SciMedCentral

Journal of Cancer Biology & Research

Review Article

Advances in the Medical Treatment of Malignant Mesothelioma

Kozo Kuribayashi[1#*] and Kazuya Fukuoka[2#]

[1]Department of Respiratory Medicine, Murakami Memorial Hospital, Asahi University, Japan

[2]Department of Genetics, Hyogo College of Medicine, Japan

[#]These authors contributed equally to this work.

Abstract

Malignant Pleural Mesothelioma (MPM) is a highly lethal and refractory malignancy that is caused by asbestos exposure. Surgical resection, radiotherapy, and other local treatments are of limited efficacy. Therefore, systemic chemotherapy plays an important role in improving of treatment outcomes for MPM. The findings of a large-scale phase III study led to the approval of a novel antifolate, pemetrexed, by the U.S. Food and Drug Administration (FDA), making pemetrexed the world's first therapeutic agent for MPM. Further, the combination treatment of pemetrexed plus cisplatin has been recognized as standard chemotherapy for this disease in the first-line setting. Recent studies have provided evidence that second-line chemotherapy is associated with prolonged survival among patients with various malignancies, including MPM. To date, however, no chemotherapeutic regimens have been recommended for MPM in the second-line setting. Furthermore, although, systemic chemotherapy is carried out in the majority of medical cases of MPM, it has not been established whether this systemic chemotherapy contributes to prolonged survival. This article reviews the latest findings regarding chemotherapy in cases of MPM and focuses on new medical treatments including molecular targeted therapies.

Special Issue on

Lung Cancer

***Corresponding author**

Kozo Kuribayashi, Department of Respiratory Medicine, Murakami Memorial Hospital, Asahi University, 3-23 Hashimoto-cho, Gifu, 500-8523, Japan, Tel: +81-58-253-8001; Fax: +81-58-253-3299; Email: kuririn@murakami.asahi-u.ac.jp

Submitted: 14 February 2014

Accepted: 13 March 2014

Published: 20 March 2014

Keywords

- Malignant pleural mesothelioma
- Chemotherapy
- Pemetrexed
- First-line
- Second-line

INTRODUCTION

Malignant pleural mesothelioma and other mesotheliomas

Malignant Pleural Mesothelioma (MPM) is a malignant tumor that occurs in mesothelial cells of the parietal pleura. MPM has an exceptionally poor prognosis, including a median survival time in the region of 8–14 months [1]. As a whole, mesotheliomas are tumors that occur on the serous membrane that covers the majority of the inner surface of the body cavity. Mesotheliomas specifically arise in the pleura (85.5%), peritoneum (13.2%), pericardium (0.5%), and, with exceptionally rarity, in the tunica vaginalis (0.8%), which is a vestigial membrane of the processus vaginalis [2]. Traditionally, mesotheliomas were exceptionally rare tumors; however, most developed nations are currently experiencing a surge in the incidence of mesothelioma. The United States and Sweden are exceptions to this pattern, having already surmounted peaks in the incidence of mesothelioma.

Mortality from mesothelioma has also been increasing. In 1995, version 10 of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was introduced, substantially altering the reporting guidelines for mesothelioma as a cause of death. Since the release of ICD-10, fatal mesothelioma cases have increased 2.4-fold in Japan, from 500 deaths in 1995 to 1,258 deaths (men:women, 1007:251) in 2011.

Features of MPM and their effects on treatment

The early detection of MPM is exceptionally difficult and, partly in consequence, surgical resection is only performed in <10% of cases. Further, even when macroscopic complete resection can be achieved, a full recovery cannot be expected to result from surgical intervention alone because of the particularly high incidence of local recurrence that is associated with MPM [3].

At the cellular level, mesothelioma's sensitivity to radiation equals or slightly exceeds that of non-small cell lung cancer [4]. However, for MPM that has developed diffusely on the pleura, a very wide range of exposure is necessary for radical radiotherapy, and influences on vital organs (such as the lungs, liver, and heart) are unavoidable. Indeed, the 2010 guidelines of the European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) [5] state that radical radiotherapy should be contraindicated to preserve the lungs.

