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REVIEW

Pemetrexed in maintenance treatment of advanced non-squamous non-small-cell lung cancer

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Abstract: Pemetrexed, a multitargeting antifolate cytotoxic drug, plays a leading role in front-line chemotherapy for patients with advanced non-squamous non-small-cell lung cancer (NSCLC). Following its approval as second-line monotherapy for locally advanced or metastatic non-squamous NSCLC, pemetrexed has established itself as the first-line regimen in combination with cisplatin, and its powerful antitumor effects and less cumulative toxicities were then taken advantage of in the JMEN and PARAMOUNT trials, respectively, to pioneer a new treatment strategy of switch and continuation maintenance monotherapy. These developments have brought about a marked paradigm shift, and made pemetrexed indispensable in the treatment for non-squamous NSCLC. So far, only three drugs have been approved for maintenance therapy; pemetrexed both by switch and continuation maintenance, erlotinib by switch maintenance, and bevacizumab by continuation maintenance. Compared with observation alone after defined cycles of the first-line chemotherapy, subsequent pemetrexed maintenance therapy has provided significantly longer survival and infrequent severe adverse events. The cost-effectiveness of pemetrexed maintenance therapy is controversial, as well as the other two maintenance drugs, bevacizumab and erlotinib. The latest attractive attention is a combination maintenance therapy. We may have to consider epidermal growth factor receptor (EGFR) mutation status for selection of a combination pattern. A combination maintenance therapy of pemetrexed plus bevacizumab is potential for patients with wild-type EGFR status, while a EGFR tyrosine kinase inhibitor-containing combination is promising for patients with active EGFR mutation status. Pemetrexed will be a pivotal drug when a combination maintenance therapy is used in practice. For future maintenance therapy, we need to explore reliable predictive selection or exclusion markers that can predict who will really benefit from maintenance therapy.

Keywords: pemetrexed, maintenance therapy, continuation, switch, non-squamous non-small cell carcinoma, cost-effectiveness, epidermal growth factor mutation

Introduction

Lung cancer is a leading cause of cancer mortality and accounted for 1.59 deaths worldwide in 2012.[1] Histopathologically, lung cancer is divided broadly into two groups, ie, non-small-cell lung cancer (NSCLC) and small cell lung cancer. The former accounts for 80%–85% of all lung cancer cases, and is further divided into several subgroups, ie, adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others. Most patients with NSCLC are diagnosed when their disease has already advanced locally or metastasized systemically. For inoperable patients with good performance status, chemotherapy is a standard treatment option.

Pemetrexed (Alimta®, Eli Lilly, Indianapolis, IN, USA) is a multitargeted antifolate drug that inhibits replication and survival of cancer cells by disrupting folate-dependent

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metabolic processes. During the past decade, this drug has come to have a leading role in front-line chemotherapy for patients with advanced non-squamous NSCLC, owing to its antitumor effects and mild toxicity.

When combined with platinum in a first-line regimen for non-squamous NSCLC, pemetrexed is superior or similar in efficacy and superior in toxicities to other third-generation antitumor drugs. There were three randomized Phase III studies that compared various endpoints between platinum plus pemetrexed and conventional platinum-based doublets in NSCLC (Table 1).[2–4] Among them, a milestone was the JMDB trial,[4] in which cisplatin plus pemetrexed showed non-inferiority in overall survival (OS) and better tolerability compared with cisplatin plus gemcitabine. In addition, this trial also indicated a histological difference in efficacy. Namely, pemetrexed improved OS for patients with non-squamous histology, but failed for patients with squamous histology. These results led to the approval of cisplatin plus pemetrexed for patients with advanced non-squamous NSCLC as a first-line regimen by the European Medicines Agency in April 2008 and by the US Food and Drug Administration in September 2008. Health-related quality of life and survival without grade 3 or 4 toxicity (SWT) was compared between carboplatin plus pemetrexed and carboplatin plus gemcitabine in a Norwegian study and between carboplatin plus pemetrexed and carboplatin plus docetaxel in a multinational study, respectively.[2,3] Compared with control regimens, carboplatin plus pemetrexed provided similar health-related quality of life and OS in the Norwegian study,[2] and longer SWT but similar OS in the other study.[3] In addition, platinum plus pemetrexed was generally less toxic, except for severe nausea,[4] and generally caused less frequent severe leukopenia and neutropenia than control regimens in all studies (Table 2).[2–4]

Concerning cost-effectiveness, the platinum plus pemetrexed doublet is considered to be cost-effective, particularly in patients with non-squamous NSCLC histology (Table 3). There were two US studies with different approaches for first-line platinum plus pemetrexed.[5,6] Based on a state transition model, Klein et al concluded that cisplatin plus pemetrexed was a cost-effective treatment for patients with non-squamous NSCLC when compared with cisplatin plus gemcitabine and a commonly mentioned but unwarranted threshold of US $100,000 per life-year gained (LYG) in the USA.[5] Compared with a first-line combination of cisplatin plus gemcitabine, cisplatin plus pemetrexed led to an incremental cost per LYG of US $104,577 for patients with NSCLC regardless of histological subtype, but a cost of US $83,537 for patients with non-squamous NSCLC.

