronic search for economic evaluations yielded 45 results, out of which 13 from MEDLINE, 26 from EMBASE and six from the Cochrane library. After removing 11 duplicates, 34 titles and abstracts were screened for inclusion. Two comprehensive reports concern an evaluation by the NICE in the UK (9, 15). The article by Cordony *et al*. (39) relates to the pharmacoeconomic data supplied to the NICE by the manufacturer (9). Woods *et al*. indirectly compared the clinical and cost-effectiveness of CISPEM and CISRAL (40). Data used in these studies were derived from the RCTs comparing CISPEM and CISRAL with cisplatin (17, 18). Relevant data of the selected economic evaluations are summarized in Table II.

Table I. *Selected phase II and III studies of combination and single-agent chemotherapy trials for the first-line treatment of malignant pleural mesothelioma.*

Study (reference)	Phase	n	Regimen	Median OS (months)	TTP (months)	RR (%)
Vogelzang *et al*. 2003 (17)	III	168	CIS + PEM	13.3	6.1	45.5
		163	CIS	10.0	3.9	19.6
Van Meerbeeck *et al*. 2005 (18)	III	126	CIS + RAL	11.4	NA (PFS=5.3)	23.6
		124	CIS	8.8	NA (PFS=4.0)	13.3
Muers *et al*. 2008 (6)	III	136	VIN + BSC	9.5	NA (PFS=6.2)	31.0
		136	BSC	7.6	NA (PFS=5.1)	14.0
Dowell *et al*. 2012 (31)	II	52	CIS + PEM + BEV	14.8	NA (PFS=6.9)	40.0
Ceresoli *et al*. 2006 (20)	II	102	CAR + PEM	12.7	6.5	18.6
Castagneto *et al*. 2008 (19)	II	76	CAR + PEM	14.0	8.0	25.0
Katirtzoglou *et al*. 2010 (23)	II	62	CAR + PEM	14.0	7.0	29.0
Habib *et al*. 2013 (34)	II	19	CAR + PEM			78.9
		21	CIS + GEM			47.6
Obasaju *et al*. 2007 (35)	EAP	709	CIS + PEM	10.9	NA	20.8
Santoro *et al*. 2008 (36)	EAP	843	CIS + PEM	NA	7.0	26.3
		861	CAR + PEM	NA	6.9	21.7
Reck *et al*. 2010 (37)	EAP	191	PEM	8.7	5.5	16.0
		137	PEM + CIS	11.3	8.2	24.0
		220	PEM + CAR	9.7	6.9	18.0
Byrne *et al*. 1999 (30)	II	21	CIS + GEM	9.5	NA (PFS=5.8)	47.6
Van Haarst *et al*. 2002 (28)	II	25	CIS + GEM	9.6	6.0	16.0
Nowak *et al*. 2002 (29)	II	52	CIS + GEM	11.2	6.4	33.0
Kalmadi *et al*. 2008 (22)	II	50	CIS + GEM	10.0	NA (PFS=6.0)	12.0
Kindler *et al*. 2012 (33)	II	53	CIS + GEM + BEV	15.6	NA (PFS=6.9)	24.5
		55	CIS + GEM	14.7	NA (PFS=6.0)	21.8
Kovac *et al*. 2012 (24)	II	78	CIS + GEM	17.0	NA (PFS=8.0)	50.0
Favaretto *et al*. 2003 (21)	II	50	CAR + GEM	15.2	NA (PFS=9.2)	26.0
Sørensen *et al*. 2008 (26)	II	54	CIS + VIN	16.8	7.2	29.6
Jänne *et al*. 2008 (32)	II	56	GEM + PEM*	8.1	4.3	26.0
		52	GEM + PEM	10.1	7.4	17.1
Scagliotti *et al*. 2003 (25)	II	64	PEM	10.7	4.7	14.1
Steele et *al*. 2000 (27)	II	29	VIN	10.6	NA	24.0

CIS, Cisplatin; PEM, pemetrexed; RAL, raltitrexed; VIN, vinorelbine; BSC, best supportive care; CAR, carboplatin; GEM, gemcitabine; BEV, bevacizumab; EAP, Expanded Access Program; OS, overall survival; TTP, time-to-progression; PFS, progression-free survival; RR, response rate; NA, not applicable. *GEM on days 1 and 8 with PEM on day 8 vs. GEM on days 1 and 8 with PEM on day 1.