Because of these factors, the results of localized treatment for MPM are limited, leaving systemic chemotherapy as a central form of treatment. Yet, the results of systematic chemotherapy

are not entirely satisfactory, either. Additionally, it has not yet been clarified whether systemic chemotherapy prolongs the lives of patients with MPM [6]. Therefore, it would be difficult to claim that effective treatments have been established for MPM. This manuscript will review the latest findings that pertain to chemotherapy for MPM, including our own efforts in this challenging environment.

First-line chemotherapy

Changes in chemotherapy before the marketing of pemetrexed: Table 1 summarizes results of previous phase II trials of first-line chemotherapy. To date, a large variety of anti-cancer agents have been prescribed as potential systemic chemotherapies for MPM. This variety includes agents for which an anti-tumor effect could be expected in monotherapy, such as antifolate drugs, anthracycline derivatives, platinum formulations, and vinca alkaloid derivatives [7-9]. Combinations of these agents have been central to combination chemotherapy. In the 1990s, phase II trials were conducted that focused on combinations of doxorubicin and cisplatin, demonstrating a response rate of 20% and a median survival time of 6–12 months with this combined therapy [9]. In the 2000s, phase II clinical trials were performed for the combination therapy of gemcitabine and cisplatin, as well as the combination therapy of irinotecan, a topoisomerase I inhibitor, with cisplatin. In a single-institution study, the response rate for gemcitabine monotherapy was found to be between 0 and 31%. In another single-institution study, the response rate increased to 48% for gemcitabine and cisplatin combination therapy [10]. Further, response rates of 16–26% were reported for combined gemcitabine with platinum formulations in a multi-institution study [11]. It has been reported that the combination with oxaliplatin results in a response rate of 40% [12].

In combination therapy based on irinotecan, low doses of irinotecan are more favorable than high doses. Indeed, the combination therapy of irinotecan at 60 mg/m^2 with cisplatin showed a response rate of 26.7% [13], while the combination therapy of high-dose irinotecan (190 mg/m^2) with docetaxel exhibited high toxicity without improvements in the response rate [14]. Additionally, the combination therapy of irinotecan at 200 mg/m^2 with gemcitabine exhibited a response rate of 14.2% and the 3-agent combined therapy of moderate-dose irinotecan (100 mg/m^2) with cisplatin and mitomycin was reported to have comparatively favorable results, with a response rate of 25% and a median survival time of 10.8 months [15]. However, no studies have shown 3-agent combination therapies that contain platinum formulations to be superior to 2-agent therapies. Furthermore, large-scale clinical trials of new anti-cancer agents were being performed before any standard chemotherapy had been established from the comparatively small-scale phase II trials that utilized existing anti-cancer agents against MPM.

Table 1: Response rates with previous phase II trials of first-line chemotherapy for Malignant Pleural Mesothelioma.

Regimen	Response Rate (%)
Cisplatin+Doxorubicin[9] (1991,1993)	14-25
Cisplatin+Gemcitabine[10,11] (1999,2002)	16-48
Oxaliplatin+Gemcitabine[12] (2003)	40
CPT-11(60mg/m^2)+Cisplatin[13] (1999)	26.7
CPT-11(190mg/m^2)+Docetaxel[14] (2000)	0
CPT-11(100mg/m^2)+Cisplatin+Mitomycin C[15] (1999)	25

Chemotherapy following the emergence of pemetrexed: phase III clinical trials: In this context, the new antifolate pemetrexed was placed on the market in Japan during 2007. Table 2 summarizes studies of pemetrexed and related therapies. In contrast to preexisting anti-cancer drugs, pemetrexed showed anti-cancer activity by concurrently inhibiting several important folic acid metabolizing enzymes. Accordingly, pemetrexed is called a multitarget antifolate. The results of the phase II trials of pemetrexed alone (500 mg/m^2) were favorable for MPM, including a response rate of 14.1% and a median survival time of 10.7 months [16]. Based on these results, a group of patients (N = 226) who received the combination therapy of pemetrexed (500 mg/m^2) with cisplatin (75 mg/m^2) was compared with a group of patients (N = 222) who underwent cisplatin monotherapy (75 mg/m^2) in a large-scale randomized phase III trial. Exceptional results were obtained, suggesting that the combined therapy group had better outcomes than the cisplatin monotherapy group, including response rates of 41.3% vs. 16.7%, and median survival times of 12.1 vs. 9.3 months, respectively [17]. Based on the results of these clinical trials, the combined therapy of pemetrexed with cisplatin was established as a standard therapy for MPM and pemetrexed was approved as the therapeutic agent for MPM for the first time by the U.S. Food and Drug Administration (FDA), positioning the combined therapy of pemetrexed and cisplatin as the standard chemotherapy for MPM.