Table 1 Phase III studies of combinations of pemetrexed plus platinum compared with standard platinum-based doublets

Reference	Primary endpoint	n	Regimens	RR (%)	PFS (M)	HR *P*-value	OS (M)	HR *P*-value
Scagliottii et al[4] (JMDB trial)	OS[a]	All NSCLC, entire population						
		862	CDDP + PEM	30.6	4.8	HR 1.04	10.3	HR 0.94
		863	CDDP + GEM ×6 cycles	28.2	5.1	Non-inferior	10.3	Non-inferior
		Non-SQ NSCLC subgroup						
		512	CDDP + PEM	ND	5.3	HR 0.90	11.8	HR 0.81
		488	CDDP + GEM	ND	4.7	ND	10.4	*P*=0.005
Grønberg et al[2]	HRQoL[b]	All NSCLC, entire population						
		225	CBDCA + PEM	ND	ND	ND	7.3	HR ND
		221	CBDCA + GEM ×4 cycles	ND	ND	ND	7.0	*P*=0.63
		Non-SQ NSCLC subgroup						
		127	CBDCA + PEM	ND	ND	ND	7.8	HR ND
		121	CBDCA + GEM	ND	ND	ND	7.5	*P*=0.77
Rodrigues-Pereira et al[3]	SWT	All non-SQ NSCLC						
		128	CBDCA + PEM	34.0	5.8	HR 0.91	14.9	HR 0.93
		132	CBDCA + DTX ×6 cycles	22.9	6.0	*P*=0.534	14.7	*P*=0.698
							SWT	
		128	CBDCA + PEM				3.2	HR 0.45
		132	CBDCA + DTX				0.7	*P*<0.001

Notes: [a]Non-inferiority design; [b]defined as the four clinically relevant domains of global quality of life, nausea/vomiting, dyspnea and fatigue, and assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) and the lung cancer–specific module LC13 during the first 20 weeks.
Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; DTX, docetaxel; GEM, gemcitabine; HR, hazard ratio; HRQoL, health-related quality of life; M, months; ND, not described; RR, response rate; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; SQ, squamous cell carcinoma; SWT, survival without treatment-emergent grade 3/4 toxicity.

Table 2 Comparison of statistically significant adverse effects between pemetrexed-containing and control regimens

Reference	Scagliotti et al[4] (JMDB trial)		Grønberg et al[2]		Rodrigues-Pereira et al[3]	
Regimens	**CDDP + PEM**	**CDDP + GEM**	**CBDCA + PEM**	**CBDCA + GEM**	**CBDCA + PEM**	**CBDCA + DTX**
n	839	830	219	217	106	105
Hematologic						
Leukopenia, grade 3–4 (%)	4.8[a]	7.6	23[a]	46	16.0[a]	40.0
Neutropenia, grade 3–4 (%)	15.1[a]	26.7	40[a]	51	33.0[a]	64.8
Anemia, grade 3–4 (%)	5.6[a]	9.9	13	13	12.3[a]	1.9
Thrombocytopenia, grade 3–4 (%)	4.1[a]	12.7	24[a]	56	9.4	2.9
Non-hematologic						
Febrile neutropenia, grade 3–4 (%)	1.3[a]	3.7	ND	ND	0[a]	8.9
Alopecia, any grade (%)	11.9[a]	21.4	ND	ND	8.5[a]	42.9
Nausea, grade 3–4 (%)	7.2[a]	3.9	3	4	0.9	1.0
Diarrhea, any grade (%)	ND	ND	ND	ND	6.6[a]	20.0
Abdominal pain, any grade (%)	ND	ND	ND	ND	1.9[a]	9.5

Note: [a]Statistically significant ($P<0.05$).
Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; DTX, docetaxel; GEM, gemcitabine; ND, not described; PEM, pemetrexed.

Thus, considering the effect of prolongation of survival by the pemetrexed-containing regimen, pemetrexed was expensive but within the allowance. Based on indirect comparisons of the following three regimens in different studies because of no available head-to-head data, platinum plus pemetrexed was also considered more cost-effective than a triplet of bevacizumab combined with carboplatin plus paclitaxel, but controversial when compared with a doublet of carboplatin plus paclitaxel, as the pemetrexed-containing regimen was more costly but more effective than carboplatin plus paclitaxel.[5,6] In September 2009, the National Institute for Health and Clinical Excellence (NICE) in the UK recommended pemetrexed in combination with cisplatin as an option for the first-line treatment of patients with non-squamous NSCLC, using the single technology appraisal process and based on the Evidence Review Group's exploratory analysis indicating that the incremental cost-effectiveness ratios (ICERs) for cisplatin plus pemetrexed compared with cisplatin plus gemcitabine were between £20,000 and £30,000 per quality-adjusted life-year (QALY) gained for non-squamous NSCLC and between £17,000 and £25,000 per QALY for adenocarcinoma or large-cell carcinoma, all under the willing-to-pay threshold of £30,000 per QALY gained.[7]

Options for maintenance therapy; continuation maintenance versus switch maintenance

