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Vinorelbine and Gemcitabine as Second- or Third-Line Therapy for Malignant Pleural Mesothelioma

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Abstract

Objectives—Pemetrexed-cisplatin is the only FDA-approved regimen for malignant pleural mesothelioma (MPM), and the impact on survival is modest. No drugs have been shown to improve survival as second-line therapy, yet vinorelbine and gemcitabine are prescribed based on the results of small phase II trials. To augment the existing limited data, we examined our institutional experience with vinorelbine and gemcitabine in patients with previously treated MPM.

Materials and Methods—We reviewed charts of patients with MPM treated with vinorelbine and/or gemcitabine as second- or third-line therapy between 2003 and 2010. Toxicity was graded according to the Common Terminology Criteria for Adverse Events Version 4.0. CT scans were reviewed with a reference radiologist according to modified RECIST criteria.

Results—Sixty patients were identified: 33 treated with vinorelbine, 15 gemcitabine, and 12 both agents. Eight-three percent initially received pemetrexed-platinum. Toxicity was substantial: 46% experienced at least one episode of grade 3–4 toxicity. Of 56 patients evaluable radiologically, there was 1 partial response (gemcitabine) giving a response rate of 2% (95% CI 0–10%). Forty-six percent had stable disease. Median progression free survival was 1.7 months for vinorelbine and 1.6 months for gemcitabine. Median overall survival was 5.4 and 4.9 months, respectively.

Conclusions—Response to second- or third-line vinorelbine or gemcitabine is rare. The high rate of stable disease warrants the continued use of these agents in this setting, though the impact on survival is questionable. These data justify the choice of placebo control arms in randomized trials of novel agents in previously treated patients.

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Introduction

Most patients with malignant pleural mesothelioma (MPM) present with locally advanced disease, and treatment for these patients involves palliative chemotherapy. The combination of pemetrexed and cisplatin has become the standard first-line chemotherapy regimen based on the results of a randomized phase III trial showing that it improved median survival compared to treatment with cisplatin alone from 9.3 months to 12.1 months.[1] As the use of pemetrexed and cisplatin (or carboplatin) has become more routine, an increasing number of patients remain fit enough even after progression for consideration of second-line chemotherapy. However, the scarcity of data regarding the efficacy of further treatment leaves oncologists unsure how to proceed.

Many choose to treat their patients with either vinorelbine or gemcitabine based on subgroup analyses from first-line studies, small phase II trials, or retrospective analyses. Vinorelbine was studied in a phase II open-label trial in 63 MPM patients previously treated with chemotherapy, which did not include pemetrexed, yielding a response rate of 16%.[2] More than half of these patients also experienced severe toxicity. In an exploratory subgroup analysis of a first-line multicenter randomized trial comparing active symptom control to active symptom control plus chemotherapy with mitomycin, vinblastine, and cisplatin or weekly vinorelbine, there was a suggestion of a survival advantage with weekly vinorelbine.[3] A recent retrospective report described administration of vinorelbine to 59 MPM patients who previously received pemetrexed-platinum chemotherapy.[4] The response rate was 15.2% and median progression-free survival was 2.3 months.

Gemcitabine's efficacy was first-demonstrated as part of a phase II screening of drugs in which 27 chemotherapy naïve patients with MPM received weekly gemcitabine. The response rate was 7% and median survival was 8 months.[5] Analysis of the phase III trial that led to the approval of cisplatin and pemetrexed as first-line therapy for MPM demonstrated improved survival with the use of post-study chemotherapy, and gemcitabine was the most commonly used agent.[6] The CALGB conducted a phase II multicenter trial evaluating the activity of gemcitabine in chemotherapy naïve patients with MPM.[7] Among the 17 patients treated, there were no partial or complete responses and median survival was 4.7 months. Another phase II trial of gemcitabine in chemotherapy naïve patients with MPM demonstrated 2 objective responses among 27 patients (7%) and a median survival of 8 months.[5] Several additional studies have examined the efficacy of gemcitabine in combination with cisplatin in chemotherapy naïve patients with MPM[8–10] with response rates ranging from 16% to 47.6%. There is also a study of vinorelbine and gemcitabine given concurrently in MPM patients who previously received either single-agent pemetrexed or pemetrexed-platinum therapy showing a response rate of 10%, median time to progression of 2.8 months, and overall survival of 10.9 months.[11]

These data certainly support the inclusion of vinorelbine and gemcitabine in the National Comprehensive Cancer Center Guidelines as preferred agents in the second-line setting, yet they are quite limited in scope. As such, we sought to augment the existing information by examining our institutional experience using vinorelbine and gemcitabine in patients with previously treated MPM.

