Review Article

Medical treatment of malignant pleural mesothelioma relapses

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Abstract: There are not established treatments for patients with advanced malignant pleural mesothelioma that progressed after first-line chemotherapy with cisplatin and pemetrexed. Retrospective analyses suggest a possible role for rechallenge with pemetrexed for selected patients. Phase II trials demonstrate a modest efficacy of vinorelbine monotherapy with a response rate ranging between 0% and 18% and a tolerable toxicity profile. Combination schedules, despite an increased toxicity, fail to demonstrate an improved efficacy. To date, genome wide analyses did not show molecular targets suitable for therapy and biological drugs did not exert a significant efficacy in clinical trials. Immunotherapy has given a hint of efficacy in early clinical trials but definitive evaluations are still ongoing.

Keywords: Mesothelioma; second line chemotherapy; pemetrexed; rechallenge; vinorelbine

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Pattern of mesothelioma relapses

Patients with resectable mesothelioma can benefit from multimodality treatments that can include induction chemotherapy plus extrapleural pneumonectomy and then post-operative radiotherapy or pleurectomy decortication followed by chemotherapy. The first approach has significantly higher perioperative mortality and complications (1). Patterns of relapse are different between the two techniques. After pleurectomy decortication, local relapses are more frequent including progressions in homolateral chest and pericardium. After extrapleural pneumonectomy, progressions in distant sites were more common including contralateral lung/pleural, lymph nodes and peritoneum (2). However, extrapleural pneumonectomy also local recurrences have been reported with or without concomitant distant metastases in 31% and 46% of completely resected tumors, respectively (3). In the MARS trial, that compare extrapleural pneumonectomy with less invasive approaches, the progression free survival (PFS) was 7.6 and 9 months, respectively (4).

Unresectable patients benefit from chemotherapy, being the standard of care the combination of pemetrexed and cisplatin. In a phase III trial, 226 and 222 chemotherapy naïve mesothelioma patients were randomly assigned to receive cisplatin with or without pemetrexed, respectively (5). The combination increased survival compared with cisplatin alone: 12.1 *vs.* 9.3 months (P=0.002). Similarly, time to progression was longer in the combination arm: 5.7 *vs.* 3.9 months (P=0.001).

The French Cooperative Thoracic Intergroup conducted a phase III trial to compare the first line treatment with cisplatin-pemetrexed with or without the addiction of bevacizumab (6). Two hundred and twenty-three and 225 patients were randomly assigned to receive treatment with or without bevacizumab, respectively. The group treated with bevacizumab obtained an increased overall survival (OS) compared to the control arm (median OS 18.8 *vs.* 16.1 months, respectively; hazard ratio 0.77; P=0.0167). Similarly, an increase of PFS was observed with bevacizumab (median 9.2 *vs.* 7.3 months; P<0.0001). A higher rate of bevacizumab related side effects were observed in the experimental arm:

Table 1 Mesothelioma re-challenge

First author	Treatment	Patients	RR (%)	mTTP/mPFS (months)	mOS (months)
Bearz A (9)	Pem	9	16.7	4.0	13.6
	Pem + platinum	21	–	5.7	–
Ceresoli GL (10)	Pem	15	19.0	3.8	10.5
	Pem + platinum	16	48.0	–	–
Zucali PA (11)	Pem	11	–	2.4	4.2
	Pem + platinum	31	–	6.4	13.4

RR, response rate; mTTP, median time to progression; mPFS, median progression free survival; mOS, median overall survival; Pem, pemetrexed.

grade 3–4 hypertension (in 23% *vs.* 0%) and thrombotic events (in 6% *vs.* 1%). Therefore, the treatment with cisplatin pemetrexed and bevacizumab is considered a suitable treatment for malignant pleural mesothelioma.

Recently, the pattern of metastatic diffusion has been reported in a series of 165 malignant pleural mesotheliomas (7). Bone metastases were reported in 20%, mostly with lytic appearance. Peritoneal disease was observed in 24% with 16% of neoplastic ascites. Lung metastases were detected in 11% as diffuse miliary-type pattern. Visceral metastases (15%) were predominantly in liver (78%), but also occurred in adrenals, spleen and kidneys. Symptomatic brain metastases were recorded in 3% (7).