Table II. *Selected economic evaluations on pemetrexed for the first-line treatment of malignant pleural mesothelioma.*

Study (reference)	Type	Perspective used	Time frame (months)	Unit cost data	Source of efficacy data	Source of resource use data	Regimen	Cost-effectiveness (ICER per QALY)
NICE, 2010 (9)	Cost-effectiveness review	UK	29	Direct medical costs	Vogelzang *et al*. 2003 (17)	Vogelzang *et al*. 2003 (17)	CIS + PEM CIS	£47,567 reference
Dundar *et al*. 2007 (15)	Cost-effectiveness review	UK	29	Direct medical costs	Vogelzang *et al*. 2003 (17)	Vogelzang *et al*. 2003 (17)	CIS + PEM CIS	£37,700 reference
Cordony *et al*. 2008 (39)	Cost-effectiveness analysis	UK	29	Direct medical costs	Vogelzang *et al*. 2003 (17)	Vogelzang *et al*. 2003 (17)	CIS + PEM CIS	£29,044 reference
Woods *et al*. 2012 (40)	Cost-effectiveness analysis	UK	60	Direct medical costs	Vogelzang *et al*. 2003 (17) Van Meerbeeck *et al*. 2005 (18)	Literature	CIS + RAL CIS + PEM CIS	£13,454 dominated reference

CIS, Cisplatin; PEM, pemetrexed; RAL, raltitrexed; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

Clinical Efficacy

Pemetrexed. One phase III RCT (17) was identified which established CISPEM as the preferred regimen in the treatment of non-resectable MPM (2-4, 9-11). The risk of bias has previously been assessed in a NICE appraisal (15, 16). The authors found the lack of a double-blind design and the reported ineligibility of approximately 20% of the 574 consenting patients in the trial to be a potential risk of bias. Initial severe pemetrexed-induced toxicity, particularly neutropenia, febrile neutropenia, and diarrhea, led to the introduction of supplementary treatment with folic acid and vitamin B12, which substantially reduced grade 3/4 toxicity (except for cisplatin-induced dehydration). Supplementation was given to about 75% of patients (17). Patients responded considerably better to CISPEM than to cisplatin (Table I). Although patients were treated with a median number of six cycles, 87% of those who responded did so within the first four cycles (9). For CISPEM, the median time-to-progression (TTP) was 6.1 months as compared to 3.9 months for cisplatin alone. The median overall survival of vitamin-supplemented patients treated with CISPEM was also longer than of patients treated with cisplatin only (13.3 *vs*. 10.0 months), which was supported by the results of a long-term survival update in 2005 (41). However, the addition of pemetrexed to cisplatin resulted in a substantial increase of serious (grade 3/4) hematological and non-hematological toxicities. Nausea, vomiting and fatigue were the most common serious adverse events related to CISPEM, affecting up to 15% of patients. Up to 5% suffered from diarrhea, dehydration and stomatitis (17). In a recent non-comparative phase II study, the addition of bevacizumab to CISPEM resulted in a 40% response rate (RR) and 14.8-month median overall survival (Table I)(31). Grade 3/4 toxicities included neutropenia in 11%, fatigue in 8%, hypertension in 6%, and venous thromboembolism in 13% of patients.

For patients with unresectable MPM unfit for CISPEM combination therapy, the use of pemetrexed monotherapy might be a treatment option (2-4, 10, 11). One phase II study was identified that evaluated first-line use of pemetrexed and resulted in a 14% RR and a median overall survival of 10.7 months (25). In patients supplemented with folic acid and vitamin B12 the median overall survival amounted to 13 months (25).