Maintenance therapy after 4–6 cycles of platinum-based induction chemotherapy is a standard first-line regimen for patients with advanced non-squamous NSCLC. Maintenance therapies are classified broadly into two types, ie, continuation maintenance and switch maintenance. The former is a continuation of one or two drugs used in the induction regimen and the latter involves introduction of an additional drug that was not used in the induction regimen. Switch maintenance can be understood as an early second-line therapy. Differences in efficacy between these two maintenance strategies remain unknown. A recent meta-analysis did not detect any significant differences in OS or progression-free survival (PFS) between these two maintenance strategies.[8] In contrast, another two meta-analyses showed favorable OS benefits for switch maintenance.[9,10] In the study by Behera et al, switch maintenance provided significant benefit, both in PFS (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.57–0.67, $P<0.0001$) and OS (HR 0.84, 95% CI 0.77–0.91, $P=0.00026$). In contrast, continuation maintenance modestly improved PFS (HR 0.90, 95% CI 0.85–0.95, $P=0.007$), but did not show an OS benefit (HR 0.927, 95% CI 0.78–1.09, $P=0.33$).[9] In the study by Cai et al, PFS was prolonged by both continuation (HR 0.54, 95% CI 0.46–0.63, $P<0.00001$) and switch (HR 0.64, 95% CI 0.59–0.70, $P<0.00001$) maintenance. Switch maintenance significantly improved OS (HR 0.80, 95% CI 0.72–0.90, $P=0.0002$), while continuation maintenance did not achieve a statistically significant improvement (HR 0.82, 95% CI 0.66–1.01, $P=0.06$).[10] From the viewpoint of clinical practice, these two maintenance strategies are very different, especially at the time of transition from the induction phase to the maintenance phase. Most oncologists would hesitate to discontinue an effective and tolerable induction regimen and then introduce a new drug with unknown efficacy and adverse effects. Thus, continuation maintenance is more acceptable than switch maintenance.

Table 3 Comparison in cost-effectiveness of direct medical costs between first-line pemetrexed-containing regimen with another platinum-doublet regimen: study deigns and results (monetary unit, US $)

Reference	Methods, cost and outcome discount, study perspective, time frame	Data sources	Study population	Regimen	Histology	Cost	LYG or OS[a]	QALY	ICER[a] / LYG	ICER / QALY
Klein et al[5] (US)	Semi-Markov model No discount U.S. payer's perspective Time frame; 2 year	Clinical parameters; RCT (JMDB) Cost; Medicare reimbursement rates and average doses, PharMetrics claim database	Chemotherapy-naïve, stage IIIB/IV, non-SQ or all histology NSCLC, BSA 1.8 m^2	CDDP + PEM	Non-SQ	$ 65,517	0.9652 Y	0.5016		
					All NSCLC	$ 66,606	0.9587 Y	0.4943		
				CDDP + GEM						
								Incremental CDDP+PEM to CDDP+GEM		
					Non-SQ	$ 61,008	0.9112 Y	0.4676	$ 83,537	$ 132,829
					All NSCLC	$ 61,535	0.9102 Y	0.4661	$ 104,577	$ 179,597
				CBDCA + PTX						
								Incremental CDDP+PEM to CBDCA+PTX		
					Non-SQ	$ 52,885	0.8945 Y	0.4513	$ 178,613	$ 250,992
					All NSCLC	$ 50,283	0.8882 Y	0.4469	$ 231,291	$ 343,870
				CBDCA + PTX + Bev → Bev maintenance (Bev 15 mg/kg)						
							Incremental CBDCA+PTX+Bev→Bev to CDDP+PEM			
					Non-SQ	$ 90,044	1.0379 Y	0.5260	$ 337,179	$ 1,006,065
Shah et al[6] (US)	Retrospective cohort study of real world data documented in PMS data Time frame; 1 year	ION clinical oncology database, PMS data, SSA's Death Index Master file	First-line treatment between 2006 and 2009, advanced non-SQ NSCLC	Platinum + PEM	Non-SQ	$ 33,969	190 days	ND		
				CBDCA + PTX						
							Incremental CBDCA+PTX to Platinum+PEM for OS			
						$14,832	132 days	ND	$ 330	ND
				CBDCA + PTX + Bev → Bev maintenance						
							Incremental CBDCA+PTX+Bev→Bev to Platinum+PEM for OS			
						$ 53,915	163 days	ND	–$ 739	ND

Notes: [a]Studies by Klein et al and by Shah et al presented LYG (years) and OS (days), ICER (cost / LYG, US $) and mean incremental cost/day (US $), respectively.

Abbreviations: BSA, body surface area; Bev, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; ICER, incremental cost-effectiveness ratio; ION, International Oncology Network; LYG, life-year gained; ND, not described; NSCLC, non-small cell lung cancer; OS, overall survival; PEM, pemetrexed; PTX, paclitaxel; QALY, quality-adjusted life-year; SQ, squamous cell carcinoma; RCT, randomized controlled trial; PMS, practice management system; SSA, Social Security Administration; Y, years.

Currently, there are three drugs, comprising two molecular targeted drugs and one cytotoxic drug, approved as maintenance monotherapy after platinum-based induction chemotherapy: erlotinib (Tarceva®, Hoffmann-La Roche Ltd, Basel, Switzerland), a reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), as switch maintenance for patients with any NSCLC histology; bevacizumab (Avastin®, Hoffmann-La Roche Ltd), a humanized monoclonal antibody that inhibits vascular endothelial growth factor and thereby angiogenesis, as continuation maintenance after platinum-based and bevacizumab-containing triplet induction for patients with non-squamous NSCLC; and pemetrexed as both types of maintenance for patients with non-squamous NSCLC.

Efficacy, safety, and tolerability of pemetrexed maintenance therapy

Pemetrexed is the only successful cytotoxic drug in maintenance therapy. There are three cytotoxic drugs that have been tested as candidates of continuation maintenance in phase III trials, but they showed different results (Table 4). Paclitaxel improved neither PFS nor OS,[11] gemcitabine prolonged only PFS but not OS,[12–14] and only pemetrexed successfully extended both PFS and OS.[15,16] In addition, severe adverse effects were less frequent during the pemetrexed maintenance phase, compared indirectly with paclitaxel and gemcitabine maintenance (Table 5). Thus, pemetrexed had an advantage of less cumulative toxicity and better tolerability.