Second line chemotherapy

Pemetrexed

In 2008, Jassem and colleagues compared pemetrexed and best supportive care (BSC) in a multicenter phase III trial enrolling patients with previously treated malignant pleural mesothelioma (8). Patients were pemetrexed naïve and progressed after first line chemotherapy. Randomization was balanced for the major prognostic factors: histological subtype, prior raltitrexed therapy, sex, Karnofsky performance score and white blood cell count. Both arms had a similar time lapse between the end of first line chemotherapy to the date of randomization for the second line treatment (2.1 and 2.0 months for pemetrexed and BSC arms, respectively). The primary efficacy end-point of the trial was OS. One hundred and twenty-three patients received pemetrexed and 120 BSC. Response rate favored the pemetrexed [partial response (PR): 18.7%] compared to the BSC arm (PR: 1.7%; P<0.001). PFS was longer with pemetrexed than with BSC (P=0.0148) with a median of 3.6 and 1.5 months, respectively. There was not a significant difference in OS for pemetrexed and BSC arms (P=0.7434) with a median of 8.4 and 9.4 months, respectively. However, a higher proportion of patients in the BSC arm received chemotherapy after discontinuation of the study: 51.7% *vs.* 28.5% (P=0.002). The subsequent treatment was a schedule containing pemetrexed in 18.3% and 3.3%, for the BSC and pemetrexed arm, respectively. This could explain the absence of a significant survival difference.

The major limitation is that, in the meanwhile, cisplatin pemetrexed schedule has become the standard of care for the first line treatment of malignant pleural mesothelioma (5). Therefore, the usefulness of pemetrexed in second line treatment could appear questionable. However, in the absence of effective treatment options there is still a role for pemetrexed in further lines of treatment.

Rechallenge with pemetrexed

Patients who do not progress during the first line of chemotherapy have a potential benefit from second line treatment, whereas, chemoresistant patients less frequently respond to second line chemotherapy (8). Retrospective series suggest a possible efficacy for the rechallenge with pemetrexed in patients with a time to treatment failure longer than 6 months (*Table 1*).

Bearz *et al.* selected 30 patients from 7 Italian centers in a retrospective study (9). Mesothelioma histology was epithelioid in 28 patients and mixed in 2, 1 patient had an extra pleural localization in the tunica vaginalis. All patients received a first line chemotherapy with pemetrexed plus a platinum compound (cisplatin 21 and carboplatin 9)

Table 2 Vinorelbine trials in second line mesothelioma

First author	Treatments	Patients	RR (%)	mTTP/mPFS (months)	mOS (months)
Stebbing J (12)	Vinorelbine 30 mg/mq weekly ×6 cycles	63	16	NR	9.6
Zucali PA (13)	Vinorelbine 25 mg/mq day 1, 8 every 21	59	15	2.3	6.2
Zauderer MG (14)	Vinorelbine 25 mg/mq day 1, 8 every 21	45	0	2.5	5.0
Sørensen JB (15)	Oral vinorelbine 80 mg/mq day 1, 8 every 21	15	7	2.3	2.5
Zucali PA (16)	Vinorelbine 25 mg/mq + gemcitabine 1,000 mg/mq day 1, 8 every 21	30	10	2.8	10.9
Toyokawa G (17)	Vinorelbine 25 mg/mq + gemcitabine 1,000 mg/mq day 1, 8 every 21	17	18	6.0	11.2

RR, response rate; mTTP, median time to progression; mPFS, median progression free survival; mOS, median overall survival; mg/mq, milligrams/square meter; NR, not reported.

obtaining 15 PR and 15 stabilization of the disease (SD). The duration of the response was at least 6 months. The rechallenge chemotherapy was pemetrexed monotherapy in nine patients and combination with platinum in the remaining (5 cisplatin and 16 carboplatin). Five patients (16.7%) obtained a PR, 15 a SD (50%) and 10 a progression of the disease (33%). The median time to progression was similar between pemetrexed monotherapy (4 months) and the combination with platinum (5.7 months). The median OS was 13.6 months (9).

