Cisplatin and Vinorelbine in unresectable malignant pleural mesothelioma

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Abstract

Objective: To evaluate the activity of cisplatine and vinorelbine as a first line, in unresectable patients with malignant pleural mesothelioma.

Patients & Methods: The study included 48 patients [77%- males] epithelial subtype (73%), stage III (43%), and stage IV (52%), performance status 0, 1 and 2, 23, 73 and 4%, respectively. The median age was 57 years [22 – 65 years]. Vinorelbine 25 mg/m2 I.V. weekly and cisplatin 100 mg/m2 I.V. every 4 weeks were given with hydration and anatiemetic treatment.

Results: Median number of administered cycles was four. Objective response were observed in 29.2 % with no complete response Median time to progression was 7.8 months (1.8 – 40.2 months) and median survival 17.2 months (0.6 – 43 months). There were 14 PR (response rates 29.2%). The fraction of patients alive at 1 and 2 years were 62.5 and 31% respectively. Grade 3 or 4 leucopenia occurred in 33% and 11% of patients respectively, nausea in 10%, neurotoxicity in 12%, nephrotoxicity in 4%. There were no toxic deaths.

Conclusion: Cisplatin and vinorelbine is an active regimen in malignant pleural mesothelioma with a response rate and survival comparable to the most active regimens so far reported.

Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive malignancy with an increasing incidence world-wide, due to the widespread of asbestos containing materials on a global scale over the last five decades(1).

Most patients with MPM, treated or untreated, will die from complications of local disease due to increasing tumor bulk. The diffuse spreading growth of this neoplasm makes surgery difficult and hence an option for only a minority of the patients (2).

Chemotherapy is the treatment of choice in the majority of cases. Among recently introduced chemotherapeutic agents only vinorelbine, edatrexate, gemcitabine and raltitrexed have demonstrated 20% of response rates (RR) (3).

Platinum compounds and doxorubicin are active and are usually included in the chemotherapy regimens for MPM (4).

Cisplatin alone showed a response rate of 14% as a single agent and about 30% response rate when used in a combination regimen. Doxorubicin has been studied extensively in the treatment of MPM. It demonstrated a response rate of 18% as a single agent and 25 – 28% when used in a combination regimen. High – dose methotrexate was the most active antimetabolite, with a response rate of about 38%(1).

The third generation vinca alkaloid vinorelbine has attracted interest in a phase II trial using vinorelbine 30 mg/m2 i.v. weekly. Each cycle consisted of 6 weekly injections and the median number of injections was 12. The intention to treat response rate among chemotherapy – naive MPM patients was 24% (95% confidence level 10 – 44%) and the fraction of patients alive at 1 year from time of first treatment was 41%, which ranks vinorelbine among the most active agents in MPM. Toxicity of this regimen was modest (5).

On the basis of these results, we decided to evaluate the activity of vinorelbine in combination with cisplatin as first line treatment in MPM.

Materials and Methods

Patients were eligible if they had histological proven MPM, no previous radiotherapy or chemotherapy, measurable disease, ECOG performance status (PS) score ≤ 2 or less, life expectancy ≥ 3 months, age ≥ 18 years and written informed consent.

Adequate organ functions were required, defined as WBC ≥ 3000 UL-1, platelets ≥ 100000 UL-1, hemoglobin > 10 gm/dl, total bilirubin < 1.5 times the upper limit of normal (ULN), AST and ALT < 2 times the ULN, serum creatinine < 2.0 mg per 100 ml, or a calculated serum creatinine clearance > 60 ml/min.

Exclusion criteria included: significant medical or psychiatric co-morbidity, brain metastases, pregnant or lactating women, and previous or concurrent malignancies. All patients of fertile capacity were to use safe contraception.

Treatment plan

Vinorelbine 25 mg/m2 was administrated i.v. weekly as a 10 – min infusion, cisplatin 100 mg/m2 was administrated as a 1h. i.v. infusion together with intravenous hydration and antiemetic treatment, every 4 weeks. Weekly complete blood cell counts and chemistry panel were performed. Treatment was delayed by 1 week in case of bone marrow suppression (WBC < 3000 UL-1, neutrophil count < 1500 UL-1 or platelets < 100000 UL-1).

