Anti-Cancer Drugs 2000, **11,** pp. 257–261

Clinical report

Docetaxel and irinotecan (CPT-11) in the treatment of malignant pleural mesothelioma—a feasibility study

Aija Knuuttila,[1] Tiina Ollikainen,[2] Maija Halme,[1] Pekka Mali,[3] Leena Kivisaari,[4] Kaija Linnainmaa,[2] Antti Jekunen[3] and Karin Mattson[1]

[1]Department of Medicine, Division of Pulmonary Medicine, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki, Finland. [2]Finnish Institution of Occupational Health, 00290 Helsinki, Finland. [3]Department of Oncology, Turku University Hospital, 20520 Turku, Finland. [4]Department of Radiology, Helsinki University Central Hospital, 00290 Helsinki, Finland.

We chose to treat malignant pleural mesothelioma with a combination of docetaxel and irinotecan (CPT-11), because there have been preliminary reports that CPT-11 is active against mesothelioma, and docetaxel and CPT-11 were the most active agents in our *in vitro* experiments in human mesothelioma cell lines. Fifteen previously untreated patients with pleural mesothelioma (IMIG Stage III–IV) were given docetaxel 60 mg/m^2 followed by CPT-11 190 mg/m^2 on day 1, repeated every 3 weeks. All the patients were evaluable for toxicity and 13 patients were evaluated for response. No objective responses (complete or partial) were achieved, but there were two minor responses (overall response rate 15%) each of a duration of 4 months. Three patients had stable disease (23%); median time to progression was 7 months. Median survival in all the patients was 8.5 months from the first chemotherapy cycle and 11 months from diagnosis. Toxicity was severe with seven of 15 patients suffering neutropenic fever and six of 15 patients grade 3–4 diarrhea. The trial was discontinued because of toxicity and lack of activity. We do not recommend the combination of docetaxel and CPT-11 using the schedule presented here for further investigation in malignant mesothelioma. However, CPT-11 and docetaxel, individually, still warrant further study in this disease, especially in combination with cisplatin.

Key words: Chemotherapy, docetaxel, irinotecan, mesothelioma, mesothelioma cell lines.

Introduction

Mesothelioma is a primary neoplasm of the mesothelial lining of pleural or peritoneal cavities. In most cases it is already a diffuse disease at the time of diagnosis with the tumor spreading locally and often invading thoracic structures. Mesothelioma is highly lethal with a median survival of 8–18 months and it is a particularly resistant tumor upon which chemotherapy has so far had only minor impact. Neither is mesothelioma curable by surgery or by chemo- and radiotherapy. Various chemotherapeutic agents have been tested in mesothelioma, but only a few have consistently induced a response rate higher than 20% in phase II trials.[1] High-dose methotrexate has shown the most activity in mesothelioma. Solheim *et al.* achieved a reported response rate of 37% using methotrexate as a single agent in a phase II study.[2] Halme *et al.* combined interferons with methotrexate, but did not achieve improvement in response rate.[3] At the time of starting this study there was an abstract published suggesting that CPT-11 is an active compound against mesothelioma in combination with cisplatin.[4]

Docetaxel and CPT-11 are interesting new chemotherapeutic agents with different mechanisms of aciton. Docetaxel is a potent microtubule stabilizing agent, and CPT-11, a semisynthetic derivative of camptothecin, is a potent inhibitor of topoisomerase I activity and therefore involved in the inhibition of DNA replication. In a preclinical study using a colony-forming assay, CPT-11 has demonstrated cytotoxic activity against mesothelioma.[5] Our *in vitro* sensitivity testing in mesothelioma cell lines had shown that docetaxel and CPT-11 are both active against mesothelioma cells as single agents.[6] This background and the intention to avoid platinum compounds encouraged us to choose the combination of docetaxel and CPT-11 for a feasibility study in malignant pleural mesothelioma. The aim of this study was to evaluate the toxicity

Correspondence to A Knuuttila, Department of Medicine, Division of Pulmonary Medicine, Helsinki University Central Hospital, PO Box 340, 00029 Helsinki, Finland.
Tel: (+358) 9 47172270; Fax: (+358) 9 47175791;
E-mail: aija.knuuttila@hus.fi

and to investigate the activity of this combination, which to our knowledge has not been previously studied in mesothelioma.

