Original article

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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

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Background: A phase III trial in patients with malignant pleural mesothelioma demonstrated a survival advantage for pemetrexed plus cisplatin compared with single-agent cisplatin. Because post-study chemotherapy (PSC) may have influenced the outcome of the trial, we examined its use and association with survival.

Patients and methods: Eighty-four patients from the pemetrexed plus cisplatin arm and 105 patients from the single-agent cisplatin arm received PSC. Kaplan–Meier survival estimates were compared by treatment groups, and by PSC and non-PSC subgroups.

Results: The percentage of patients receiving PSC was imbalanced between the treatment arms. Fewer pemetrexed plus cisplatin treated patients received PSC (37.2% versus 47.3%). A multiple regression analysis performed in this trial showed that PSC had a statistically significant correlation with prolonged survival ($P<0.01$), adjusting for baseline prognostic factors and treatment intervention. The adjusted hazard ratio for PSC over non-PSC subgroups was 0.56 (confidence interval 0.44–0.72).

Conclusions: PSC in malignant pleural mesothelioma was significantly associated with prolonged survival. It is not known whether the reduced risk of death was associated with PSC or whether patients who had prolonged survival tended to receive more PSC. The pemetrexed plus cisplatin treatment group had a statistically significant survival advantage even though fewer patients from that arm of the trial received PSC. The potentially beneficial role of PSC should be assessed in prospective trials.

Key words: malignant pleural mesothelioma, pemetrexed, second-line chemotherapy

Introduction

Until the recent Food and Drug Administration approval of pemetrexed (ALIMTA®; Eli Lilly and Company, Indianapolis, IN, USA) plus cisplatin, there had not been any regulatory-approved first-line treatment for malignant pleural mesothelioma (MPM). Over the past 20 years, a number of chemotherapeutic agents have been studied in phase II MPM trials and have shown modest activity. Response rates (RR) of 10% to 20% have been demonstrated by single agents such as gemcitabine, raltitrexed and doxorubicin, and for the combination of gemcitabine plus cisplatin [1–7]. The usefulness of data from past phase II studies has been limited by the small number of patients enrolled, varying methods used to evaluate response and variable characteristics of patients entered [8].

Chemotherapy has not been commonly accepted as standard treatment for MPM [9], until recently, perhaps, when the results of the largest trial in patients with unresectable MPM were reported [10]. This trial demonstrated that combination chemotherapy (pemetrexed plus cisplatin) was well tolerated and survival time was significantly increased (median survival time 12.1 versus 9.3 months; log-rank $P=0.020$; hazard ratio 0.77). Time to disease progression was significantly longer in the pemetrexed plus cisplatin arm (median time to progression 5.7 versus 3.9 months; log-rank $P=0.001$) as opposed to the cisplatin arm, and the response rates were significantly higher (41.3% versus 16.7%; $P<0.001$). Pemetrexed plus cisplatin treated patients also demonstrated improvement in pulmonary function [11] and reported improvement in dyspnea and pain

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[12]. The addition of folic acid and vitamin B_{12} supplementation resulted in a significant reduction in pemetrexed-related toxicity, without adversely affecting survival time. Thus pemetrexed plus cisplatin is likely to be used widely as first-line chemotherapy for MPM.

Patients who experience clinical benefit from such first-line chemotherapy are frequently still healthy when radiological progression of MPM is documented, and commonly inquire about second-line therapy. Few data are available to guide the oncologist in selecting second-line chemotherapy, because the vast majority of MPM chemotherapy trials have included only chemotherapy-naïve patients. However, several recent phase II trials have evaluated the effectiveness of chemotherapy in previously treated patients. Giaccone et al. [13] examined the efficacy and safety of ZD0473, a cisplatin analog, in the second-line setting in MPM. This study substantiated the ability to accrue healthy patients to second-line chemotherapy trials, but no major responses were seen with this agent. A slightly more promising second-line chemotherapy trial was reported by Fizazi et al. [1]. Their study enrolled both chemotherapy-naïve and previously treated patients to receive combination therapy of the thymidylate synthase inhibitor, raltitrexed, and oxaliplatin. The study showed activity, acceptable tolerability and an overall response rate of 20% for both patient groups. Other smaller studies have suggested benefit of second-line chemotherapy as well. For example, Vogelzang [14] observed a favorable response to cisplatin plus gemcitabine in two of three patients who failed prior treatment with single-agent doxorubicin.