CARPEM. With respect to non-hematological toxicity (nausea, vomiting, renal function), carboplatin is generally better-tolerated than cisplatin (2-4). Carboplatin is therefore considered an alternative for patients intolerant to cisplatin (2, 10, 11). For this combination, one recently published phase II RCT was identified in which CARPEM was compared with the combination of CISGEM. RRs were 78.9% in the CARPEM group compared with 47.6% in the CISGEM group. Cumulative survival proportion at 18 months was 57.8% and 41%, respectively. Most common grade 3/4 toxicities were leukopenia (15% *vs*. 38%), thrombocytopenia (10% *vs*. 24%), and nausea/vomiting (0% *vs*. 33%). Two Italian phase II studies evaluated carboplatin in combination with pemetrexed and reported RRs of 19% and 25% (19, 20). The median TTP and overall survival were 6.5-8 months and 12.7-14 months, respectively (Table I). Serious grade 3/4 toxicities consisted of hematological side-effects, particularly anemia and neutropenia, in up to 25% of patients using CARPEM. Serious non-hematological toxicities, nausea, vomiting, diarrhea and conjunctivitis, were observed in about 5% of patients (19, 20). Similar trends were reported in patients older than 70 years of age compared with those under 70; older patients, however, experienced greater hematologic toxicity (42). The results of a recent phase II trial (n=62) with CARPEM were in line with those of the Italian trials (Table I) (23).

CISPEM vs. CARPEM. The large non-randomized open-label, under the manufacturer-sponsored International EAP study in European (36, 37) and US patients (35) compared CISPEM with CARPEM. The efficacy of CARPEM was similar to that of CISPEM; for both doublets, the median TTP was between seven and eight months, the median overall survival ranged from 12 to 14 months and the 1-year survival rate was close to 60% (Table I). In European patients, the most common grade 3/4 toxicities were neutropenia (24% *vs*. 36%), leukopenia (13% *vs*. 21%), anemia (7% *vs*. 14%), and thrombocytopenia (5 *vs*. 14%), indicating that CARPEM induces somewhat greater hematological toxicity than CISPEM. However, nausea and vomiting occurred in about 3% of patients treated with either CISPEM or CARPEM (36). The incidence of grade 3/4 toxicity was similar in the German EAP study, with neutropenia occurring in 29% *vs*. 37%, leukopenia in 22% *vs*. 22%, anemia in 16% *vs*. 20%, and thrombocytopenia in 13% *vs*. 17%, for patients treated with CISPEM or CARPEM (37). The most common investigator-reported hematological toxicities in the EAP study including US patients treated with CISPEM were anemia (2.3%) and thrombocytopenia (1.3%). Neutropenia was reported in <1% of patients (35).

Raltitrexed. In one small open phase III RCT in 250 chemotherapy-naïve patients with good performance status, the effect of the combination CISRAL was compared to that of cisplatin monotherapy (18). The results of this trial were of limited power. An Independent Data Monitoring Committee recommended to extend patient inclusion after two interim analyses, but this could not be realized due to lack of funding. The lack of a double blind design may have introduced bias in investigator assessments. The median overall survival was 11.4 months for patients treated with

CISRAL as compared to 8.8 months for those treated with cisplatin. However, improvements in RR and progression-free survival (PFS) were not significant (Table I). Serious hematological toxicity was limited to neutropenia occurring in 16% of patients using CISRAL compared to 8% of patients using cisplatin. Leukopenia and anemia occurred in fewer than 10% of patients in both arms. Serious non-hematological toxicity was largely restricted to nausea (CISRAL, 14% *vs*. cisplatin, 10%), vomiting (13% *vs*. 7%) and fatigue (12% *vs*. 6%).

Vinorelbine. One phase III RCT was identified in which the combination of BSC with chemotherapy was investigated (6). A total of 409 patients with MPM were randomly assigned to three treatment groups: BSC-only, BSC plus mitomycin-vinblastine-cisplatin (MVP), or BSC plus vinorelbine. The results of the trial may have been influenced by selection bias. The trial aimed to recruit 840 patients. However, patient recruitment was slower than required, and therefore the study design was changed into a comparison of two groups: BSC-only *versus* BSC plus either one of the chemotherapeutic treatments. The methods for randomization were not clearly explained and the lack of a double blind design may also have introduced bias. Treatment with BSC plus vinorelbine resulted in a 31% RR (*vs*. 14% for BSC) and a median overall survival of 9.5 months (*vs*. 7.6 months for BSC) (Table I). There was no evidence of a survival benefit with BSC plus MVP. The only comparisons showing evidence of increased side-effects were for alopecia (BSC plus vinorelbine, 6% *vs*. BSC, 0%), lethargy (45% *vs*. 30%), and hematological toxicity, which became apparent in the latter half of the trial (36% *vs*. 0%). No significant differences between treatments were recorded at 6 months (6).