In an observational study, Ceresoli *et al.* evaluated the rechallenge treatment in patients that progressed after at least 3 months from the end of first line chemotherapy. First line treatment was pemetrexed plus carboplatin in 27 or plus cisplatin in 4 patients (10). Eighteen patients received the rechallenge in second line of treatment and the remaining subsequently after treatment with vinorelbine or gemcitabine. The rechallenge was pemetrexed monotherapy in 15 and the combination with platinum in 16 patients. One patient obtained a complete response and 5 a PR. The response rate was 19% in patients re-treated with pemetrexed alone and 48% in combination with platinum. The median PFS and OS were 3.8 and 10.5 months, respectively. Significantly longer PFS and OS were observed in those patients who achieved a disease control longer than 12 months to the first line treatment (10).

Zucali and colleagues retrospectively report results of second line chemotherapy of 181 patients with malignant pleural mesothelioma (11). Among patients treated with a first line chemotherapy containing pemetrexed, 42 patients received a second line therapy with pemetrexed and 78 without. Patients retreated with pemetrexed presented a better disease control rate compared to those treated with different chemotherapeutic agents (70.7% *vs.* 52%, respectively). The rechallenge treatment was pemetrexed alone in 11 patients and the combination with a platinum compound in 31. There was a significant better median PFS (6.4 *vs.* 2.4 months; P=0.003) and OS (13.4 *vs.* 4.2 months; P<0.001) in patients retreated with pemetrexed with or without platinum (11). The retrospective nature of the trial does not allow drawing any conclusion since patients receiving the combination schedule were younger, in better physical conditions and obtained a better response to first line chemotherapy (11).

Vinorelbine

Phase II clinical trials and retrospective series have shown a modest efficacy of vinorelbine in the second line treatment of patients with malignant pleural mesothelioma (*Table 2*).

For this setting, Stebbing and colleagues conducted a phase II clinical trial enrolling 63 patients. All patients received only one previous line of treatment, 78% had an Estern Cooperative Oncology Group (ECOG) performance status (PS) <2, and 39% progressed during the first line treatment. The histology was epithelioid in 62% of tumors. There has been a 6-month median interval between the end of the first-line chemotherapy and the start of second-line. Ten patients (16%) achieved a PR with a median OS of 9.2 months (12).

Zucali *et al.* retrospectively collected data from 59 patients who received vinorelbine in second (57.6%) or further line of treatment (42.4%). Sixteen point nine percent of patients progressed during the first line treatment

and 55.9% had a first line PFS longer than 6 months. The histology was epithelioid in 89.9% of tumors. A PR was achieved in 15.2% of patients; the median PFS and OS were 2.3 and 6.2 months, respectively (13).

The retrospective evaluation of Zauderer and colleagues included 45 pretreated mesothelioma patients who received vinorelbine. Fifty-three point three percent of patients received vinorelbine in second-line, 46.7% such as further line of treatment. The histology was epithelioid in 67% of patients. There were not objective responses. The median PFS and OS were 1.7 and 5.4 months, respectively (14).

In these reports vinorelbine was well tolerated being the main side effects grade 3–4 neutropenia (range, 8–55%), anemia (17%), constipation (8–12%) and peripheral neuropathy (11%) (12-14).

Sørensen *et al.* evaluated oral vinorelbine 80 mg/mq day 1 and 8 every 3 weeks in patients with mesothelioma who progressed after a fist line treatment with platinum and pemetrexed. Fifteen patients were enrolled; the histology was epithelioid in 53% and ECOG PS 2 in 33%. One patient achieved a PR (7%), median PFS and OS were 2.3 and 4.5 months, respectively. Grade 4 leukopenia and thrombocytopenia were 20% and 7%, respectively, with 3 cases of febrile neutropenia and 1 toxic death. The use of oral vinorelbine with a metronomic schedule appears feasible and is currently under evaluation in different institutions (18,19).