The retrospective analysis presented in our trial was performed to characterize patients with advanced MPM who received post-study chemotherapy (PSC) treatment, the type of chemotherapy received and the potential impact further treatment may have on survival time. Since an unknown number of patients received additional therapy beyond second-line chemotherapy, we use the term post-study chemotherapy in this report rather than the term second-line chemotherapy.

Patients and methods

This retrospective analysis was conducted using data from patients with MPM who had received PSC following participation in the phase III study of pemetrexed plus cisplatin versus single-agent cisplatin. Data regarding PSC were captured on the patient case report form. The following information was collected on all patients reaching their first visit following cessation of study chemotherapy (i.e. the first post-study visit): (i) whether or not the patient received post-study therapy of any kind (yes or no); (ii) if the patient did receive post-study therapy, the start date of the specific type of post-study therapy given; specifically, if it was PSC, then the start date of the first intervention of PSC provided; and (iii) if the patient received PSC, the brand or trade name(s) of the agent(s) provided.

On subsequent post-study visits, data regarding PSC were collected only if it was the first time the patient received PSC. Investigators were not instructed to collect data on PSC if it was third-line (or greater).

Inclusion criteria

All 448 randomized and treated patients of the phase III trial were included in the current analysis. Patients were classified into two groups, PSC or no PSC. Patients were assigned to the PSC group if they received PSC either as a single agent or as combination therapy.

Data collection

Baseline demographics included age, gender, performance status, disease stage, histology and geographic region (Table 1). The PSC agent administered was recorded, but dose, schedule, duration of therapy, response to PSC and time to progression related to PSC were not recorded, since these data were not a primary or secondary end point of the study. Survival time was recorded from randomization to death or date of last contact.

Statistical analysis

Estimates of survival were calculated using Kaplan–Meier methods. Cox regression analysis was done to test any association between receipt of PSC and survival. Because patients were not randomized to received PSC or observations, it is impossible to conclude that receipt of PSC is responsible for any prolonged survival, or that patients who had prolonged survival received more PSC.

Results

Patients

Out of 448 possible patients, a total of 189 received PSC (42%); 84 from the pemetrexed plus cisplatin arm (37.2%) and 105 from the cisplatin arm (47.3%) (see Figure 1).

Table 1. Patient characteristics for post-study chemotherapy patients

Factor	Total number of patients	Patients with post-study chemotherapies [*n* (%)]
Geography		
North America	91	53 (58.2)
Western Europe	226	89 (39.4)
Australia	32	14 (43.8)
Central/South America	31	10 (32.3)
Eastern Europe	39	14 (35.9)
Other[a]	29	9 (31.0)
Karnofsky performance status		
High (90, 100)	242	123 (50.8)
Low (70, 80)	206	66 (32.0)
Stage[b]		
Early (<3)	98	41 (41.8)
Late (≥3)	347	146 (42.1)
Histology		
Epithelial	306	138 (45.1)
Sarcomatoid	43	16 (37.2)
Mixed	73	29 (39.7)
Other	26	6 (23.1)
Gender		
Male	365	152 (41.6)
Female	83	37 (44.6)

[a]Includes Taiwan, Turkey and India.
[b]International Mesothelioma Interest Group staging method; two patients' stage unknown.