Indeed, we have also confirmed the safety and efficacy of combined therapy with pemetrexed and cisplatin in over 900 patients in Japan [18].

Raltitrexed is another new antifolate drug. However, while pemetrexed inhibits multiple folic acid metabolizing enzymes, raltitrexed exhibits anti-tumor results by inhibiting thymidylate synthase alone. The results of phase III trials of the combined therapy of raltitrexed and cisplatin versus cisplatin monotherapy have shown that the combined therapy group has a significantly longer median survival time than the monotherapy group. Specifically, median survival times were 11.4 vs. 8.8 months and 1-year survival rates were 46% vs. 40%, respectively (p = 0.048) [19]. In these large-scale phase III trials, it was shown that median survival times were extended by 2.8 and 2.6 months for pemetrexed and raltitrexed, respectively, as compared with cisplatin monotherapy. Based on the reproducibility of these results, it can be concluded that the combined therapy of cisplatin with a new antifolate drug results in significantly longer expectancies than cisplatin monotherapy for untreated MPM. As noted in the National Comprehensive Cancer Network (NCCN) guidelines, other combinations have also been raised as options for therapy (pemetrexed with carboplatin, as well as gemcitabine with cisplatin), as have other monotherapies (pemetrexed and vinorelbine) [6].

During the same period, a clinical trial in England investigated the additional merits of palliative chemotherapy for untreated MPM. Its final results were published in 2008 [20]. This trial compared 3 groups, comprising a control group who received active symptom control (ASC), including palliative radiotherapy (N = 136); a combined chemotherapy group who received mitomycin, vinblastine, and cisplatin (MVP; N = 137); and a group who received vinorelbine monotherapy (N = 136). Using these groups, a phase III trial was performed to investigate whether chemotherapy improves quality of life among patients with MPM. The median survival time, median progression-free survival time, and 1-year survival rate were 7.6 months, 5.1 months, and 29%, respectively, for the palliative treatment group. For patients who received chemotherapy in addition to palliative treatment (including the MVP and vinorelbine groups), analogous values were 8.5 months, 5.6 months, and 32%. No significant differences were found between the groups in terms of any of the evaluation criteria. However, among the groups that received chemotherapy, the group that was administered vinorelbine had a median survival time of 9.5 months and a median progression-free survival of 6.2 months. Although these are marginal improvements, they represent a tendency towards prolonged survival in comparison with the palliative therapy group. The results of this study did not offer any clear indications of superior overall survival for chemotherapy in addition to palliative care, but it was concluded that further investigation was warranted on the topic of additional vinorelbine chemotherapy. However, it was also pointed out that the efficacy of chemotherapy for MPM may have been underestimated in this study because standard chemotherapies were not invested, including the key drug pemetrexed.

Second-line treatments

Table 3 summarizes studies of potential second-line chemotherapies for MPM. Second-line chemotherapy (secondary treatment) has not yet been established for patients with a medical history of MPM [15,21-28]. Based on a subset analysis of phase III comparative trials of first-line of cisplatin with or without pemetrexed, it has been shown that second-line chemotherapy after the end of experimental treatment contributes to overall survival [29]. Results have also been reported from a phase III trial focusing on cases of MPM that were treated with non-pemetrexed chemotherapy [25]. This trial compared a best supportive care (BSC) group and a BSC with pemetrexed monotherapy group, showing that pemetrexed alone provided a 19.2% response rate with a 59.3% rate of disease control. Median progression-free survival was significantly prolonged in the BSC with pemetrexed monotherapy group, as compared with the BSC group (3.8 months vs. 1.5 months, p = 0.0002). The study results also suggested an effect on overall survival following treatment, although the difference between the groups was not significant. Based on the results of this study, the administration of pemetrexed as second-line chemotherapy has been recommended for patients who have not received pemetrexed previously [6].