Table 4 Phase III studies comparing a maintenance cytotoxic monotherapy with observation alone after induction chemotherapy

Reference	PEP	n	Induction	Maintenance	PFS or TTP (M)	HR *P*-value	OS (M)	HR *P*-value
Continuation maintenance								
Belani et al[11]	RR	401 enrolled	3 regimens of					
	TTP	130 randomized	CBDCA + PTX	Survival from randomization before induction chemotherapy				
		65	(arm 1–3)[a]	w PTX	8.9	*P*=0.124	17.5	*P*=0.243
		65		Obs	6.8		14.0	
Brodowicz et al[13]	TTP	352 induction	CDDP + GEM					
(CECOG trial)		257 non-PD	×4 cycles					
		215 randomized		Survival from first treatment administration				
		138		GEM	6.6	HR ND	13.0	HR ND
		68		Obs	5.0	*P*<0.001	11.0	*P*=0.195
				Survival from randomization after induction chemotherapy				
		138		GEM	3.6	HR ND	10.2	HR ND
		68		Obs	2.0	*P*<0.001	8.1	*P*=0.172
Belani et al[12]	OS	519 enrolled	CBDCA + GEM					
		255 randomized	×4 cycles	Probably from randomization after induction chemotherapy				
		128		GEM	3.9	HR ND	8.0	HR 0.97
		127		Obs	3.8	*P*-value ND	9.3	*P*=0.84
Perol et al[14]	PFS	834 enrolled	CDDP + GEM					
(IFCT-GFPC0502 trial)		464 randomized	×4 cycles	Survival from randomization after induction chemotherapy				
		154		GEM	3.8	HR 0.56	12.1	HR 0.89
		155		Obs	1.9	*P*<0.001	10.8	*P*=0.3867
Paz-Ares et al[15,16]	PFS	939 induction	CDDP + PEM	OS of randomly assigned patients, from start of induction chemotherapy				
(PARAMOUNT trial)		539 non-PD	×4 cycles					
		359		PEM			16.9	HR 0.79
		180		Obs			14.0	*P*=0.0191
				Survival from randomization after induction chemotherapy				
		359		PEM	4.4	HR 0.60	13.9	HR 0.78
		180		Obs	2.8	*P*<0.001	11.0	*P*=0.0198
Switch maintenance								
Ciuleanu et al[29]	PFS		Plt-based regimens	Survival from randomization after induction chemotherapy				
(JMEN trial)		441	×4 cycles	PEM	4.3	HR 0.50	13.4	HR 0.79
		222		Placebo	2.6	*P*<0.0001	10.6	*P*=0.012

Notes: [a]Arm 1, CBDCA (AUC 6 mg/mL · min, day 1) plus PTX (100 mg/m^2, days 1, 8, and 15) every 4 weeks; arm 2, CBDCA (AUC 2 mg/mL min, days 1, 8, and 15) plus PTX (100 mg/m^2, days 1, 8, and 15) every 4 weeks; arm 3, CBDCA (AUC 2 mg/mL · min) plus PTX (150 mg/m^2 in cycle 1 and 100 mg/m^2 in cycle 2) weekly for 6 of 8 weeks.
Abbreviations: AUC, area under the curve; CDDP, cisplatin; GEM, gemcitabine; HR, hazard ratio; M, months; ND, not described; Obs, observation alone; OS, overall survival; PEP, primary endpoint; PD, progressive disease; PEM, pemetrexed; PFS, progression-free-survival; Plt, platinum; PTX, paclitaxel; RR, overall response rate; TTP, time to progressive disease; w PTX, weekly paclitaxel.

Table 5 Comparison of grade 3–4 adverse events during monotherapy maintenance phase (incidence rate ≥1% in any study)

Reference	Brodowicz et al[13] (CECOG trial)	Belani et al[12]		Perol et al[14] (IFCT-GFPC0502 trial)		Paz-Ares et al[16] (PARAMOUNT trial)		Ciuleanu et al[29] (JMEN trial)	
n	138	128	127	154	155	359	180	441	222
Maintenance regimens	GEM	GEM	BSC	GEM	BSC	PEM	BSC	PEM	BSC
Hematologic									
Leukopenia (%)	2.3	ND	ND	ND	ND	2.2	0	2	<1
Neutropenia (%)	14.9	13.3	1.6	20.8	0.6	5.8	0	3	0
Anemia (%)	2.6	9.4	2.4	2.6	0.6	6.4	0.6	3	<1
Thrombocytopenia (%)	1.7	9.4	1.4	6.5	0	1.9	0	ND	ND
Non-hematologic									
Fatigue (%)	ND	3.9	1.6	ND	ND	4.7	1.1	5	<1
Alopecia (%)	4.3	ND	ND	ND	ND	ND	ND	ND	ND
Deterioration of general condition (%)	ND	ND	ND	3.2	3.9	ND	ND	ND	ND
Pneumonia (%)	ND	ND	ND	3.2	1.3	ND	ND	ND	ND
Anorexia (%)	ND	ND	ND	0.6	0.6	0.3	0	2	0
Asthenia (%)	ND	ND	ND	1.9	0	ND	ND	ND	ND
Febrile neutropenia (%)	ND	ND	ND	ND	ND	1.9	0	ND	ND
Infection (%)	ND	ND	ND	1.3	0	ND	ND	2	0
Pain (%)	ND	ND	ND	ND	ND	1.1	0	ND	ND

Notes: Study by Brodowicz et al (CECOG trials)[13] did not describe adverse events in the control arm. No study compared adverse events statistically.
Abbreviations: BSC, best supportive care; GEM, gemcitabine; ND, not described; PEM, pemetrexed.