Patients and methods

Patient eligibility

The criteria for eligibility were previously untreated, histologically confirmed malignant pleural mesothelioma; measurable or assessable disease by magnetic resonance imaging (MRI) or computed tomography (CT). Additional entry criteria were age 18–70 years, performance status WHO 0–2, adequate bone marrow reserve (WBC $> 1 \times 10^9\ l^{-1}$ and platelet count $> 100 \times 10^9\ l^{-1}$), and adequate liver and renal function (serum creatinine and serum bilirubin within normal range, and transaminase levels >3 times the upper normal limit). Previous surgical procedures including palliative pleurectomy or decortication were allowed, provided that the tumor was still assessable and the time interval between surgery and chemotherapy was at least 4 weeks. Patients with other malignant disease or other severe medical condition were excluded. All the patients gave a written informed consent before participating in this study. The study was approved by the Ethics Committee of the Department of Medicine at the Helsinki University Central Hospital.

Treatment schedule

Patients were assigned to receive three cycles of treatment. For those who achieved a response, or for whom it was in their best interest, treatment could continue for a maximum of six cycles. Chest radiographs and laboratory tests, including total blood count and transaminases, alkaline phosphatase, serum bilirubin, potassium, sodium, C-reactive protein and creatinine levels, were checked before each treatment cycle and at the end of the treatment. Responses were evaluated from thoracic MRI (or CT of the chest and upper abdomen) after three and six treatment cycles and at any suspicion of tumor progression. The treatment was discontinued if progressive disease was detected or in the case of unacceptable toxicity. Docetaxel (Taxotere®) 60 mg/m^2 was administered as an i.v. infusion over 1 h and followed by CPT-11 (Campto®) 190 mg/m^2 as an i.v. infusion over 1 h on day 1 of a 21 day cycle. The patients were given 3 days of oral dexamethasone, 8 mg b.i.d., beginning on the day before the treatment, to prevent fluid retention and allergic reactions associated with docetaxel. As concurrent therapy patients were instructed to begin oral loperamide at the earliest signs of diarrhea occurring more than 24 h after receiving CPT-11. Drug toxicity was graded according to the WHO toxicity scales. Pleural effusions were also reviewed from MRI (or CT) employing a qualitative visual assessment. If present, pleural effusions were classified as 'small', 'moderate' or 'large' (occupying less than one-third, between one-third to two-thirds and greater than two-thirds of the hemithorax, respectively). Survival was calculated from the first treatment dose and also from the date of diagnosis.

Response criteria

Tumor response was assessed from MRI or CT depending on which imaging method more accurately showed the growth of the tumor in each case, according to the WHO criteria. An independent radiologist reviewed all the imaging data. Complete response (CR) was defined as the disappearance of all tumor tissue and pleural exudate lasting at least 4 weeks. Partial response (PR) was defined as a decrease in tumor size of 50% or more within all marker lesions, and minor response (MR) as a decrease of tumor size, but less than 50%. Progressive disease (PD) was defined as an increase in tumor size of at least 25% or an appearance of a new tumor lesion. Any change in tumor size between PR and PD was described as no change (NC). Patients were evaluable for response after receiving a minimum of one treatment cycle, and with an interval of at least 4 weeks between the treatment and the radiographic imaging.

Statistical analysis

A minimum of 15 patients was to be accrued for the first stage of this study. If fewer than two objective responses were observed or if unacceptable toxicity occurred, the study would be stopped. In the event of more than two objective responses, the study would remain open for an additional 15 patients. Survival was estimated using the life-table method. Binomial distribution was used when computing the confidence interval for the response rates.

Results

Patient characteristics

The characteristics of the 15 patients entered in the study between November 1997 and May 1999 are summarized in Table 1. According to the IMIG staging system,[7] three patients had stage III disease (20%) and 12 patients had stage IV disease (80%). Fourteen

patients were evaluated from MR images and one from a CT scan. Mean time between radiographic imaging and the first treatment cycle was 11 days (range 3–24 days). Eight patients had epithelial subtype tumors, three had mixed type tumors, two had sarcomatoid tumor and in two cases the subtype was undefined. On admission six patients had 'small' pleural effusions, four had 'moderate' effusions and three had 'large' pleural effusions, while two patients did not have noticeable pleural fluid. Thirteen patients (87%) were known to have had an occupational exposure to asbestos. All the patients were evaluable for toxicity and 13 patients were evaluable for response. Two patients were considered non-evaluable for response; one of them suffered early progression 2 weeks after the first treatment cycle and the general condition of the other patient was too poor for MRI to be carried out after the first treatment cycle.