However, few studies have investigated second-line chemotherapy for cases involving relapse after first-line combined therapy with pemetrexed and cisplatin, or cases where the tumor has become unresponsive to treatment. Regimens that include vinorelbine or gemcitabine are possible candidates for second-line chemotherapy in these cases [6]. Further, the repetition of chemotherapy that includes pemetrexed has been considered as a second-line chemotherapy for patients who received first-line chemotherapy including pemetrexed and experienced more than 12 months of progression-free survival [28].

Molecular targeted therapies

Resistance of MPM to conventional treatment and poor clinical outcome has prompted basic research to identify possible new molecular targets. Randomized phase II trials, with or without new drugs, may be able to give a better signal activity than single arm phase II trials. Table 4 shows the results obtained from most important clinical trials carried out with new drugs in patients with MPM. Furthermore, Table 4 shows the results of main clinical trials carried out with novel drugs in patients with advanced or unresectable MPM as first-or second-line treatment. Details are shown below.

These molecular targeted therapies naturally fall into 5 groups

Signal transduction inhibitors: Signal transduction through

Table 2: Randomized Phase III Studies of Patients with Malignant Pleural Mesothelioma.

Study	Regimen	No. of patients	RR (%) p-value	MST (mo) HR (95% CI), p-value	mTTP (mo)	1-y survival rate (%)
Vogelzang[17]	Cisplatin	222	17	9.3	3.9	38
(2003)	Cisplatin+ pemetrexed	226	41	12.1	5.7	50
			p<0.001	0.77 (0.60-0.90), p=0.002		
van Meerbeeck[19]	Cisplatin	124	14	8.8	4.0	40
(2005)	Cisplatin+raltitrexed	126	24	11.4	5.3	46
			p=0.056	0.76 (0.58-1.00), p=0.048		
Muers[20]	ASC	136	-	7.6	5.1	29
(2008)	ASC+Chemotherapy (MVP, VNR)	273	MVP:10 VNR:16	8.5 VNR:9.5	5.6 VNR:6.2	32
				0.89 (0.72-1.1), p=0.29		

RR: Response Rate; MST: Median Survival Time; mTTP: Median Time To Progression; HR: Hazard Ratio; CI: Confidence Interval; ASC: Active Symptom Control; MVP: Mitomycin + Vinblastine + Cisplatin; VNR: Vinorelbine.

Table 3: Studies of Second-line Chemotherapy for Patients with Malignant Pleural Mesothelioma.

Study	Regimen	No of patients	RR (%)	DCR (%)	mTTP	MST
Pemetrexed-naïve patients						
Giaccone (2002)[21]	ZD0437 (platinum analog)	47	12*	55.8	2.5 mo	6.7 mo
Fizazi (2003) [22]	Raltitrexed+oxaliplatin	15	20	-	27 wks	44 wks
Porta (2005) [23]	Raltitrexed+oxaliplatin	14	0	28.6	1.9 mo	3.2 mo
Sorensen (2007) [24]	Pemetrexed	28	21	NR	147 d	294 d
Sorensen (2007) [24]	Pemetrexed+carboplatin	11	18	NR	222 d	258 d
Fennell (2007) [15]	Irinotecan+cisplatin+mitomycin	10	30	80	7.3 mo	7.3 mo
Jassem (2008)# [25]	Pemetrexed	123	19.2	59.3	3.8 mo	8.6 mo
Pemetrexed-pretreated patients						
Serke (2006) [26]	Oxaliplatin+/-gemcitabine	18	22*	50	NR	NR
Zucali (2008) [27]	Gemcitabine+vinorelbine	30	10	43.3	2.8 mo	10.9 mo
Re-treatment with pemetrexed Ceresoli (2011) [28]	PCis/PCa/P	31	19	48.0	[mPFS] 3.8 mo	[mOS] 10.5 mo

RR: response rate; DCR: disease control rate; mTTP: median time to progression; MST: median survival time; mPFS: median progression-free survival; mOS: median overall survival; PCis: Pemetrexed/Cisplatin; PCa: Pemetrexed/Carboplatin; P: Pemetrexed alone; NR: not reported; +/-, with or without.
*Responses were reported as "minor responses".
#Randomized trial of pemetrexed versus best supportive care (data reported for pemetrexed arm only).