Erlotinib switch maintenance has never been compared with pemetrexed switch or continuation maintenance in a head-to-head Phase III trial. Bevacizumab combined with carboplatin plus paclitaxel has been directly compared with pemetrexed continuation maintenance in two Phase III studies (Table 6).[17,18] These two studies, PRONOUNCE and ERACLE, defined unique primary endpoints of PFS without grade 4 adverse events[18] and difference in QoL,[17] respectively, instead of the usual efficacy parameters of PFS or OS. Thus, these studies provided little information with

Table 6 Phase III studies comparing bevacizumab with pemetrexed or pemetrexed plus bevacizumab

Reference	PEP	n	Induction	Maintenance	PFS (M)	HR *P*-value	OS (M)	HR *P*-value
Zinner et al[18] (PRONOUNCE trial)	G4PFS	361	CBDCA + PEM	PEM	Survival from random assignment before induction chemotherapy G4PFS			
			CBDCA + PTX + Bev ×6 cycles	Bev				
		182		PEM	3.9	HR 0.85	10.5	HR 1.07
		179		Bev	2.9	*P*=0.176	11.7	*P*=0.615
					PFS			
		182		PEM	4.4	HR 1.06		
		179		Bev	5.5	*P*=0.61		
Galetta et al[17] (ERACLE trial)	QoL[a]	118						
		60	CDDP + PEM	PEM	ND	HR 0.62	ND	HR 0.69
		58	CBDCA + PTX + Bev ×6 cycles	Bev	ND	*P*=0.03	ND	*P*=0.08
Barlesi et al[34,35] (AVAPERL trial)	PFS	376 induction	CDDP + PEM + Bev ×4 cycles					
		253 non-PD		Survival from random assignment after induction chemotherapy				
		128		PEM + Bev	7.4	HR 0.57	17.1	HR 0.87
		125		Bev	3.7	*P*<0.0001	13.2	*P*=0.29
Patel et al[36] (PointBreak trial)	OS							
		934 randomized		Survival from random assignment before induction treatment				
		472	CBDCA + PEM + Bev	PEM + Bev	6.0	HR 0.83	12.6	HR 1.00
		467	CBDCA + PTX + Bev ×4 cycles	Bev	5.6	*P*=0.012	13.4	*P*=0.949

Note: [a]EQ5D Index (EQ5D-I) and EQ5D-VAS (Euro-QoL questionnaire) at 12 weeks during maintenance therapy.
Abbreviations: Bev, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; G4PFS, progression-free survival without grade 4 adverse event; HR, hazard ratio; M, months; ND, not described; OS, overall survival; PD, progressive disease; PEM, pemetrexed; PEP, primary endpoint; PFS, progression-free survival; PTX, paclitaxel; QoL, quality of life.

regard to deciding which regimen is superior as the first-line regimen for patients with non-squamous NSCLC.

Cost-effectiveness of pemetrexed maintenance therapy

The cost-effectiveness of maintenance treatment with pemetrexed monotherapy is debatable (Table 7). There were five pharmacoeconomic analyses from various countries addressing this problem.[19–23] Four analyses were based on a switch maintenance trial (JMEN),[19–22] while the other was a continuation maintenance trial (PARAMOUNT).[23] Three of these analyses concluded that pemetrexed maintenance is not cost-effective, irrespective of switch and continuation.[21–23] In the pharmacoeconomic analyses from Japan, Switzerland, and the People's Republic of China, each willingness-to-pay threshold was assumed as ¥5–6 million per LYG (US $43,478–52,174 per LYG),[22] €72,000 per QALY gained (Swiss federal court decision, November 23, 2010),[21] and US $13,527 per QALY gained (3× the per capita gross domestic product),[23] respectively. All ICERs based on LYG or QALY were more than these thresholds.[21–23] The UK analysis also found that the most plausible ICER was £47,000 per QALY gained, which was above the standard NICE willingness-to-pay range (£20,000 to £30,000 per QALY).[19] Considering that maintenance treatment with pemetrexed fulfilled the end-of-life criteria, NICE in the UK optionally recommended switch maintenance by pemetrexed only for patients with non-squamous histology.[24] In contrast, NICE did not recommend continuation maintenance by pemetrexed because the most plausible ICER, approximately £74,500 per QALY gained, was higher than that normally considered to be cost-effective, even if the supplementary advice of NICE on end-of-life treatments was taken into consideration.[25] The US analysis indicated that pemetrexed may be considered cost-effective.[20] The ICER for pemetrexed to observation alone, ie, US $122,371, may not be cost-effective when compared with a commonly mentioned threshold of US $100,000 per LYG, but may be cost-effective when compared with a range of US $95,000 to US $264,000 per LYG, a recently revised plausible lower and upper bounds for cost-effectiveness decision rule in the USA.[26]

Comparison of cost-effectiveness between different types of maintenance is more difficult because of a lack of head-to-head clinical trials. Three studies have indirectly compared direct medical costs between maintenance with pemetrexed and maintenance with another drug (Table 8).[20,27,28] A US study showed that pemetrexed maintenance is more cost-effective for patients with non-squamous NSCLC than erlotinib, because the ICER for pemetrexed versus erlotinib (US $150,260/LYG) is within the acceptable range of willingness to pay.[20] Another UK study also showed a clear advantage in favor of pemetrexed, ICER for erlotinib versus pemetrexed, £84,029/QALY gained.[27] In contrast, a European cross-market cost comparison showed that total monthly treatment costs per patient, including acquisition costs, administration costs, and costs of treating adverse events, were more reasonable for erlotinib than for pemetrexed, ie, €2,140 for erlotinib versus €3,453 for pemetrexed in France, €2,732 versus €5,534 in Germany, €1,518 versus €2,921 in Italy, and €2,048 versus €3,164 in Spain.[28] Thus, it remains unknown which maintenance strategy is the most cost-effective.