One recent non-comparative Danish phase II trial (N=54) was identified which showed that treatment with cisplatin in combination with weekly-dosed vinorelbine resulted in a 29.6% RR and a median survival and median TTP of 16.8 months and 7.2 months, respectively (Table I) (26). The most common grade 3/4 hematological toxicity was leukopenia (48%), and the most common non-hematological grade 3/4 toxicities were nausea (13%), neurotoxicity (11%), and toxicities such as tiredness or constipation in 9%. In another phase II study, first-line treatment with vinorelbine monotherapy resulted in a 24% RR and a median overall survival of 10.6 months (27).

Gemcitabine. Eight phase II studies were identified concerning the effect of gemcitabine (21, 22, 24, 28-30, 33, 34), out of which two were randomized (33, 34). The combination CISGEM resulted in an RR ranging from 12 to 48%, a median TTP of 5.8-6.4 months and a median survival of 9.5-11.2 months (Table I) (22, 28-30). Serious toxicity was predominantly hematological. A recently performed phase II study on CISGEM resulted in a 50% RR and a median PFS and median survival of 8 and 17 months, respectively (Table I)(24). Neutropenia (23%) was the most common grade 3/4 hematological toxicity. CISGEM, alone or in combination with bevacizumab, has also been studied in an open, placebo-controlled phase II RCT (33). The addition of bevacizumab (BEVCISGEM) did not improve the treatment result of CISGEM but the 15-month duration of the median overall survival for both regimens is among the longest recorded (Table I). The incidence of grade 3/4 toxicity was not significantly different between CISGEM and BEVCISGEM, with neutropenia occurring in 40% *vs*. 42%, anemia in 15% *vs*. 4% and thrombocytopenia in 25% *vs*. 38% of patients, respectively.

Gemcitabine has also been studied in combination with carboplatin (21). Overall, 26% of the patients had partial responses but none of the patients had a complete response. Treatment resulted in a median PFS and overall survival of 9.2 and 15.2 months, respectively (Table I). The most commonly reported grade 3/4 toxicity was thrombocytopenia, occurring in 34% of patients (21).

Pemetrexed-gemcitabine. Attempts to identify less toxic but equally effective combinations of agents such as antimetabolites, antracyclines and topoisomerase inhibitors have failed (2-4). We identified one study exploring the activity of pemetrexed in combination with gemcitabine, with gemcitabine administered on days 1 and 8 plus pemetrexed on day 8 (n=56) *vs*. pemetrexed on day 1 (n=52) (32). Treatment resulted in 26% and 17% RR, a median TTP of 4.3 and 7.4 months, and a median survival of 8.1 and 10.1 months, respectively (Table I). Incidence of grade 4 neutropenia was 25.0% and 29.4%, grade 4 thrombocytopenia 14.3% and 3.9%, grade 3/4 anemia 5.4% and 5.9%, and grade 3/4 fatigue 23.2% and 15.7%, respectively.

Second-line chemotherapy. Pemetrexed has also been evaluated as second-line treatment in patients previously treated with chemotherapy (2-4, 10, 11, 43). We identified one phase III RCT in which pemetrexed plus BSC was compared with BSC-alone in 243 pemetrexed-naïve patients with chemotherapy-relapsed MPM (44). Tumor response and PFS were improved with pemetrexed but active treatment did not influence overall survival. Subgroup analysis showed that patients who responded to first-line chemotherapy tended to have a longer survival when treated with pemetrexed in second line (43, 44). Trial results and observational study data also suggest that patients may benefit from re-treatment with pemetrexed (alone or in combination with cisplatin/carboplatin) with acceptable toxicity (2-4, 43, 45, 46). A recently published open-label phase III RCT investigated the combination of BSC with thalidomide in patients with unresectable MPM or peritoneal mesothelioma

who had completed first-line chemotherapy (47). A total of 222 patients were randomly assigned to receive either maintenance thalidomide combined with BSC, or BSC-alone. Treatment with thalidomide plus BSC resulted in a median TTP of 3.6 months and a median overall survival of 10.6 months (*vs*. 3.5 and 12.9 months for BSC, respectively). Grade 3/4 toxicity occurred in 39% for the thalidomide group (*vs*. 28% for BSC). Phase II trial results of patients out of which many were previously treated with pemetrexed, with vinorelbine-only and gemcitabine in combination with vinorelbine or epirubicine yielded RRs between 10 and 16% and a median overall survival of around 10 months (2-4, 43).