Platelet-Derived Growth Factor Receptor (PDGFR) and Epidermal Growth Factor Receptor (EGFR) contributes to the propagation and development of MPM. Although the PDGFR and c-kit tyrosine kinase inhibitor imatinib was not found to be effective as a monotherapy, there is presently a phase II trial relating to its use in combination with chemotherapy [30]. Similarly, EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, were not found to be effective for MPM. Therefore, it appears that the activating mutations in the *EGFR* gene are not usually found in MPM.

Anti-angiogenic agents: Signal transduction through Vascular Endothelial Growth Factor (VEGF) also plays an important role in tumor development and the prediction of prognosis in MPM. A few phase II trials have investigated the combination of a bevacizumab, a monoclonal antibody to VEGF, with standard first-line chemotherapies. Yet, the combination with bevacizumab was not observed to have a significant effect on longevity in any of the studies [31,32]. It has been suggested that the anti-tumor results of monotherapy with multiple target tyrosine kinase inhibitors are limited by the selection of medical cases. (These multiple target tyrosine kinase inhibitors, such as sorafenib, sunitinib, and vatalanib, also target the VEGF receptor.) However, the multiple target tyrosine kinase inhibitor cediranib has been shown to have moderate anti-tumor activity in monotherapy targeting previously treated MPM. Currently, randomized phase II trials are investigating the combination therapy of cediranib with pemetrexed and cisplatin in untreated individuals [30].

Recently, results of the NVALT phase III trial have been presented [33] , which explored thalidomide as maintenance therapy in 222 patients who did not progress after first-line treatment with at least 4 cycles of platinum–pemetrexed schedule. Patients were randomly assigned to thalidomide (200 mg/day, orally) for one year as maintenance therapy, or observation. The thalidomide and palliative treatment groups did not differ significantly in terms of progression-free survival, which was the primary endpoint [34]. In conclusion, the more convenient administration of maintenance therapy in patients with MPM is still an open question and the only randomized phase III trial that has evaluated this issue has yielded disappointing results (Table 5).

Histone deacetylase inhibitor; HDAC inhibitor: Phase I trials of monotherapy and combined therapy with the DNA histone deacetylase inhibitor Suberoylanilide Hydroxamic Acid (SAHA, or vorinostat) in patients with malignant tumors showed remarkable control of the disease, including among patients who were previously treated for MPM. Following these phase I trials, international phase III comparative trials were performed to investigate the efficacy of vorinostat versus placebo in 661 patients with MPM who were unresponsive or resistant to combined therapy with pemetrexed and cisplatin. However, the results did not indicate a significant life-prolonging effect for vorinostat. Specifically, the median survival times were 27 weeks in the placebo group and 31 weeks in the vorinostat group, which did not constitute a significant difference (Table 5) [35].

Immunotherapy: NGR-hTNF is a complex of the tumor homing peptide (asparagine-glycine-arginine: NGR) and human tumor necrosis factor (hTNF). NGR-hTNF exhibits anti-tumor activity by selectively targeting tumor blood vessels. Following the promising results of phase II trials [36], a comparative phase III clinical trials has been initiated to investigate the combined effect of second line chemotherapy with NGR-hTNF among patients with previously treated MPM. The results of this study are greatly anticipated [30].

The glycoprotein mesothelin, which is produced in MPM, has both a diagnostic role [37] and, according to basic research, is an important target molecule in immunotherapy. Phase II trials have been performed using the chimeric monoclonal antibody to mesothelin, amatuximab (MORAb-009), in combination with pemetrexed and cisplatin for patients with untreated MPM. Following the introduction of amatuximab into the combined chemotherapy, 63% of cases continued monotherapy

Table 4: Clinical Trials of Molecular Targeted Therapies for Malignant Pleural Mesothelioma.