Between one and six cycles of treatment (mean 2.7) were given to each patient, but only two patients received the maximum of six cycles. Five patients, of whom two had sarcomatoid subtype tumors, received only one cycle of chemotherapy. Treatment was discontinued due to toxicity in three of them, and because of early progression in one and poor general condition in one. Reduced doses were given in seven cycles to four patients.

Three patients received palliative thoracic radiotherapy (20–33 Gy) after progression. Another two patients received additional chemotherapy (one patient methotrexate+vinorelbine and one patient methotrexate first and then cisplatin+gemcitabine) after progressing on the study drugs.

Table 1. Patient characteristics

N	15
Sex	
male	13
female	2
Age (years)	
mean	61
range	51–70
Occupational asbestos exposure [no. (%)]	13 (87%)
Smoking history [no. (%)]	9 (60%)
Stage (IMIG) [no. (%)]	
I–II	0 (0%)
III	3 (20%)
IV	12 (80%)
Histological subtype [no. (%)]	
epithelial	8 (53%)
mixed	3 (20%)
sarcomatoid	2 (13%)
undefined	2 (13%)
Performance status (WHO grade)	
0	3 (20%)
1	10 (67%)
2	2 (13%)
Mean symptom duration before diagnosis [months (range)]	3 (2–12)

Response

Thirteen patients (87%) were evaluable for tumor response. No CRs or PRs were observed. Two patients achieved MR, to give an overall response rate of 15% (two of 13) (95% confidence interval 2–45%). The duration of MR was 4 months in both cases and both patients had epithelial subtype tumors. Three patients had NC status after three treatment cycles and the time to progression ranged from 4.5 to 8 months. These patients also had epithelial subtype tumors. The disease progressed in three patients after one cycle, in four patients after three cycles and in two patients after six treatment cycles.

Survival

All 15 patients were included in the survival analysis. Six patients were alive at the time of evaluation (two with MR, two with NC and two with PD). Median survival from the start of the treatment was 8.5 months

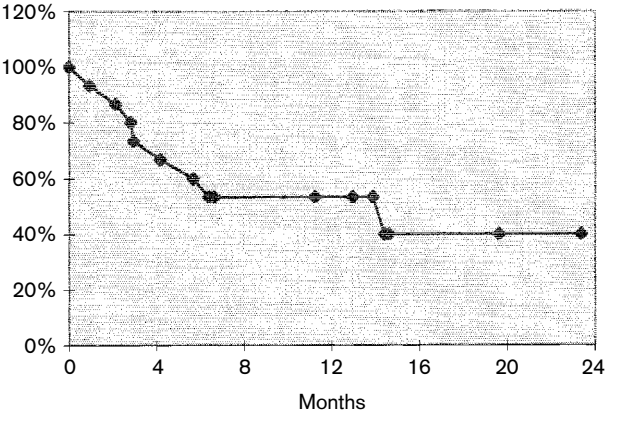

Figure 1.

Table 2. Toxic side effects

Toxicity	Grade (WHO criteria)			
	1	2	3	4
Hematological				
neutropenia	0	1	3	1
neutropenic fever	0	0	0	7
Infection	1	0	3	0
Gastrointestinal				
diarrhea	1	3	2	4
nausea/vomiting	2	1	4	1
gastrointestinal bleeding	0	1	0	0

(range 1–26+ months). The 1-year survival rate was 47% (Figure 1). Median survival from diagnosis was 11 months (range 2–28+ months). The five patients who received only one treatment cycle had a median survival of 3 months from the start of chemotherapy and of 4 months after the diagnosis.

Toxicity

All the patients could be evaluated for toxicity and the findings relating to toxic side effects are shown in Table 2. Generally the toxicity of this chemotherapy combination was not well tolerated. Three patients discontinued treatment after only one cycle due to toxicity. Neutropenic fever was the most common hematological toxicity occurring after the first treatment cycle in seven patients (47%). These patients were given prophylactic granulocyte colony stimulating factors during the following treatment cycles and neutropenic fever did not reoccur. Non-hematological toxicities were diarrhea and nausea, but neither grade 3–4 elevation of liver enzymes nor permanent deterioration of renal function was seen. Diarrhea responded well to early loperamide therapy in many cases. However, the diarrhea was severe in 40% of patients and required hospitalization. These patients received prophylactic oral antibiotic (ciprofloxacin) in subsequent cycles in order to avoid the diarrhea. One patient had an acute colinergic reaction during CPT-11 infusion (flushing, sweating), which reacted well to atropine and did not lead to treatment discontinuation. One patient had reversible polyuria after each cycle, but this did not affect the treatment schedule. In one patient, subileus in combination with neutropenic fever occurred after the first cycle and treatment was discontinued. Both patients with sarcomatoid tumors suffered grade 4 neutropenia, and grade 3–4 nausea and diarrhea after the first treatment cycle, which lead to discontinuation. The amount of pleural effusion did not correlate with the toxicity observed.