Quality of Life

Symptoms such as cough, dyspnea, (chest) pain, night sweats, tiredness and weight loss, as well as rapid disease progression, severely impair the health-related QoL of patients with advanced MPM (1, 2, 6, 14). Palliative treatment is predominantly aimed at disease stabilization and symptom control but adverse effects associated with chemotherapy should not compromise the treatment aim (1-4, 6). In a large phase III trial comparing BSC plus chemotherapy with BSC, chemotherapy was associated with a slight decrease of pain and increase of lethargy, whereas the scores for physical functioning and global QoL remained essentially unchanged regardless of whether chemotherapy was given or not (6). In several trials, treatment was reported to induce a better control of MPM-associated symptoms, dyspnea and pain in particular (2-4, 17, 18). However, to a considerable extent, this effect was offset by chemotherapy-induced fatigue, gastrointestinal symptoms, nausea and stomatitis (1, 2, 14, 17, 18). In the phase III trials comparing CISPEM and CISRAL with cisplatin, it also appeared that combination treatment did not result in clinically relevant improvements of major symptom scores (pain, dyspnea, fatigue, anorexia and cough) and global QoL. On the other hand, the addition of pemetrexed or raltitrexed to cisplatin had no detrimental effect on QoL but resulted in a stabilization of QoL over the course of treatment (17, 18, 48, 49). In the light of the small but clinically relevant gain in overall survival, this might be considered a valuable treatment effect. No RCT demonstrated the impact of pemetrexed as second-line treatment on survival or QoL (2).

Economic Evaluations

In 2007, the NICE published its first full guidance for the treatment of MPM and the use of pemetrexed based on a systematic review of clinical data (16) and an economic evaluation (15). In 2010, a revised version was published (9). The revised appraisal considered three cost-effectiveness studies. Two of these were submitted by the manufacturer and comprised a pharmacoeconomic analysis of CISPEM *versus* cisplatin (model 1), and CISPEM *versus* BSC plus MVP and/or BSC plus vinorelbine (with or without platinum) (model 2). Data on the clinical effectiveness of the comparator treatments of model 2 were gathered from market research surveys commissioned by the manufacturer (9). It is unclear if or to what extent these data correspond with the results of a UK RCT in which these alternative regimens were compared to BSC (6). At present the treatment options of model 2 are not recommended (2, 9-11), while in the revised appraisal, there is no distinction between the effects and costs contribution of vinorelbine and CISVIN (9). The data of model 2 are, therefore, considered largely irrelevant. Model 1 (CISPEM *vs*. cisplatin) was also evaluated by a NICE assessment group (9). The revised NICE appraisal contains an updated version of this analysis with respect to costs and estimates of cost-effectiveness (9). According to the manufacturer, the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained was £47,567 (€63,974). Taking into account the lower QoL of patients with MPM towards the end of their life, the NICE panel used a lower (mean) utility value than the manufacturer, who did not include disease progression in its models. The NICE panel's estimate of the ICER per QALY gained amounted to £37,700 (€50,704). In the case that, in addition to a 500-mg vial, pemetrexed would also be available in a 100-mg vial the ICER would amount to £34,500 (€46,400) per QALY gained. These estimates are below the UK threshold for cost-effectiveness of about £40,000 (nearly €50,000) (15). Moreover, on considering that MPM is a rare and aggressive malignant disease, that 100 mg vials would become available, treatment for most patients would be limited to four cycles and QoL benefits might have been underestimated in the pharmaco-economic analysis in 2010, the NICE recommended CISPEM as an option for first-line treatment of patients with non-resectable, advanced MPM and good condition (9). In the Netherlands and several other EU countries, pemetrexed is also recommended for treatment of this patient group (2, 50).