There were many study limitations in these pharmacoeconomic analyses; for example, a lack of clinical trials and detailed information about quality of life, imbalanced accrual in trials, and a variety of medical services among countries and territories. A Japanese study of direct medical cost by Tsuchiya et al[22] was based on clinical results of JMEN study[29] and Japanese health care system. Although the JMEN study included 32% of Asian population in pemetrexed switch maintenance group mainly from the People's Republic of China and Korea, no Japanese patient participated in this trial. The PARAMOUNT trial, undertaken in 93 center in 16 countries, included Asian population in only 4% of all cases.[30] Therefore, we Japanese and Asian can not refer to clinical results of this trial for a pharmacoeconomic study. There were three Japanese single-arm, Phase II studies evaluating a combination of carboplatin plus pemetrexed followed by pemetrexed maintenance for patients with non-squamous NSCLC. These trials provided an impressive median OS of more than 20 months not only from maintenance chemotherapy in patients who had received maintenance therapy[31,32] but also from induction chemotherapy in all enrolled patients.[32,33] In contrast, the JMEN and PARAMOUNT studies showed a median OS of 16.5 and 16.9 months, respectively, from induction chemotherapy for patients who had proceeded into the maintenance phase (Table 9).[15,16,29] OS in the Japanese single-arm, Phase II studies was much longer (by approximately 4 months) than in the multinational randomized placebo-controlled studies. Thus, the Japanese medical economic study possibly underestimated pemetrexed maintenance when based on clinical data from other ethnic groups and countries. Further studies and discussions are warranted with regard to pemetrexed maintenance.

Future directions

A recent interesting challenge is doublet combination maintenance (Table 6).[34–36] We may have to consider EGFR mutation

Table 7 Comparison in cost-effectiveness of direct medical cost between maintenance with pemetrexed *vs.* observation alone after induction chemotherapy: study designs and results

Reference	Methods, costs and outcomes discount, study perspective, time frame and reference year for cost	Data sources	Study population	Regime	Cost	LYG or OS	QALY	ICER[a] / LYG	ICER[a] / QALY
Greenhalgh et al[19] (UK)	ERG report reviewing the manufacturer's evidence submission, de novo economic model Cost discount ND Time frame; lifetime Reference year; ND	Clinical parameters: RCT (JMEN trial)	Subgroup of 481 patients in JMEN trial	PEM maintenance Submitted base case[b] Combined effect of changes BSC alone Submitted base case[b] Combined effect of changes	 £17,455 £20,925 £8,318 £8,370	15.5 M 10.3 M 	 0.9697 0.9539 0.6988 0.6881	 ND ND 	 £33,732 £47,239
Klein et al[20] (US)	Semi-Markov model Discounted at 3% US payer's perspective Time frame; 3 years Reference; 2009 US$	Clinical parameters: RCT (JMEN, ATLAS, SATURN trials) Cost: Medicare reimbursement rate and analysis of claim database (PharMetrics)	Advanced NSCLC patients who have completed first-line platinum double chemotherapy without progression	PEM maintenance Non-SQ All NSCLC BSC alone Non-SQ All NSCLC	 $96,774 $89,289 $64,830 $61,036	 1.3412 Y 1.2434 Y 1.0802 Y 1.1060 Y	 ND 	 $122,371 $205,597 	 ND
Tsuchiya et al[22] (Japan)	Markov model Discounted at 3% annually Japanese healthcare payer perspective Time frame; ND Reference; 2009 US$ (assumed US $1 to JPY 115)	Clinical parameters: RCT (JMEN trial)	Advanced NSCLC (either non-SQ or all histology), Japanese men in their 60s, height 164.6 cm, weight 64.5 kg, BSA 1.70 m^2	PEM maintenance Non-SQ All NSCLC BSC alone Non-SQ All NSCLC	 $68,536 $64,409 $39,872 $38,843	 489.4 D 451.8 D 359.5 D 366.2 D	 0.7321 0.6770 0.5411 0.5511	 $80,563 $109,024 	 $150,115 $203,022
Matter-Walstra et al[21] (Switzerland)	Markov model No discount Swiss health care system perspective Time frame; lifetime Reference; 2010 Swiss prices (€0.72 / Swiss franc)	Clinical parameters: RCT (JMEN trial) Cost: literature	Advanced non-SQ NSCLC, BSA 1.77 m^2	PEM maintenance BSC alone	€99,705 €71,316	15.6 M 10.7 M	0.82 0.56	ND	€106,202

Zeng et al[23] (People' Republic of China)	Markov model Discounted at 3% annually Chinese health care system perspective Time frame: 1,2,5 and 10 year Reference: 2010 US$ (assumed 1 US$ to 6.6515 Chinese yuan)	Clinical parameters: RCT (PARAMOUNT trial) Cost: BSC and AE costs from literature, market share and local charges in the People's Republic of China	Advanced non-SQ NSCLC, weight 65 kg, BSA 1.72 m^2	PEM maintenance 1-year 2-year 5-year 10-year BSC alone 1-year 2-year 5-year 10-year	$36,443 $55,532 $72,103 $73,955 $28,255 $44,181 $54,790 $55,607	0.760 Y 1.140 Y 1.444 Y 1.477 Y 0.718 Y 1.026 Y 1.230 Y 1.245 Y	0.440 0.631 0.776 0.791 0.396 0.541 0.637 0.644	$193,796 $99,183 $80,792 $79,134	$183,589 $126,353 $124,766 $124,793

Notes: [a]Incremental pemetrexed maintenance to BSC; [b]data based upon the evidence submission from the manufacturer (Eli Lilly) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process.