Cisplatin was not administrated if creatinine clearance below < 50 ml min-1.

Dose was adjusted in case of grade 4 hematological toxicity, or grade 3-4 non-hematological toxocities. Dose-delay up to 3 weeks were permitted for recovery from drug toxicity. Granulocyte colony stimulating factors were not routinely used.

Treatment assessment

Baseline complete history, physical examination, complete blood cell count, liver and renal function tests, blood electrolytes were done.

Baseline creatinine clearance was performed and then before every second treatment (every 8 weeks). Spiral CT-scan was performed at baseline, before start of every other treatment cycle (every 8 weeks), and every 2 months after end of therapy. Chest x – ray was performed at baseline and before each treatment cycle. Response was assessed by new modified RECIST criteria, (8).

Change in disease was assessed by measuring the tumor thickness perpendicular to the chest wall or mediastinum in up to three involved areas of pleural rind at least 2 cm apart on computed tomography scan, at baseline and at every other cycle (at least one measurement was > 1.5 cm). A reduction of at least 30% on two occasions 4 weeks apart defined a partial response, an increase of 20% over the nadir measurement, progressive disease.A complete response (CR) was defined as complete absence of all signs of disease without any new lesions or disease – related symptoms.

Statistical Analysis

Survival was defined as the time from onset of treatment to the time of death from any cause. Time to progressive disease was defined as the time from onset of treatment until progression or death from any cause. Statistical analysis was done using Kaplan – Meier method to estimate overall survival and time to progression.

Results

Patients characteristics

Forty eight patients were enrolled from March 2006 till November 2008. Most patients were males (77%), had epithelial subtype (73%), performance status 0 – 1 (96%), previous asbestos exposure (83%), and IHIG stage III – IV (94%) (Table 1). Median age was 57 years (range 22 – 65 years).

Table 1: Patients Characteristics

Variables Total	No. of patients (%) 48 (100)
Gender	
Male	37 (77)
Female	11 (23)
Asbestos exposure	
No	8 (17)
Yes	40 (83)
Pathology	
Epithelial	35 (73)
Sarcomatous	4 (8)
Biphasic	9 (19)
IMIG stage	
I	-
II	3 (6)
III	20 (42)
IV	25 (52)
Performance status	
0	11 (23)
1	35 (73)
2	2 (4)
Age	
Median	57 years
Range	(22 – 65)

Toxicity

A total of 248 treatment courses were given, with a median of 4 (range 1 – 6). Grade 3 or 4 leucopenia occurred in 21 patients (44%), with 5 patients having grade 4 (11%) (Table 2). Four patients (8%) had febrile neutropenia with no septic deaths. None had grade 3 or 4 thrombocytopenia. Non-hematological grade 3 or 4 toxicity occurred with respect to nausea (10%), neurotoxicity (12%), nephrotoxicity (4%) and other toxicities as constipation and tiredness in 8%. Seven patients (15%) were hospitalized due to toxic effects of chemotherapy. One patient died due to pulmonary embolism.

Table 2: Toxicity Profile

Grades	No. of patients (%) 0	1	2	3	4
Hematologic Toxicity					
Leucopenia	10 (21)	3 (6)	14 (29)	16 (33)	5 (11)
Neutropenia	7 (15)	7 (15)	17 (35)	13 (27)	4 (8)
Thrombocytopeni	44 (92)	3 (6)	1 (2)	-	-
Non-hematologic Toxicity					
Nausea	17 (36)	21 (44)	5 (10)	5 (10)	-
Vomiting	29 (60)	10 (21)	9 (19)	-	-
Nephrotoxicity	23 (48)	11 (23)	12 (25)	2 (4)	-
Neurotoxicity	19 (40)	15 (31)	8 (19)	4 (8)	2 (4)
Other toxicity	5 (10)	21 (44)	18 (38)	3 (6)	1 (2)