Discussion

This is the first clinical report of the treatment of mesothelioma using a combination of docetaxel and CPT-11. After we had initiated this study an abstract was published describing the treatment of pleural mesothelioma with docetaxel.[8] Only one response was achieved in 17 patients (6%) and there was at least one treatment-related death. This suggests that docetaxel as a single agent is not active against mesothelioma. Recently, Nakano *et al.* have reported a study in which CPT-11 60 mg/m^2 (days 1, 8 and 15) and cisplatin 60 mg/m^2 (day 1) were given in a 4 week cycle. They reported an overall response rate of 40% in 15 patients, with tolerable toxicity.[9] Topotecan, another camptothecin analog like irinotecan, has also been studied as a single agent in malignant mesothelioma, but there were no objective responses in 22 treated patients.[10]

We have found that the *in vitro* sensitivity testing of chemotherapeutic agents on mesothelioma cell lines is a useful tool for choosing drugs for clinical trials. Methotrexate was shown to be highly active against mesothelioma cell lines *in vitro*[11] and this activity was confirmed in a clinical trial of high-dose methotrexate in combination with interferons in pleural mesothelioma.[3] In subsequent *in vitro* studies we tested the sensitivity of mesothelioma cell lines to four new chemotherapeutic agents: gemcitabine, CPT-11, docetaxel and paclitaxel. Cell lines from different patients diverged in their sensitivity to different drugs, but overall gemcitabine showed the least activity and docetaxel caused the most.[6] Based on these results and on the preliminary clinical reports at that time of the activity of CPT-11 in combination with cisplatin against mesothelioma, we chose to combine CPT-11 and docetaxel. Docetaxel as a mitotic spindle poison seemed a promising contributor to the mechanism of action of CPT-11 (inhibitor of DNA replication). The doses and the schedule of this treatment were designed to be suitable for out-patient treatment. The feasibility of this schedule had been established in an ongoing phase II study of docetaxel 60 mg/m^2 and CPT-11 200 mg/m^2 once every 3 weeks for recurrent ovarian cancer.[12]

The toxicity in our patient group was not acceptable with seven of 15 patients suffering neutropenic fever, six of 15 patients grade 3–4 diarrhea and three patients discontinuing treatment after first cycle because of toxicity. This rather severe toxicity profile was not consistent with the good tolerance of the same regime seen in the patients with ovarian cancer. Thirteen of our patients had a very good performance status (WHO 0–1) on admission, so it is unlikely that the patients' general condition explains the toxicity observed. There is some cautionary information that patients with large pleural effusions or ascites might have an increased risk of accumulating CPT-11 resulting severe toxicity.[13] However, Nakano *et al.* did not find any excess toxicity in mesothelioma patients with large pleural effusions treated with CPT-11, although the different administration schedule for CPT-11 (60 mg/m^2 day 1, 8 and 15) may have contributed to the lower level of toxicity in their patients. We could find no definitive relation between the toxicities and the amount of pleural effusions. Without precise determination of drug concentrations in the body fluids, it is impossible to draw any conclusions on the role of pleural fluid in the

toxic accumulation and the tolerance of CPT-11, especially with the high single dose of CPT-11 used here. Docetaxel has been successfully used in even higher doses (75 mg/m^2) in combination therapy in non-small cell lung cancer and we found that it was not the dose in this schedule that was the reason for toxicity, but the drug itself which seemed to be poorly tolerated by mesothelioma patients. The finding is consistent with that of Belani *et al.*, who used single-agent docetaxel (100 mg/m^2 every 3 weeks) in 17 patients with mesothelioma.[8]