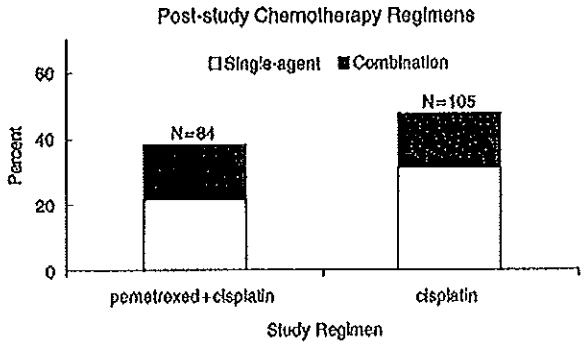

Figure 1. The percentage of patients receiving post-study chemotherapy in the two treatment arms: pemetrexed + cisplatin and cisplatin.

A similar percentage of male and female patients went on to receive PSC. As would be predicted, patients receiving PSC were more likely to have good prognostic factors at entry on the randomized trial, i.e. those with initially high Karnofsky performance status (90/100), and epithelial histological subtype. Median time to progression after first-line therapy was similar for both the PSC and no PSC groups (4.7 and 4.6 months, respectively). Finally, the median age of patients receiving PSC was 59.3 years (range 19.5–85.6), slightly younger than the median age of those entering the randomized trial (63 years). The median time from completion of first-line treatment to initiation of second-line therapy was 3.3 and 0.7 months ($P=0.006$) for pemetrexed plus cisplatin and for cisplatin treated patients, respectively. This interval was examined according to response status at completion of first-line treatment. For the pemetrexed plus cisplatin and cisplatin arms, respectively, complete/partial response patients had median time of 4.5 months ($n=35$) and 3.8 months ($n=15$), respectively, stable disease patients had median time of 5.1 months ($n=15$) and 3.4 months ($n=23$), progressive disease patients had median time of 0.5 months ($n=31$) and 0.3 months ($n=57$). Approximately 60% of patients from North America and 40% from Western Europe went on to receive PSC (see Table 1).

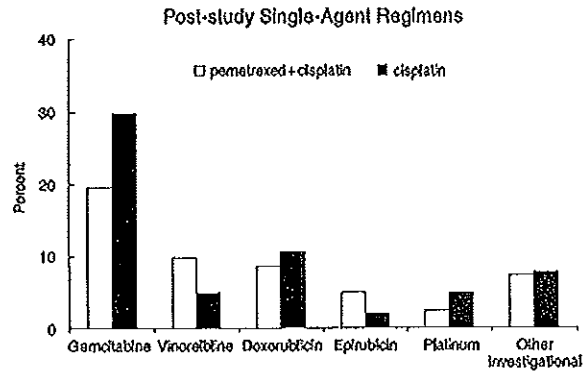

Figure 2. Single-agent regimens received by patients in the two treatment arms: pemetrexed + cisplatin and cisplatin.

Chemotherapy

One hundred and eighteen of the 189 (62%) PSC patients were treated with single-agent therapy (48 from the pemetrexed plus cisplatin arm and 70 from cisplatin arm), while 71 patients (38%) received combination chemotherapy (36 from the pemetrexed plus cisplatin arm and 35 from the cisplatin arm) (Figure 1). Gemcitabine was the most commonly administered single agent (Figure 2). The second most commonly used agent in PSC was an anthracycline, either doxorubicin ($n=19$) or epirubicin ($n=4$) (Table 2). Gemcitabine plus cisplatin or gemcitabine plus a non-platinum agent were the most commonly administered combination regimens. Ninety-two of the 189 patients (49%) received gemcitabine alone or in combination (see Table 2). It was a protocol violation for patients randomized to the cisplatin arm to receive subsequent pemetrexed therapy.