Treatment intensity is shown in table 3 where a median of 4 treatment courses were given

Table 3:Treatment Intensity

Variables	
No. of treatment courses	No. of patients (%)
1	2 (4)
2	2 (4)
3	3 (6)
4	3 (6)
5	7 (15)
6	31 (65)

Dose reduction was necessary in 17 patients (35%) most frequently due to hematological toxicity (9 patients) nephrotoxicity (2 patients) or neurotoxicity (6 patients), other less frequent causes were nausea, hearing loss and tinnitus. These reasons were non-exclusive. Retreatment postponement due to delayed hematological recovery occurred in 18 patients (37.5%). These delay were due to non – exclusive reasons as delayed hematologic recovery, hematuria, pneunomonia and poor performance

Response and Survival

Fourteen cases responded to this protocol with an overall response rate of 29.2% (CR 0%, PR 29.2%), Thirty four patients (71%) had stable and progressive disease(S.D. in 16 patients (33.3%) -P.D in 18 patients (37.5%). Eleven responses occurred among the 35 cases having epithelial subtype (31.4%) and in one and two patients respectively among the 4 sarcomatous and nine biphasic cases. Six responses were noted among 11 female patients (54.5%) compared to eight responses among 37 males (29%). The fractions of patients alive after 1 and 2 years were 30 patients (62.5%) and 15 patients (31%), respectively. Median time

to progression was 7.8 months (1.8 – 40.2 months), whereas median survival was 17.2 months (0.6 – 43 months). Curves of overall survival and time to progression are shown in figure 1 and 2, respectively.

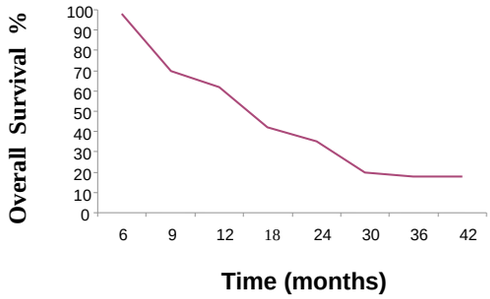

Fig 1: Overall survival.

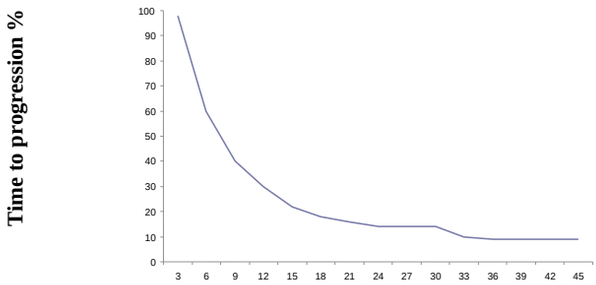

Fig 2: Time to progression.

Discussion

Patients with MPM are reported to have poor survival rate because of the advanced stage of disease at presentation and its chemoresistance (9). In 1996, Ong and Vogelzang(10) identified only six regimens showing a response rate superior than 20%.They recommended further Phase II trials to search for agents that are effective against local and systemic disease .. In this study, the response rate of 29% is noteworthy, if compared to the most used regimens in MPM (table 4). However, it is difficult to compare differences in activity between the regimens due to several reasons. First, most of the studies are phase II trials or retrospective analyses except for the randomized trials by Vogelzang et al, 2003(11) and van Meerbeeck et. al, 2005 (12), which usually showed tendency towards higher response rates in the very selective non-randomized trials. Second, is the different prognostic variables between the trials. (table 4)