Cisplatin-gemcitabine has been considered the standard of treatment in the first line setting until the advent of pemetrexed. Gemcitabine monotherapy has shown a modest effect in malignant pleural mesothelioma with response rate in the range of 10–31% (16,20,21). Therefore, in platinum-pemetrexed pretreated patients the combination of vinorelbine and gemcitabine has been evaluated. Zucali and colleagues treated 30 patients in a prospective phase II trial with a schedule of gemcitabine 1,000 mg/mq day 1 and 8 and vinorelbine 25 mg/mq day 1 and 8 every 3 weeks. The histology was epithelioid in 70% of tumors, ECOG PS was >1 in 17% of subjects and the time to progression from the first line was <6 months in 63% of patients. Three patients (10%) achieved a PR; median time to progression and OS were 2.8 and 10.9 months, respectively. The schedule was well tolerated being grade 3 and 4 neutropenia the main toxicity that was observed in three patients. Authors concluded that the activity of the schedule was between insufficient and moderate (16).

Using a similar schedule, Toyokawa and colleagues treated 17 Japanese patients with malignant pleural mesothelioma that progressed after chemotherapy with pemetrexed plus platinum. The response to first line chemotherapy has been PR or SD in 10 patients (58%), whereas 35% progressed at the first evaluation. ECOG PS was 1 in the majority of patients: 71%. The histological type was epithelioid in 82% of tumors. PR and DCR were 18% and 82%, respectively. Median PFS and OS were 6.0 and 11.2 months. Grade 3 or 4 neutropenia and anemia occurred in 41% and 29% of patients and one patient experienced febrile neutropenia (17). With a modest evidence of efficacy and an increase of grade 3–4 side effects, the combination of vinorelbine and gemcitabine is not the standard treatment for the second line chemotherapy of malignant plural mesothelioma (22).

Other drugs evaluated in recurrent mesothelioma

Retrospective series and phase II clinical trials showed the chance of additional responses in pretreated mesothelioma patients using conventional chemotherapeutic drugs including: raltitrexed, oxaliplatin, and anthracyclines. Response rate ranges from 0–20% suggesting the possibility of a mild efficacy in this setting (*Table 3*). Therefore, an increasing interest has been reserved to target therapies that have become available in the recent years. Unfortunately, genome wide analyses of mesothelioma failed to identify molecular targets suitable for therapy. Indeed, the most frequently mutated genes were BAP1, NF2 and TP53 in addition to occasional focal deletion of CDKN2A locus (30,31). Mesothelin and the neoangiogenic pathway are emergent targets that have shown clinical efficacy. However, nintedanib and bevacizumab are giving interesting results in the first line setting (6,32). Similarly, anti-mesothelin antibodies are under investigation in treatment naïve patients (33).

Three phase-III trails evaluated the efficacy of vorinostat, NGR-hTNF and thalidomide against BSC without any evidence of survival improvement (*Table 4*). Similarly, small phase II trials of several compounds, against intriguing targets, failed to demonstrate a major anticancer effect in pretreated mesothelioma patients with response rate ranging between 0% and 12% (*Table 4*).

Recently, immunotherapy has become a widely used therapy in thoracic malignancy and trials have been conducted in mesothelioma (*Table 5*). In a phase III trial, the CTLA4 inhibitor tremelimumab has not shown any survival benefit compared to placebo 7.7 *vs.* 7.3 months (53). Trials of anti-PD1 and anti-PDL1 antibodies are ongoing

Table 3 Chemotherapy trials in pretreated mesothelioma patients

First author	Phase	Drugs	Patients	RR (%)	mTTP/mPFS (months)	mOS (months)
de Lima VA (23)	II	Carboplatin, liposomal-doxorubicin, gemcitabine	43	14	4.1	6.8
Cortinovis DL (24)	II	Trabectedin	23	0	–	–
Tourkantonis I (25)	II	Gemcitabine, docetaxel	37	19	7.0	16.2
Fennel DA (26)	II	Irinotecan, cisplatin, mitomycin-C	13	20	7.3	7.3
Porta C (27)	II	Raltitrexed, oxaliplatin	39	0	2.0	3.2
Fizazi K (28)	II	Raltitrexed, oxaliplatin	15	20	6.2	10.1
Giaccone G (29)	II	ZD0473	47	0	2.5	6.8

RR, response rate; mTTP, median time to progression; mPFS, median progression free survival; mOS, median overall survival.