Material and Methods

With the approval of the Memorial Sloan-Kettering Cancer Center Institutional Review Board, we reviewed the clinical records of all patients treated with vinorelbine and/or gemcitabine as second- or third-line therapy for MPM between 2003 and 2010. Clinical characteristics were extracted, including age at diagnosis, sex, histology, stage, smoking status, asbestos exposure, prior therapy including surgery, chemotherapy, and radiation, as well as survival status. Although the patients included in this analysis were not treated on a protocol, the chemotherapy regimens and follow-up were quite similar across the group. Vinorelbine was administered at a dose of 25 mg/m^2 days 1 and 8 in a 3-week cycle. Gemcitabine was given at 1000 mg/m^2 days 1 and 8 in 21 day cycles or days 1, 8, and 15 in 28 day cycles. CT scans were generally performed after every two cycles.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events Version 4.0. Imaging studies were reviewed with a radiologist according to the modified RECIST criteria[12] and classified as complete response (CR), partial response (PR), stable disease (SD), and progression of disease (PD).

Overall survival (OS) and progression-free survival (PFS) analyses were conducted for patients who received vinorelbine and/or gemcitabine. Each of the two drugs was analyzed separately, with patients who received both drugs contributing to both cohorts. OS was defined as the time from the start of the respective treatment until death. Failures for progression-free survival (PFS) analysis were defined as disease progression or death within six weeks of last follow-up, and PFS was defined as the time from the start of the respective treatment to failure. Patients who did not experience the event of interest were censored 6 weeks after the last follow-up. OS and PFS were estimated by Kaplan-Meier methods.

Results

Patient Characteristics

Sixty unique patients were identified. Thirty-three were treated with vinorelbine, 15 with gemcitabine, and 12 with both agents sequentially. Patient characteristics are displayed in Table 1. As is typical for MPM, the majority of patients were men and the predominant histology was epithelioid. Stage at diagnosis was divided as 32% stage II, 37% stage III, and 30% IV. The median age at diagnosis was 67 with a range of 41–85. Eight-three percent had received pemetrexed and platinum as their initial chemotherapy and the most common response to first-line therapy as assessed by the treating clinician was stable disease (57%), followed by progressive disease (33%), and partial response (27%).

Toxicity

Forty-six percent of patients experienced at least one episode of grade 3–4 toxicity, with 38% experiencing at least one episode of grade 3–4 non-hematologic toxicity (Table 2). The most common non-hematologic toxicities were neutropenic fever, fatigue, dyspnea, nausea and vomiting. There were no therapy related deaths. Six patients (13%) discontinued vinorelbine due to toxicity while 7 (26%) patients stopped gemcitabine for toxicity.

Response and Patient Outcomes

Of the 72 treatment courses received by the 60 patients, only 56 treatment courses had follow up imaging available for review. Eight patients had clinical progression prior to repeat imaging. Three patients had non-measurable disease. Another three patients had image files that were not accessible. One patient did not receive follow up care at our institution and another patient did not receive follow up imaging.

Among the 56 measurable cases, there was one partial radiographic response (Figure 1) giving a response rate of 2% (95% CI 0–5%). With gemcitabine, 10 patients (37%) had radiographic progression, 6 (22%) had clinical progression, 6 (22%) had radiographic stable disease, 4 (15%) had clinically stable disease, and 1 (4%) had radiographic partial response. With vinorelbine, 20 patients (43%) had radiographic progression, 2 (4%) had clinical progression, 19 (42%) had radiographic stable disease, 4 (8%) had clinically stable disease, and there were no responses.

The single responder was a 50 year old man who had stage III epithelioid disease at diagnosis and no identifiable asbestos exposure. He achieved stable disease with his initial therapy of pemetrexed-cisplatin but did have an indolent disease course and survived almost 43 months from his diagnosis. Among the 56 cases, there was no association between best response to initial therapy and best response with vinorelbine and/or gemcitabine. Furthermore, there was no association between time to progression with first-line therapy and response to vinorelbine or gemcitabine.

Among the 45 patients who received vinorelbine, median PFS was 1.7 months (95% CI: 1.3–2.9) and median OS was 5.4 months (95% CI: 3.8–7.4). Among the 27 who received gemcitabine, median PFS was 1.6 months (95% CI: 1.3–3.6) and median OS was 4.9 months (95% CI: 3.6–8.8).