Table 4: Selected combination chemothegrapy regimes in MPM

Author, year	Regimen	N	Response rate (%)	Median survival (months)	Time to PD (months)	1- year survival (%)
Current study	CDDP+vinorelbine	48	29.2	17.2	7.8	62.5
Van Meerbeeck, 2005[a]	CDDP+raltitrexed	126	24.0	11.4	5.3	46
Vogelzang, 2003[a]	CDDP+pemetrexed	226	41.3	12.1	5.7	51
Obasaju, 2007	CDDP+pemetrexed	728	20.5	10.8	NA	45
Santoro, 2007	CBDCA+pemetrexed	861	21.7	NA	NA	64
Ceresoli, 2006	CBDCA+pemetrexed	102	18.6	12.7	6.5	52
Andreopoulou, 2004	CDDP+MMC+VBL	150	15.3	7.0	NA	31
Byrne, 1999	CDDP+gemcitabine	21	48.0	10.0	NA	NA
Van Haarst, 2002	CDDP+gemcitabine	32	16.0	9.6	6.0	36
Favaretto, 2003	CBDCA+gemcitabine	50	26.0	14.7	8.9	53
Berghmans, 2005	CDDP+epirubicin	69	19.0	13.3	NA	50

CDDP – cisplatin; CBDCA = carboplatin; MMC = mitomycin C; VBL = vinblastine, NA = not available, a = Data from randomized trial.

In CALGB (13), EORTC (14), and in the randomized trial by van Meerbeeck(12), they pointed to better outcome for MPM patients having epithelial histological subtype. The frequency of epithelial subtype in the current study was 73%, which is higher than that in Vogelzang et al (15), thus explaining the tendency towards a higher response rate. The frequency of epithelial subtype was however, similar to that in newer studies, such as those by Vogelzang et al 2003 (11) (68% epithelial), van Meerbeeck et al 2005 (12) (75%), Berghmans et al, 2005 (15) (74%), and van Haarst et al 2002 (16) (81%), pointing toward a uniform rate of epithelial subtype of 70 – 80% in more recent trials and with the current study being in accordance

with these trials. In the current study,the response rate is comparable to that of single agent vinorelbine, which revealed a 24% partial response rate (5).

Hematological toxicity was relatively high in the current study where 44% of the patients experienced Grade 3 or 4 leucopenia (Table 2). This was in accordance with Berghmans et al, 2005 (15) and lower than the 81% of NSCLC patients who had Grade 3 or 4 granulocytopenia in the randomized SWOG trial (6). It's however, considerably higher than was observed in randomized trial in MPM patients with cisplatin and pemetrexed (18%) (11), or cisplatin and ralitrexed (7%) (12). Also, febrile neutropenea was somewhat higher, being 8% compared to 2 and 1% respectively, in the two randomized trials cited above. There were no septic deaths. The febrile neutropenia rate of 8% in this study is not only a potential risk but also an inconvenience for those patients who have to be admitted for intravenous antibiotics, as well as a cost for the healthcare system. Other toxicities weren't pronounced (Table 2).

In the current study, a median survival of 17.2 months and 2 year survival rate of 31% were impressive, even though patients with adverse prognostic variables such as performance status 2 was included (Table 1). The survival results compares favorably with those reported on for either active regimens, ranking this regimen among the most active cytotoxic treatments for MPM reported to date (Table 4). On the other hand, this regimen is inconvenient for patients and for health care system because of the weekly administration but still it could be more convenient to be used in an oral form. Both cisplatin and pemetrexed as well as cisplatin and raltitrexed have proved superior to single agent treatment with cisplatin in randomized trials (11, 12). The high antitumor activity of cisplatin and vinorelbine deserves attention for use as induction treatment before surgery in resectable cases. Development of platinum compounds, together with vinorelbine in the palliative setting, also seems justified both in the light of the documented activity of the two–drug combination used in the current study and also because the single agent activity of vinorelbine with a response rate of 24% (5) which ranks this agent among the most active single agent in MPM. However, it must be kept in mind that these results are obtained from relatively small and non – randomized trials. Improvement of the current regimen is necessary if it is to be used in palliative situation to make it more feasible & vinorelbine may be applied in the oral formulation. Also, evaluation of new targeted agents is necessary to improve prognosis for this dismal disease. Vinorelbine may also be explored as second – line treatment for patients not previously exposed to this drug.

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