Table 4 Clinical trials of target therapies in second line mesothelioma

First author	Phase	Drugs	Patients	RR (%)	mTTP/mPFS (months)	mOS (months)
Krug LM (34)	III	Vorinostat	329	–	1.5	7.2
		BSC	332	–	1.4	6.3
Gregorc V (35)	III	NGR-hTNF	200	–	–	8.4
		BSC	200	–	–	7.9
Buikhuisen WA (36)	III	Thalidomide	111	–	3.6	10.6
		BSC	111	–	3.5	12.9
Ou SH (37)	II	Everolimus	59	2	2.8	6.3
Maron SB (38)	II	ARQ197	18	0	1.9	12.2
Wheatley-Price P (39)	II	PF-03446962	17	0	1.7	–
Nowak AK (40)	II	BNC105P	30	4	1.6	8.2
Dubey S (41)	II	Sorafenib	51	6	3.6	9.7
Fennel DA (42)	II	Bortezomib	23	5	2.1	5.8
Nowak AK (43)	II	Sunitinib	53	12	3.5	6.1
Dudek AZ (44)	II	Dasatinib	46	5	2.0	6.0
Papa S (45)	II	Sorafenib	53	6	5.1	9.0
Laurie SA (46)	II	Sunitinib	17	0	2.8	8.3
Garland LL (47)	II	Cediranib	54	9	2.6	9.5
Gregorc V (48)	II	NGR-hTNF	43	2	2.8	12.1
Ramalingam SS (49)	II	Belinostat	13	0	1.0	5.0
Jakerman DM (50)	II	Erlotinib bevacizumab	21	0	2.2	5.8

RR, response rate; mTTP, median time to progression; mPFS, median progression free survival; mOS, median overall survival.

Table 5 Immunotherapy for mesothelioma

First author	Phase	Schedule	Patients	RR (%)	mTTP/mPFS (months)	mOS (months)
Calabrò L (51)	II	Tremelimumab	29	3.0	6.2	11.3
Hassan R (52)	Ib	Avelumab	53	9.0	4.0	–
Maio M (53)	IIb	Tremelimumab	382	4.5	2.8	7.7
		Placebo	189	1.1	2.7	7.3
Alley EW (54)	Ib	Pembrolizumab	25	20.0	–	–
Quispel-Janssen J (55)	II	Nivolumab	38	13.2	–	–

RR, response rate; mTTP, median time to progression; mPFS, median progression free survival; mOS, median overall survival.

with preliminary results suggesting a response rate of 20% with pembrolizumab, similarly to what observed in second line treatment of NSCLC. The selection of patients upon the expression of PDL1 seems a predictive marker of response (56).

Recommendation for upcoming clinical trials

More effective drugs for malignant pleural mesothelioma are undoubtedly needed. However, some considerations should be made in the prospective to design further clinical trials for recurrent mesothelioma. Authors suggest that clinical trials are feasible in this setting of patients but the chances to get meaningful information from single arm phase II study are limited. Indeed, Zucali *et al.* demonstrated that the radiologic response not necessary correlates with an increased survival (11). Moreover, the evaluation of response can be challenging using conventional RECIST criteria to measure dimensions of mesotheliomas for the typical conformational growth of the tumor. Thus, response rate is a weak primary endpoint. Nevertheless, we have observed that patients can have a heterogeneous clinical behavior in terms of survival depending on multiple prognostic factors including histology (epithelioid *vs.* sarcomatoid/biphasic), tumor stage, patients' PS and response to first line chemotherapy. Indeed, some patients progress during chemotherapy whereas others experience disease progression after more than 12 months from the treatments. All these factors confound the interpretation of OS and PFS in single arm trials. Beside known prognostic factors, there are still unknown conditions that limit our chance to predict prognosis in mesotheliomas. Therefore, randomized trials with a substantial number of patients should be needed with a careful stratification for prognostic factors. However, mesothelioma remains a relatively rare disease limiting our chance to easily conduct such kind of trials.

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Footnote

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