Discussion

Since the trial that led to the FDA approval of pemetrexed-platinum chemotherapy as first-line therapy for MPM 10 years ago,[1] there have been no therapeutic advances for this disease. Yet, at the time of progression after therapy with pemetrexed-platinum, many patients are candidates for further therapy. Patients are often treated with vinorelbine or gemcitabine in this setting, yet the data supporting these choices were not necessarily obtained in similar patients. As summarized above, most of the prior trials with vinorelbine or gemcitabine were conducted in chemo-naïve patients, in patients not previously treated with pemetrexed, or in combination with other therapies. Here we add to the existing limited data and show that the efficacy of second-line vinorelbine or gemcitabine is minimal. In our institutional experience, we only observed one partial response with either agent, out of 56 measurable cases. The reasonably high rate of stable disease, 46%, does suggest some level of activity of these agents and they, therefore, remain reasonable standard therapeutic options. Toxicity, however, was significant, progression free survival was only 1.4 months, and the overall survival was comparable to the placebo arm in the randomized phase III trial of vorinostat as second-line therapy.[13]

This analysis has several limitations. The retrospective nature of this project may have precluded comprehensive capture of chemotherapy-associated toxicity. Several patients did not have imaging adequate or available for RECIST review. This cohort of patients was treated over a span of 7 years during which extrapleural pneumonectomies became less commonly performed at our institution and differences in treatment could impact tolerance and outcomes with subsequent therapy. One-third of patient also received radiation as part of their multimodality treatment approach. Certainly the receipt of particular prior therapies may influence the pattern of responses in this cohort. Furthermore, a large fraction of these patients had sarcomatoid or mixed histology MPM (35%) which, given the tendency toward chemotherapy resistance among sarcomatoid disease, may have contributed to the observed low response rate. Among this cohort, compared to vinorelbine, gemcitabine was more frequently administered in the second-line setting (Table 1, 80% versus 55%) and line of administration can certainly influence toxicity and may have an impact on activity. Additionally, a small subset of patients did receive both vinorelbine and gemcitabine sequentially. Finally, all of these patients were treated at one particular tertiary care center and our observations may not be generalizable to the mesothelioma population at-large.

Conclusion

Ultimately, the lack of impact on survival of second-line therapy is discouraging. Perhaps biomarkers, such as BRCA1 expression which may predict benefit from vinorelbine, could be used to better select patients.[14] Ideally, though, novel therapeutics need to be discovered. Given the orphan nature of this disease and the associated limitations on drug development resources, future studies must be thoughtfully planned with strong preclinical rationale, in the appropriate clinical context, and with an optimized trial design. Based on the existing data for second-line treatments, we believe placebo-control arms are reasonable for randomized studies of second-line therapies in MPM. If, however, vinorelbine or gemcitabine are chosen as a control arm, the results of this retrospective analysis provide further information regarding the expected low response rate from the “standard” therapy.

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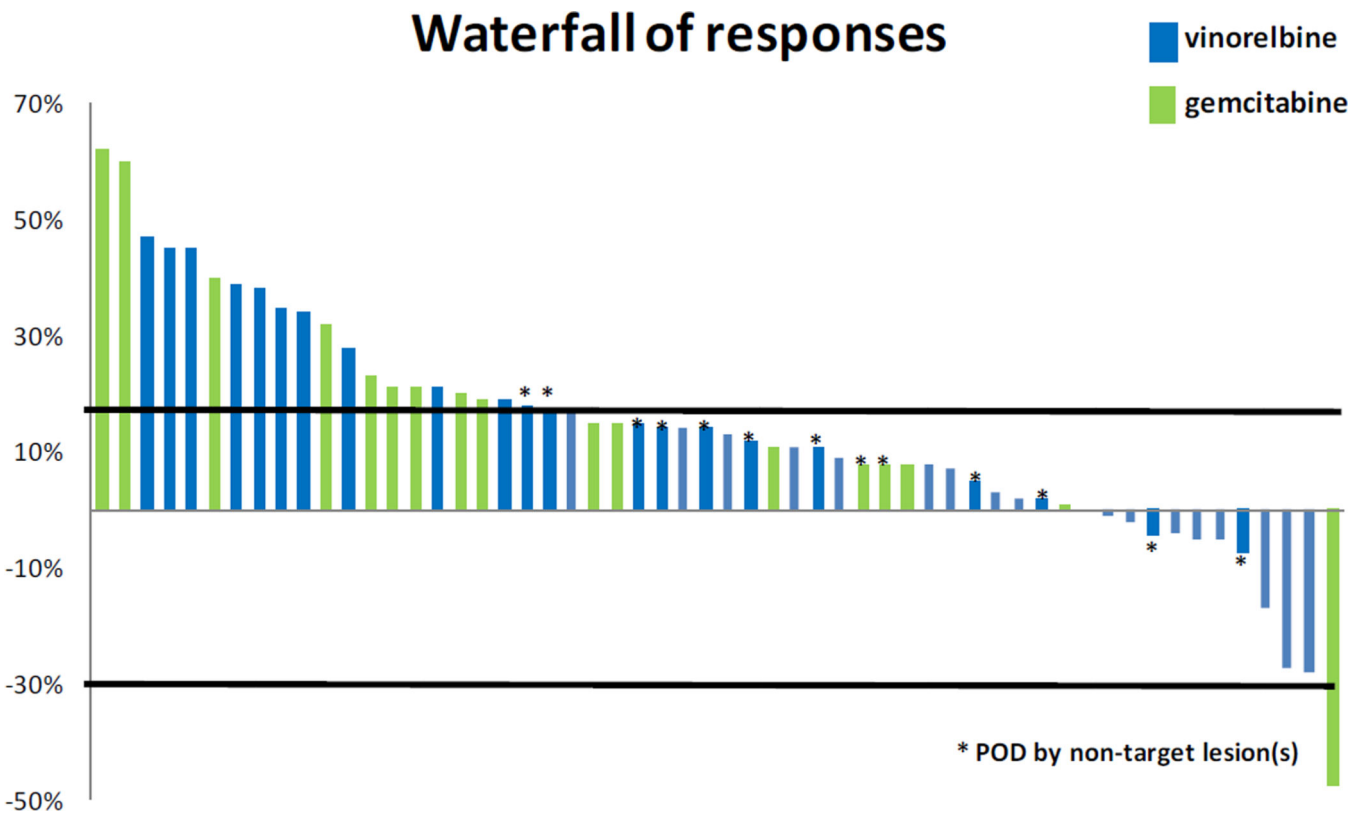