Survival time

The Kaplan–Meier estimates of survival by treatment arm and PSC subgroups are presented in Figure 3. These analyses reveal that, in general, patients receiving PSC had longer survival. However, within each subgroup of patients (with and without PSC) patients on the pemetrexed plus cisplatin arm had longer survival time than those on the cisplatin arm. For patients receiving PSC, median survival time for pemetrexed plus cisplatin was 15.3 months [confidence interval (CI) 13.3–18.9] with 39.3% censoring, compared with 12.2 months (CI 9.9–14.2) and 31.4% censoring for the cisplatin arm. For patients not receiving PSC, median survival time for pemetrexed plus cisplatin was 9.8 months (CI 8.1–11.7) with

Table 2. Summary of most common post-study chemotherapy

	Pemetrexed/cisplatin group ($n=226$) [n (%)]	Cisplatin group ($n=222$) [n (%)]
All second-line PSC	84 (37.2[a])	105 (47.3[a])
Single-agent therapy		
Gemcitabine	17 (20.2[b])	32 (30.5[b])
Vinorelbine	8 (9.5)	5 (4.8)
Doxorubicin	7 (8.3)	12 (11.4)
Other	9 (10.7)	8 (7.6)
Epirubicin	2 (2.4)	2 (1.9)
Platinum agents	5 (6.0)	11 (10.5)
Combination therapy		
Gemcitabine/platinum agents	16 (19.0)	17 (16.2)
Other gemcitabine combinations	8 (9.5)	2 (1.9)
Pemetrexed/vinorelbine[c]	0 (0)	3 (2.9)
Other	12 (14.3)	13 (12.4)

[a]Percentages calculated from total treatment arm sample sizes.
[b]Percentages calculated from number of patients receiving PSC.
[c]Receipt of pemetrexed by patients randomized to the cisplatin group was a protocol violation.

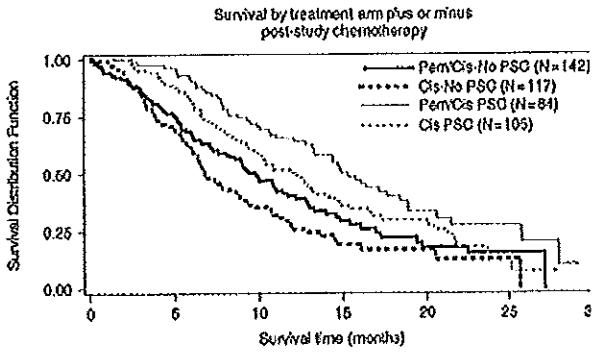

Figure 3. Kaplan–Meier estimates of survival times for four different patient categories in second-line study. Pem, pemetrexed; Cis, cisplatin; PSC, post-study chemotherapy.

33.8% censoring, compared with 6.8 months (CI 6.3–8.7) and 25.6% censoring for the cisplatin arm. Multiple regression analysis showed that PSC was statistically significantly correlated with extended survival ($P<0.001$), adjusting for prognostic factors and treatment group. The adjusted hazard ratio for PSC over the non-PSC subgroup was 0.56 (CI 0.44–0.72). These results indicate that, adjusting for imbalances in baseline prognostic factors, patients receiving PSC had a lower risk of death as compared with the non-PSC group. This analysis cannot establish that the lower risk of death was a result of PSC activity, but does quantify the association between survival and the decision to receive PSC.

Discussion

This analysis demonstrated that PSC was commonly used in the randomized trial of pemetrexed plus cisplatin versus cisplatin in MPM patients. Approximately 42% of all patients received some form of PSC. However, the use of PSC was more prevalent in the USA (58%) than in non-US countries (39%). More than half of the patients receiving PSC (50.8%) had a high Karnofsky performance status (90–100) at the time of randomization to either arm of this trial. Epithelial histology was the most prevalent subtype of MPM for patients receiving PSC. Multiple regression analysis showed that, adjusting for these imbalances, the PSC subgroup still had a markedly longer survival time than the non-PSC subgroup. However, this analysis cannot definitively establish that extended survival was due to the activity of any PSC. In fact, some clinically recognized combination of factors such as good performance status, epithelial histology, early stage disease and slightly younger age may have encouraged patients and physicians to pursue PSC, thereby explaining this finding.