Study	Regimen	No. of patients	RR (%)	DCR (%)	mTTP (mo)	MST (mo)
Second line						
Jahan et al. (2012)	Vatalanib	47	6	78	4.1	10
Garland et al. (2011)	Cediranib	54	9	43	2.6	9.5
Campbell et al. (2011)	Cediranib	50	10	44	1.9	4.4
Rossoni et al. (2012)	NGR-hTNF	57	2	46	2.8	12.1
Stevenson et al. (2012)	GC-1008	13	NR	23	1.4	14
Garland et al. (2007)	Erlotinib	63	NR	42	2	10
Laurie et al. (2011)	Sunitinib	35	NR	NR	2.8	8.3
Dubey et al. (2010)	Sorafenib	51	6	60	3.6	9.7
Garland et al. (2012)	Everolimus	61	NR	NR	3	5
First line						
Hassan et al. (2012)	Amatuximab	89	39	90	6.1	14.5
O'Brien et al. (2012)	Bortezomib	82	NR	NR	5.1	13.5

RR: Response Rate; DCR: Disease Control Rate; mTTP: Median Time To Progression; MST: Median Survival Time; NR: Not Reported.
*Responses were reported as "minor responses".
#Randomized trial of pemetrexed versus best supportive care (data reported for pemetrexed arm only).

Table 5: Phase III Comparative Trials of Maintenance Therapy and Second-line Treatment for Malignant Pleural Mesothelioma.

Study (year)	Treatment group	No. of patients	RR (%), p-value	MST HR, p-value	mTTP HR, p-value
Jassem et al.	Palliative treatment group	120	1.7	9.7 mo	1.5 mo
(2008)	Palliative treatment +pemetrexed group	123	18.7	8.4 mo	3.7 mo
			p<0.0001	p=0.74	p=0.0002
Krug et al.	Placebo group	332	0.3	27 wks	6.1 wks
(2011)	Vorinostat group	329	0.6	31 wks	6.3 wks
				0.98, p=0.858	0.75, p<0.001
Buikhuisen et al.	Palliative treatment group	111	-	12.9 mo	3.5 mo
(2013)	Palliative treatment + thalidomide group (maintenance therapy)	111		10.6 mo	3.6 mo
				1.2, p=0.21	0.95, p=0.72

RR: Response Rate; MST: Median Survival Time; mTTP: Median Time To Progression

administered as a maintenance therapy. The highly favorable results included a response rate of 39%, a disease control rate of 89%, a median progression-free survival of 6.1 months, and a median survival time of 14.5 months [30]. Recently, it has been reported that ipilimumab, the completely humanized monoclonal antibody to cytotoxic T lymphocyte antigen-4 (CTLA-4), enhances anti-tumor immune response through T-cell activation, thereby significantly improving survival in advanced malignant melanoma. Phase II trials are currently investigating the efficacy of tremelimumab, which is the same variety of antibody, against MPM [38].

Cell cycle modifiers and other related approaches: G2 checkpoint inhibitors (CBP501), Src family kinase inhibitors (dastanib), ribonucleases (ranpirnase), mammalian target of rapamycin (mTOR) inhibitors (everolimus), and other drugs have been prescribed for MPM in monotherapy and combined therapy; however, no clear efficacy has been shown. Currently, phase II trials are underway for combined therapy with proteasome inhibitors (bortezomib) and cisplatin in untreated MPM patients [30].

DISCUSSION

In a previous study, we reported that a relatively favorable response rate of 38.1% and mean overall survival of 19.6 months were obtained using combined therapy with gemcitabine and methotrexed for MPM [39]. However, we note that these results were based on a single institution and used preexisting anti-cancer agents. Additionally, therapy with gemcitabine and methotrexed provides a non-platinum doublet combined therapy that may be acceptable chemotherapy for the elderly and patients with poor performance status. Accordingly, this non-platinum doublet combined therapy may have hidden potential as a second-line chemotherapy.

CONCLUSION

It has been predicted that the incidence of MPM will continue to increase in Japan. To date, however, no era-defining advances have been established for second-line chemotherapy or molecular targeted therapy for MPM. To improve treatment results, a better

understanding of the biology of this cancer is urgently needed, particularly the molecular mechanism of its progression and proliferation, which could serve as a foundation to the search for biomarkers. Additionally, it is essential to develop drugs for new molecular targets.

Research on treatments for MPM has been unforgiving and appears to remain firmly stuck at an exploratory level. Yet, these obstacles should strengthen our resolve to identify effective treatments for MPM. The pursuit of treatments for MPM must be continued in earnest to improve the poor prognosis of this disease.