Figure 1.
Responses to vinorelbine and gemcitabine

Table 1

Characteristics of 60 MPM patients receiving second- or third-line treatment with vinorelbine or gemcitabine

	Vinorelbine N=33 (%)	Gemcitabine N=15 (%)	Both N=12 (%)	All N=60 (%)
Gender				
Male	26 (79)	13 (87)	8 (67)	47 (78)
Female	7 (21)	2 (13)	4 (33)	13 (22)
Age median (range)	65 (41–85)	71 (50–83)	67 (60–84)	67 (41–85)
Stage at diagnosis				
I	0 (0)	0 (0)	0 (0)	0 (0)
II	12 (36)	4 (27)	3 (25)	19 (32)
III	9 (27)	7 (47)	7 (58)	23 (38)
IV	12 (36)	4 (27)	2 (17)	18 (30)
Histology				
Epithelioid	22 (67)	9 (60)	8 (67)	39 (65)
Sarcomatoid	6 (18)	2 (13)	2 (17)	10 (17)
Mixed	5 (15)	4 (27)	2 (17)	11 (18)
Surgery				
EPP	6 (18)	4 (27)	3 (25)	13 (22)
P/D	9 (27)	3 (20)	3 (25)	15 (25)
None	18 (55)	8 (53)	6 (50)	32 (53)
Radiation Therapy				
Yes	11 (33)	6 (40)	3 (25)	20 (33)
No	22 (67)	9 (60)	9 (75)	40 (67)
1st line therapy				
Pemetrexed + platinum	25 (76)	14 (93)	11 (92)	50 (83)
Gemcitabine + platinum	6 (18)	0 (0)	0 (0)	6 (10)
Pemetrexed	0 (0)	1 (7)	1 (8)	2 (3)
Clinical trial	2 (6)	0 (0)	0 (0)	2 (3)
Response to 1st line therapy[1]				
CR	0 (0)	0 (0)	0 (0)	0 (0)
PR	11 (33)	1 (7)	4 (33)	16 (27)
SD	17 (52)	12 (80)	5 (42)	34 (57)
PD	5 (15)	1 (7)	3 (25)	9 (15)
Line				
Second	18 (55)	12 (80)	NA	NA
Third	15 (45)	3 (20)	NA	NA

EPP=extrapleural pneumonectomy; P/D=pleurectomy/decortication

CR=complete response; PR=partial response; SD=stable disease; PD=progression of disease

[1] Response was based on treating physician's assessment and interpretation of imaging studies and radiology report.

Table 2

Toxicity from second- or third-line vinorelbine and gemcitabine

	Vinorelbine N=45 (%)	**Gemcitabine N=27 (%)**
Grade 3–4 hematologic toxicity	11 (24)	6 (22)
• Leukopenia	• 7 (16)	• 0 (0)
• Neutropenia	• 7 (16)	• 1 (4)
• Anemia	• 5 (11)	• 5 (19)
• Thrombocytopenia	• 0 (0)	• 0 (0)
Grade 3–4 non hematologic toxicity	15 (33)	12 (44)
• Neutropenic fever	• 3 (7)	• 0 (0)
• Fatigue	• 3 (7)	• 3 (11)
• Dyspnea	• 2 (4)	• 4 (15)
• Nausea & Vomiting	• 2 (4)	• 1 (4)
Any grade 3–4 toxicity	17 (38)	16 (59)

* Other severe toxicities occurring in <4% of patients were as follows: for vinorelbine syncope, pain, and infection; for gemcitabine thromboembolic event, hyponatremia, infection, hypertension, edema, bowel obstruction, and pneumonitis.