An alternative explanation is that the chemotherapy agents used in PSC may have altered the natural history of MPM. Gemcitabine, as a single agent and in combination, was the most commonly used agent in PSC. Single-agent gemcitabine has had a variable rate of activity reported in the treatment of MPM (0% to 31%) [15]. It is not known to be cross-resistant with pemetrexed and gemcitabine/cisplatin is an active combination in MPM in the first-line setting, producing objective response rates of 20% to 30%, and symptomatic relief in patients who have stable or responding disease [16, 17].

Kaplan–Meier estimates of survival showed that PSC is associated with significantly prolonged survival (Figure 3). Interestingly, in our study, in spite of the larger number of patients in the cisplatin arm receiving PSC, the pemetrexed plus cisplatin arm experienced a significantly longer survival time (log-rank $P=0.02$). Moreover, the longer median time from completion of first-line therapy to the start of second-line therapy observed in the pemetrexed plus cisplatin treated patients exemplifies the effectiveness of the pemetrexed plus cisplatin combination. Because receipt of PSC was not randomized, it is impossible to conclude that receipt of PSC was responsible for any prolonged survival. Patients who had prolonged survival may simply have received more PSC.

The observed differences in median time from completion of first-line therapy to the initiation of second-line therapy suggest that a randomized trial in the second-line setting may need to be stratified by this interval. The interval may be prognostic for benefit and a randomized second-line trial is needed to make this determination.

A literature survey recently identified 16 published phase II mesothelioma chemotherapy trials that included second-line patient populations [18]. Remarkably, only one was a dedicated phase II trial [13]. In spite of that deficiency, partial responses to a variety of agents and combinations were observed in 5% to 10% of patients in many of these studies. Furthermore, according to this survey, the number of patients demonstrating benefit in the second-line setting seems to be steadily increasing. This survey, and our phase III study, suggest that chemotherapy drug sensitivity and potentially non-cross resistance among chemotherapy drugs exists in MPM as it does in other diseases, and could be explored for patient benefit.

Our findings, in conjunction with the previously mentioned studies in the second-line setting, suggest the feasibility of conducting second-line phase II chemotherapy trials perhaps with gemcitabine as a single agent, or in combination, after pemetrexed/cisplatin therapy. However, cumulative cisplatin neuro- and ototoxicity limit the enthusiasm for a cisplatin combination approach. Alternatively, carboplatin could be combined with gemcitabine, as it shows lesser neuro- and ototoxicity [19–21]. The oxaliplatin/gemcitabine combination is also an attractive candidate for further study owing to favorable tumor responses for oxaliplatin in cisplatin-pretreated patients [1] and because this combination has activity in MPM [22]. Fizazi et al.'s data [1] suggest a lack of resistance or non-cross-resistance with oxaliplatin plus raltitrexed in cisplatin-pretreated MPM patients.

Recently, Van Meerbeeck et al. [23] presented the results of a 250-patient randomized study of cisplatin with or without raltitrexed as first-line treatment of MPM. Treatment with raltitrexed and cisplatin produced superior response rate and survival time compared with cisplatin, and was well tolerated. These results further demonstrate the utility of anti-folates

in MPM. It will be interesting to know how many patients from this trial received PSC, the patient characteristics agents used and the impact PSC may have had on the survival results.

A number of questions should be addressed prior to initiating phase II and particularly phase III trials for second-line chemotherapy in MPM. For instance, assignment of risk/prognostic groups, prior response duration, optimal duration of treatment and consequences of long-term therapy for patients. To determine the extent of benefit from PSC, or from non-cytotoxic treatment, randomized controlled trials would need to be performed against the current standard, namely best supportive care. As demonstrated in randomized trials of second-line therapy in non-small-cell lung cancer, the interval from completion of first-line therapy to the beginning of second-line therapy is prognostic for survival. In our trial, the high variability in time from completion of first-line therapy to the initiation of second-line therapy suggests that a second-line MPM trial may need to be stratified by this interval.

This retrospective analysis of patients receiving PSC from our phase III trial of pemetrexed plus cisplatin in MPM suggests that PSC has a positive impact on survival. In view of this observation, the role of PSC should be prospectively assessed.

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