Only a small number of patients were enrolled in our study, but we considered it unethical to continue with the toxicity and the poor results reported here. Although no objective responses were achieved, the 1-year survival rate was 47%, and two female patients with epithelial subtype tumors had already survived more than 22 and 26 months at the time of writing this article. The epithelial subtype tumors are known to have the best prognosis, but it cannot be ruled out that chemotherapy confers clinical benefit on all mesothelioma patients, even though objective responses are not seen.[14] Moreover, response rate is probably not the best indicator of any clinical benefit achieved by chemotherapy. All our patients had very advanced disease, which naturally affected the survival. We suspect that the very advanced disease which we observed was because we used MRI, which provides more accurate images of the invasive growth of the tumor into the thoracic structures than CT.[15] The five patients who received only one treatment cycle were as fit as the other patients, but their mean survival was only 3 months and two of these patients had sarcomatoid tumors which are know to have a worse prognosis than the other subtypes.

Conclusion

We do not recommend the combination of docetaxel and irinotecan, using the dose and schedule presented here, for further studies in the treatment of mesothelioma. Docetaxel as a single agent seems inactive in this disease, but CPT-11 and docetaxel individually still warrant further interest and investigation in different dose schedules, especially in combination with platinum compounds.

References

1. Ong ST, Vogelzang NJ. Chemotherapy in malignant pleural mesothelioma. A review. *J Clin Oncol* 1996; **14**: 1007–17.
2. Solheim OP, Saeter G, Finnanger AM, Stenwig AE. High-dose methotrexate in the treatment of malignant mesothelioma of the pleura. A phase II study. *Br J Cancer* 1992; **65**: 956–60.
3. Halme M, Knuuttila A, Vehmas T, *et al*. High-dose methotrexate in combination with interferons in the treatment of malignant pleural mesothelioma. *Br J Cancer* 1999; **80**: 1781–5.
4. Nakano T, Shinjo M, Togawa N, *et al*. A pilot phase II study of irinotecan (CPT-11) in combination with cisplatin administered intravenously to patients with malignant mesothelioma (abstract). Philadelphia, PA: International Mesothelioma Interest Group (IMIG), 1997.
5. Shimada Y, Rothenberg M, Hilsenbeck SG, Burris III HA, Degen D, Von Hoff DD. Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumor colony-forming units. *Anti-Cancer Drugs* 1994; **5**: 202–6.
6. Ollikainen T, Knuuttila A, Suhonen S, *et al*. *In vitro* sensitivity of normal human mesothelial and malignant mesothelioma cells lines to four new chemotherapeutic agents. *Anti-Cancer Drugs* 2000; **2**: 93–9.
7. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. *Lung Cancer* 1996; **14**: 1–12.
8. Belani C, Adak S, Aisner S, Stella PJ, Levitan N, Johnson DH. Docetaxel for malignant mesothelioma: phase II study of the Eastern Cooperative Oncology Group. *Proc Am Soc Clin Oncol* 1999; **18** (abstr.)
9. Nakano T, Chahinian AP, Shinjo 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**: 2375–84.
10. Maksymiuk AW, Marschke Jr RF, Tazelaar HD, *et al*. Phase II trial of topotecan for the treatment of mesothelioma. *Am J Clin Oncol* 1998; **21**: 610–3.
11. Hand A, Pelin K, Mattson K, Linnainmaa K. Interferon (IFN)-alpha and IFN-gamma in combination with methotrexate: *in vitro* sensitivity studies in four human mesothelioma cell lines. *Anti-Cancer Drugs* 1995; **6**: 77–82.
12. Mäenpää J, Käär K, Kivinen S, Pohto M, Jekunen A. Docetaxel and CPT-11 for recurrent ovarian cancer—a phase II study. *Proc Am Soc Clin Oncol* 1999; **18** (abstr).
13. *Society of Japanese Pharmacopoeia*. Irinotecan hydrochloride, summary basis of approval. Tokyo: Pharmaceuticals Affairs Bureau 1996: 105.
14. Huncharek M, Kelsey K, Mark EJ, *et al*. Treatment and survival in diffuse malignant pleural mesothelioma; a study of 83 cases from the Massachusetts General Hospital. *Anticancer Res* 1996; **16**: 1265–8.
15. Knuuttila A, Halme M, Kivisaari L, Kivisaari A, Salo J, Mattson K. The clinical importance of magnetic resonance imaging versus computed tomography in malignant pleural mesothelioma. *Lung Cancer* 1998; **22**: 215–25.

(Received 12 February 2000; accepted 17 February 2000)