Abbreviations: AE, adverse events; BSA, body surface area; BSC, best supportive care; D, days; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; JPY, Japanese Yen; LYG, life-year gained; M, months; ND, not described; NSCLC, non-small cell lung cancer; OS, overall survival; PEM, pemetrexed; QALY, quality-adjusted life-year; RCT, randomized controlled trial; SQ, squamous cell carcinoma; Y, years.

status for selection of a combination pattern. For patients with non-squamous NSCLC histology and positive EGFR mutation status, combination patterns of EGFR TKI with pemetrexed or bevacizumab are promising. A randomized Phase III trial is underway comparing gefitinib monotherapy with doublet continuation maintenance of pemetrexed plus gefitinib after triplet induction with carboplatin, pemetrexed, and gefitinib in patients with non-squamous NSCLC and positive EGFR mutations (NEJ009, trial number: UMIN000006340). This study potentially develops a first-line regimen for such patients. On the other hand, combination maintenance of bevacizumab plus an EGFR TKI is an alternative candidate treatment for these patients. Erlotinib provided an add-on effect with regard to PFS (bevacizumab plus placebo versus bevacizumab plus erlotinib; 3.7 versus 4.8 months from time of random assignment after induction chemotherapy, HR 0.71, 95% CI 0.58–0.86, $P<0.001$), but failed in OS (13.3 versus 14.4 months, respectively, HR 0.92, 95% CI 0.70–1.21, $P=0.5341$), when a maintenance combination of erlotinib plus bevacizumab was introduced after four cycles of a bevacizumab-containing platinum-doublet chemotherapy for NSCLC patients who had not been selected by EGFR mutation status (ATLAS).[37] For a subgroup with active EGFR mutations, compared with the wild-type subgroup, this combination maintenance therapy also achieved greater improvement in PFS (HR 0.44, 95% CI 0.22–0.86 for the EGFR mutation-positive subgroup [n=52] versus HR 0.85, 95% CI 0.64–1.13 for the EGFR wild-type subgroup [n=295]), but there was no statistically significant difference in OS outcome (HR 0.46, 95% CI 0.21–1.02 versus HR 0.86, 95% CI 0.65–1.15, respectively). Thus, for patients with wild-type EGFR and unknown EGFR mutation status, maintenance therapy of bevacizumab plus erlotinib is not recommended, while subgroup analyses of this randomized Phase III study suggested a potential efficacy of this maintenance combination for patients with active EGFR mutations. A recent randomized Phase II study in Japan (JO25567) also demonstrated that first-line bevacizumab plus erlotinib markedly improved PFS compared with erlotinib alone (16.0 months for erlotinib plus bevacizumab [n=77] versus 9.7 months for erlotinib alone [n=77], HR 0.54, 95% CI 0.36–0.79, $P=0.0015$).[38] This study suggests that, for patients with active EGFR mutation status, combination of these two molecularly targeted drugs potentially yields a better survival benefit than erlotinib alone. We hope that this combination is beneficial in the maintenance setting, as well as in the first-line setting.

For patients with non-squamous NSCLC and wild-type or unknown EGFR mutation status, pemetrexed plus bevacizumab

Table 8 Comparison in cost-effectiveness of direct medical cost between pemetrexed and other maintenance therapy: study designs and results

Reference	Methods, costs and outcomes discount, study perspective, time frame and reference year for cost	Data sources	Study population	Regime	Costs	LYG / OS	QALY	ICER / LYG	ICER / QALY
Klein et al[20] (US)	See Klein et al[20]			PEM					
				Non-SQ	$96,774	1.3412 Y	ND		
				All NSCLC	$89,289	1.2434 Y	ND		
				Erlotinib					
								Incremental PEM to Erlotinib	
				Non-SQ	$72,300	1.1784 Y	ND	$ 150,260	ND
				All NSCLC	$71,147	1.1854 Y	ND	$ 312,341	ND
				Bev (15 mg/kg)					
								Incremental Bev to PEM	
				Non-SQ	$105,961	1.2933 Y	ND	Dominated	ND
Dickson et al[27] (UK)	ERG report reviewing the manufacturer's evidence submission, de novo economic model Cost discount; ND Time frame; lifetime Reference year; ND	Clinical parameters: RCT (SATURN, JMEN trial)	Model 1; SD, All NSCLC: Erl vs. placebo Model 2; SD, SQ: Erl vs. placebo Model 3; SD, non-SQ: Erl vs. PEM	PEM					
				SD, non-SQ	£26,608	1.5495 Y	0.9229	ND	ND
				Erlotinib					
								Incremental PEM to Erlotinib	
				SD, non-SQ	£18,148	1.4213 Y	0.8222	ND	£84,029
Nuijten et al[28] (France, Germany, Italy and Spain)	Cross-market cost comparison Perspective of national health-care decision-makers or purchasers. Time frame; monthly Reference; 2008 Euro	Clinical parameters: RCT (SATURN, JMEN trial) Cost; literatures, National drug tariffs for France, Germany, Italy and Spain	Advanced NSCLC	PEM		ND	ND	ND	ND
				France	€3,453				
				Germany	€5,534				
				Italy	€2,921				
				Spain	€3,164				
				Erlotinib		ND	ND	ND	ND
				France	€2,140				
				Germany	€2,732				
				Italy	€1,518				
				Spain	€2,048				