REFERENCES

1. British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK, 2007. Thorax. 2007; 62 Suppl 2: ii1-1ii19.
2. Gemba K, Fujimoto N, Kato K, Aoe K, Takeshima Y, Inai K, et al. National survey of malignant mesothelioma and asbestos exposure in Japan. Cancer Sci. 2012; 103: 483-490.
3. Flores RM. Induction chemotherapy, extrapleural pneumonectomy, and radiotherapy in the treatment of malignant pleural mesothelioma: the Memorial Sloan-Kettering experience. Lung Cancer. 2005; 49 Suppl 1: S71-S74.
4. Häkkinen AM, Laasonen A, Linnainmaa K, Mattson K, Pyrhönen S. Radiosensitivity of mesothelioma cell lines. Acta Oncol. 1996; 35: 451-456.
5. Scherpereel A, Astoul P, Baas P, Berghmans T, Clayson H, de Vuyst P, et al. European Respiratory Society/European Society of Thoracic Surgeons Task Force. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J. 2010; 35: 479-495.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). Malignant pleural mesothelioma. 2nd edn NCCN; 2012.
7. Kindler HL. Malignant pleural mesothelioma. Curr Treat Options Oncol. 2000; 1: 313-326.
8. Kindler HL. Systemic therapy for malignant mesothelioma. American Society of Clinical Oncology 2002 Educational Book. Perry MC, editor. In: Alexandria (VA): ASCO. 2002: 359-367.
9. Steele JP, Klabatsa A. Chemotherapy options and new advances in malignant pleural mesothelioma. Ann Oncol. 2005; 16: 345-351.
10. Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. J Clin Oncol. 1999; 17: 25-30.
11. van Haarst JM, Baas P, Manegold Ch, Schouwink JH, Burgers JA, de Bruin HG, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer. 2002; 86: 342-345.
12. Schutte W, Blankenburg T, Lauerwald K, Schreiber J, Bork I, Wollscgkaeger B, et al. A multicenter phase II study of gemcitabine and oxaliplatin for malignant pleural mesothelioma. Clin Lung Cancer. 2003; 4: 294-297.
13. Nakano T, Chahinian AP, Shinjo M, Togawa N, Tonomura A, Miyake M, et al. Cisplatin in combination with irinotecan in the treatment of patients with malignant pleural mesothelioma: a pilot phase II clinical trial and pharmacokinetic profile. Cancer. 1999; 85: 2375-2384.
14. Knuuttila A, Ollikainen T, Halme M, Mali P, Kivisaari L, Linnainmaa K, et al. Docetaxel and irinotecan (CPT-11) in the treatment of malignant pleural mesothelioma--a feasibility study. Anticancer Drugs. 2000; 11: 257-261.
15. Fennell DA, Steele JP, Shamash J, Evans MT, Wells P, Sheaff MT, et al. Efficacy and safety of first- or second-line irinotecan, cisplatin, and mitomycin in mesothelioma. Cancer. 2007; 109: 93-99.
16. Scagliotti GV, Shin DM, Kindler HL, Vasconcelles MJ, Keppler U, Manegold C, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. J Clin Oncol. 2003; 21: 1556-1561.
17. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003; 21: 2636-2644.
18. Kuribayashi K, Voss S, Nishiuma S, Arakawa K, Nogi Y, Mikami K, et al. Safety and effectiveness of pemetrexed in patients with malignant pleural mesothelioma based on all-case drug-registry study. Lung Cancer. 2012; 75: 353-359.
19. van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol. 2005; 23: 6881-6889.
20. Muers MF, Stephens RJ, Fisher P, Darlison L, Higgs CM, Lowry E, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. Lancet. 2008; 371: 1685-1694.
21. Giaccone G, O RJ, Fisher P, Darl, Bard M, Kaukel E, et al. Phase II trial of ZD0473 as second-line therapy in mesothelioma. Eur J Cancer. 2002; 38: S19-S24.
22. Fizazi K, Doubre H, Le Chevalier T, Riviere A, Viala J, Daniel C, et al. Combination of raltitrexed and oxaliplatin is an active regimen in malignant mesothelioma: results of a phase II study. J Clin Oncol. 2003; 21: 349-354.
23. Porta C, Zimatore M, Bonomi L, Imarisio I, Paglino C, Sartore-Bianchi A, et al. Raltitrexed-oxaliplatin combination chemotherapy is inactive as second-line treatment for malignant pleural mesothelioma patients. Lung Cancer. 2005; 48: 429-434.
24. Sørensen JB, Sundstrøm S, Perell K, Thielsen AK. Pemetrexed as second-line treatment in malignant pleural mesothelioma after platinum-based first-line treatment. J Thorac Oncol. 2007; 2: 147-152.
25. Jassem J, Ramlau R, Santoro A, Schuette W, Chemaissani A, Hong S, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol. 2008; 26: 1698-1704.
26. Serke M, Xanthopoulos A, Bauer T. Second line chemotherapy in malignant pleural mesothelioma with oxaliplatin/gemcitabine. Ann Oncol. 2006; 17: 231a.
27. Zucali PA, Ceresoli GL, Garassino I, DeVincenzo F, Cavina R, Campagnoli E, et al. Gemcitabine and vinorelbine in pemetrexed-pretreated patients with malignant pleural mesothelioma. Cancer. 2008; 112: 1555-1561.
28. Ceresoli GL, Zucali PA, De Vincenzo F, Gianoncelli L, Simonelli M, Lorenzi E, et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. Lung Cancer. 2011: 72: 73-77.
29. Manegold C, Symanowski J, Gatzemeier U, Reck M, von Pawel J, Kortsik C, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus

cisplatin alone in malignant pleural mesothelioma. Ann Oncol. 2005; 16: 923-927.

30. Remon J, Lianes P, Martínez S, Velasco M, Querol R, Zanui M. Malignant mesothelioma: new insights into a rare disease. Cancer Treat Rev. 2013; 39: 584-591.

31. Kindler HL, Karrison TG, Gandara DR, Lu C, Krug LM, Stevenson JP, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol. 2012; 30: 2509-2515.

32. Ceresoli GL, Zucali PA, Mencoboni M, Botta M, Grossi F, Cortinovis D. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer. 2013; 109: 552-558.

33. Baas P, Buikhuisen W, Dalesio O, Vincent A, Pavlakis N, Van Klaveren R, et al. A multicenter, randomized phase IIImaintenance study of thalidomide (arm A) versus observation (arm B) in patients with malignant pleural mesothelioma (MPM) after induction chemotherapy. ASCO Meeting Abstracts. 2011; 29: 7006.

34. Buikhuisen WA, Burgers JA, Vincent AD, Korse CM, van Klaveren RJ, Schramel FM, et al. Thalidomide versus active supportive care for maintenance in patients with malignant mesothelioma after first-line chemotherapy (NVALT 5): an open-label, multicentre, randomised phase 3 study. Lancet Oncol. 2013; 14: 543-551.

35. Krug LM, Curley T, Schwartz L, Richardson S, Marks P, Chiao J, et al. Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. Clin Lung Cancer. 2006; 7: 257-261.

36. Gregorc V, Zucali PA, Santoro A, Ceresoli GL, Citterio G, De Pas TM, et al. Phase II study of asparagine-glycine-arginine-human tumor necrosis factor alpha, a selective vascular targeting agent, in previously treated patients with malignant pleural mesothelioma. J Clin Oncol 2010; 28: 2604-2611.

37. Fukuoka K, Kuribayashi K, Yamada S, Tamura K, Tabata C, Nakano T. Combined serum mesothelin and carcinoembryonic antigen measurement in the diagnosis of malignant mesothelioma. Mol Clin Oncol. 2013; 1: 942-948.

38. Grosso JF, Jure-Kunkel MN. CTLA-4 blockade in tumor models: an overview of preclinical and translational research. Cancer Immun. 2013; 13: 5.

39. Kuribayashi K, Miyata S, Fukuoka K, Murakami A, Yamada S, Tamura K, et al. Methotrexate and gemcitabine combination chemotherapy for the treatment of malignant pleural mesothelioma. Mol Clin Oncol. 2013; 1: 639-642.

Cite this article

Kuribayashi K, Fukuoka K (2014) Advances in the Medical Treatment of Malignant Mesothelioma. J Cancer Biol Res 2(1): 1037.