The acquisition price is an important factor underlying cost-effectiveness estimates. Following introduction in the Netherlands in 2005, the list price of a 500 mg vial rose from €1,617 to €1,733 (ex. VAT) in 2009 (51, 52). As the result, on the basis of the mean body surface (1.7 m^2: dose of 850 mg) the costs of a three-week cycle amounted to €3,234. In 2012, largely as the result of governmental price control measures, the maximum price per vial was lowered to €1,334, making the costs per cycle €2,668 (53). Since pemetrexed is now also available in 100 mg vials [€288 (ex. VAT)], as anticipated by the NICE (9), the use of these vials would lower the theoretical costs of treatment per cycle to €2,380. Accordingly, at present the ICER per QALY gained would be considerably lower than the 2010 NICE estimate of £34,500 (€46,400).

The effect of the acquisition price is also illustrated by the recent comparison of CISPEM with CISRAL sponsored by the UK holder of the raltitrexed marketing authorization (40). Raltitrexed is not available in the Netherlands, but on the basis of list prices in 2009, the costs of raltitrexed were found to be lower than those of pemetrexed by 266% in the UK to around 500% in France and Spain, and to nearly 750% in Italy (40). On the basis of RCT data and assumptions essentially similar to those underlying the recent NICE evaluation (9), it was concluded that as compared to CISRAL, CISPEM offered marginally lower QALY gained at a substantially higher total cost and was economically inferior to CISRAL with an ICER of £13,454 (€16,757) per QALY gained as compared to cisplatin.

Discussion

As compared to BSC, or antimetabolite, or vinca-alkaloid-based monotherapy in patients with advanced non-resectable MPM and a good performance status, platinum doublet therapy with pemetrexed, supplemented with folic acid and vitamin B_{12}, results in a survival gain of about three months. Although the RRs of CARPEM (20-30%) are lower than for CISPEM (25-40%), for both combinations, the overall survival time is similar. The same applies to cisplatin in combination with the antifolate raltitrexed. Phase II and III trial results with cisplatin in combination with either gemcitabine or vinorelbine, agents with activity similar to that of pemetrexed when used as single agents, are similar to those obtained with CARPEM and CISRAL. Phase III trial data with pemetrexed and raltitrexed were obtained about 10-15 years ago. Recent trial data suggest that the efficacy of platinum doublet therapy can be improved by alternative dosing schedules and supportive care improvements. Treatment of MPM with CISPEM and other platinum-based combinations results in considerable hematological and non-hematological toxicity. In spite of the already impaired health-related QoL of patients with advanced MPM and the toxic effects of treatment, platinum doublet chemotherapy appears to have no detrimental effect over the course of treatment with respect to disease symptoms and global QoL.

In the UK, treatment of MPM with CISPEM was not considered cost-effective. However, as in other countries, the treatment costs were considered acceptable in view of the poor prognosis of advanced MPM and the lack of effective treatment alternatives. Acquisition costs of chemotherapeutic agents are an important factor in determining cost-effectiveness. As a result of its considerably lower price, CISRAL, if available, might be considered a much more cost-effective treatment option than CISPEM. This may also apply for platinum doublet therapy with gemcitabine and vinorelbine, which are considered useful alternatives for patients who cannot be treated with CISPEM. In contrast to pemetrexed, both agents can now be obtained from generic manufacturers. As a result, in the Netherlands, the costs of gemcitabine and vinorelbine per three-week treatment cycle, based on their maximum prices, amount to only 30 and 10% of those of pemetrexed, respectively (53). Although the value of pemetrexed in the management of advanced MPM is supported by the phase III trial results, these data have not been updated by more recent trials, while RCT data comparing CISPEM with other platinum doublets are lacking. Guidelines also recommend the use of CISGEM and CISVIN largely on the basis of encouraging phase II trial results (22, 24, 26, 28-30, 33, 34) whereas in a large ongoing RCT, CISPEM has been chosen as a comparator, to evaluate the activity of bevacizumab (38). In view of the data presently available on the efficacy of various platinum doublets, a more cost-effective treatment approach for advanced MPM would be strongly benefited by results of RCTs and full economic evaluations comparing the recommended CISPEM doublet directly with CISRAL, CISGEM, and/or CISVIN doublets.

Conflicts of Interest

The Authors received research funding from ZonMw, the Netherlands Organisation for Health Research and Development. ZonMw had no involvement in the collection, analysis, and interpretation of data for this article or the writing of this article. The Authors declare no other conflict of interest related to this work.

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