Abbreviations: Bev, bevacizumab; Erl, erlotinib; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; ND, not described; NSCLC, non-small-ell lung cancer; OS, overall survival; PEM, pemetrexed; QALY, quality-adjusted life-year; RCT; randomized controlled trial; SD, stable disease; SQ, squamous cell carcinoma; Y, years.

Table 9 Comparison of efficacy of the first-line combination of pemetrexed plus platinum followed by pemetrexed maintenance between Japanese Phase II studies and multinational Phase III studies

Reference	Country	Phase	Patients	Treatment	PFS and OS from induction (M)
Ciuleanu et al[29] (JMEN trial)	Multi	R-p3	441 NSCLC, including 26% SQ	Plt-based doublet ×4 cycles → PEM maintenance	PFS 7.7 OS 16.5
Paz-Ares et al[15,16] (PARAMOUNT trial)	Multi	R-p3	359 non-SQ	CDDP + PEM ×4 cycles → PEM maintenance	PFS ND OS 16.9
Okamoto et al[33] (JACAL trial)	Japan	S-p2	109 non-SQ	CBDCA + PEM ×4 cycles → PEM maintenance	PFS 5.7 OS 20.2
Minami et al[32] (OULCSG0902 trial)	Japan	S-p2	34 non-SQ	CBDCA + PEM ×4 cycles → PEM maintenance	PFS 5.2 OS 23.3
Karayama et al[31]	Japan	R-p2	26 non-SQ	CBDCA + PEM ×4 cycles → PEM maintenance	PFS 7.4 OS 25.0

Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; M, month; Multi, multinational; ND, not described; NSCLC, non-small-cell lung cancer; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; Plt, platinum; R-p2, randomized phase II; R-p3, randomized phase III; S-p2, single-arm phase II; SQ, squamous cell carcinoma.

is possibly promising. Compared with bevacizumab alone, continuation maintenance of pemetrexed plus bevacizumab significantly prolonged PFS by a median of 3.7 months, but did not achieve a significant improvement in OS, despite a difference of 3.9 months in median OS after four cycles of bevacizumab combined with cisplatin plus pemetrexed (AVAPERL).[35] Another Phase III study (PointBreak) showed that continuation maintenance of pemetrexed plus bevacizumab after an induction triplet of bevacizumab combined with carboplatin plus pemetrexed was similar in OS but significantly superior in PFS when compared with continuation maintenance of bevacizumab alone after bevacizumab combined with carboplatin plus paclitaxel.[36] Thus, even the combination of pemetrexed plus bevacizumab remains unable to show an OS benefit when compared with bevacizumab alone. Adverse effects of anemia, thrombocytopenia, and fatigue were significantly more frequent on combination maintenance than on bevacizumab alone in the PointBreak trial (Table 10).[36] Benefit in terms of cost-effectiveness should be investigated for these combination maintenance therapies when their significant survival benefits are demonstrated, because these drugs are all very expensive.

Table 10 Comparison of grade 3–4 adverse events during maintenance phase (incidence rate ≥1% in any study)

Reference	Barlesi et al[34,35] (AVAPERL trial)		Patel et al[36] (PointBreak trial)	
n	125	120	292	298
Maintenance regimen	PEM + Bev	Bev	PEM + Bev	Bev
Hematologic				
Leukopenia (%)	ND	ND	ND	ND
Neutropenia (%)	5.6	0	14.0	11.4
Anemia (%)	3.2	0	11.0[a]	0.3
Thrombocytopenia (%)	0	0	7.2[a]	2.3
Non-hematologic				
Fatigue (%)	2.4	1.7	9.6[a]	1.7
Hypertension (%)	4.8	2.5	3.1	6.0
Sensory neuropathy (%)	ND	ND	0[a]	4.7
Thromboembolic events (%)	ND	ND	2.4	0.7
Pulmonary embolism (%)	0.8	1.7	ND	ND
GI or pulmonary hemorrhage (%)	ND	ND	1.4	0
Febrile neutropenia (%)	0.8	0	1.0	0

Notes: AVAPERL study did not describe the result of statistical comparison. [a]Statistically significant ($P<0.05$).

Abbreviations: Bev, bevacizumab; GI, gastrointestinal; ND, not described; PEM, pemetrexed.

For the future, we may need to narrow the core patients who are predicted to benefit from maintenance therapy with pemetrexed or other drugs. Hence, more clear-cut markers are required, such as EGFR mutation status for NSCLC. The most promising predictive biomarker of the efficacy of pemetrexed at this time is the thymidylate synthase expression level. Basic research is warranted to identify a reliable biomarker than can predict the clinical benefit of pemetrexed. These personalized therapies represent appropriate treatment options and result in cost savings when using expensive drugs. Investigation of selection or exclusion biomarkers is warranted.

Disclosure

The authors report no conflicts of interest in this work.

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