Journal of BUON **16:** 166-169, 2011

ORIGINAL ARTICLE

Metastatic lung disease treated with pemetrexed-docetaxel combination chemotherapy

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Summary

Purpose: *According to the ASCO guidelines 4 cytotoxic agents are used in colorectal cancer. Numerous agents have not been used or tested and thus their effectiveness is not known. Herein we present the preliminary data of a trial whose objective was to investigate the effectiveness to 2 combined agents in patients with heavily pretreated adenocarcinomas.*

Methods: *Ten patients have been recruited up until now. Colorectal adenocarcinoma was the primary disease in 7 patients, gastric cancer in 2, and endometrial adenocarcinoma in one. All patients had undergone at least 2 lines of previous chemotherapy during 2-3 years before the trial. The lungs were the only or main site of metastases in all patients. Chemotherapy agents used were pemetrexed 500 mg/m^2 and docetaxel 75 mg/m^2, repeated every 3 weeks, with a plan to administer 6 cycles.*

Results: *The mean number of cycles were 3 (range 1-6). Total number of cycles 33. No serious toxicity was detected. One patient had complete response, 3 partial response, 5 stable disease, 1 disease progression. Median survival was 6 months (range 2-12+ months).*

Conclusion: *The effectiveness of the pemetrexed-docetaxel combination in heavily pretreated adenocarcinoma patients justifies their use when no other alternative exists.*

Key words: adenocarcinomas, combination chemotherapy, docetaxel, lung metastasis, pemetrexed

Introduction

Chemotherapy for metastatic disease is based on the location of the primary site of cancer and details of its histological characteristics. For each malignant disease a certain number of cytotoxic agents has been selected for clinical use after many trials and such agents have been established as first- or second-line treatment.

In breast cancer there are 7 main cytotoxic agents, in lung cancer 8, in ovarian cancer 6 and in colorectal cancer 4. Anthracyclines, taxanes, cisplatin and its analogues, antimetabolites and camptothecins are the main groups of agents used for the aforementioned malignancies [1-4].

In clinical practice, the approved cytotoxic drugs which are being utilized number over 60 and this does not include targeting treatments. Numerous agents have not yet been tested, and thus their effectiveness is not known. Although there are many cytotoxic agents which have been evaluated, this has not been done broadly enough to include all of the different malignancies, or all of the different combinations.

Cytotoxic agents used in 2 or 3 combinations are numerous and it could take many decades to determine and select the appropriate drug combination for each malignant tumor. Thus, in clinical practice we certainly utilize drugs that are tested and effective. Often we do succeed with respect to the response rate and survival, but we also fail. For example, in cases of tumor resistance, we do not have an established treatment to apply as second- or third-line therapy for several malignancies.

Herein we present the preliminary data of a trial whose objective was to investigate the effectiveness of two combined agents. The treatment was addressed to patients with lung metastases originating from primary colorectal, gastric and endometrial adenocarcinomas. The patients had been pretreated and were in stable or progressive disease.

Methods

Ten patients (8 males, 2 females, median age 65 years, range 55-82) have been recruited up until now.

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Received 04-09-2010; Accepted 27-09-2010

All patients but 2 had good ECOG performance status (PS). Primary histology confirmed adenocarcinoma in all cases. All patients had undergone at least 2 lines of previous treatment during 2-3 years before the trial; the lungs were the only or main site of metastases in all patients. The patient characteristics are shown in Table 1.

Chemotherapy

Before treatment, clinical examination, full blood count, liver and renal function tests and radiological examination were performed. Chemotherapy agents used were pemetrexed 500 mg/m^2 infused in 10 min and docetaxel 75 mg/m^2 infused in 90 min on day 1. Pemetrexed premedication consisted of vitamine B12 1000γ injected i.m. one day before chemotherapy. Filicine one tablet per day was also started one day before chemotherapy and continued daily as long as the treatment lasted. B12 and cytotoxic agents were repeated every 3 weeks, with a plan to administer 6 cycles. The mean number of cycles was 3 (range 1-6) and the total number of cycles 33. A thoracic CT scan was done after the 3rd cycle.

Results

Response

In 2 patients (one with primary colorectal cancer and one with endometrial cancer) FNB of the lung lesions was performed and compared with the histology of the primary disease, which confirmed their origin from the primary adenocarcinomas. The first patient, suffering from colorectal cancer, had partial response (70% tumor reduction) and time to progression 7 months. The second patient, with primary endometrial adenocarcinoma, achieved complete response (12+ months) (Table 2). In total, 1 patient (endometrial cancer) achieved complete response, 3 patients (primary colorectal cancer) had partial response, 5 stable disease (3 primary colorectal and 2 gastric cancer) and in 1 patient with colorectal cancer the disease progressed (Table 2, Figures 1, 2). No recurrence or disease progression was observed in 6 patients when data were estimated.

Survival

The study was initiated in August 2009. Follow-up duration was 1 year. At the end of the evaluation, 6 (60%) patients were alive and 4 (40%) had died due to disease progression. Median survival was 6 months (range 2-12+) (Figure 3).

Toxicity

The main cytotoxic adverse effects were nausea/vomiting and fatigue, grade 1-3 neutropenia and grade 2-3 alopecia. No patient stopped or postponed treatment because of toxicity (Table 3).

Table 1. Patient characteristics

Characteristics	*n*	*%*
Patients recruited	10	100
Age (years)		
Median 65		
Range 55-82		
Gender		
Male	8	80
Female	2	20
ECOG performance status		
0	3	30
1	5	50
2	2	20
Histology		
Adenocarcinoma	10	100
Primary site		
Colorectal	7	70
Gastric	2	20
Endometrium	1	10
Metastatic disease		
Lung deposits	10	100
Pretreatment (2 or 3 lines)		
FOLFIRI, FOLFOX	9	90
Anthracycline, cyclophosphamide, taxanes	1	10

Discussion

All of the patients enrolled in the trial had stable or progressive disease resistant to the previous (established) treatment. It is believed that the metastatic tumor is a certain clone of the primary tumor and there are different clones depending on the different sites of metastasis. The lung, liver, abdominal and other deposits may show a different resistance or sensitivity to certain cytotoxic agents. There are two indications of different cloning of metastases at different sites: 1) The

Table 2. Response to therapy

Response	*n*	*%*	*Survival, median (months)*
Complete response	1	10	12$^+$
Partial response	3	30	6§
Stable disease	5	50	4†
Disease progression	1	10	2

§range 5-8, †range 3-6

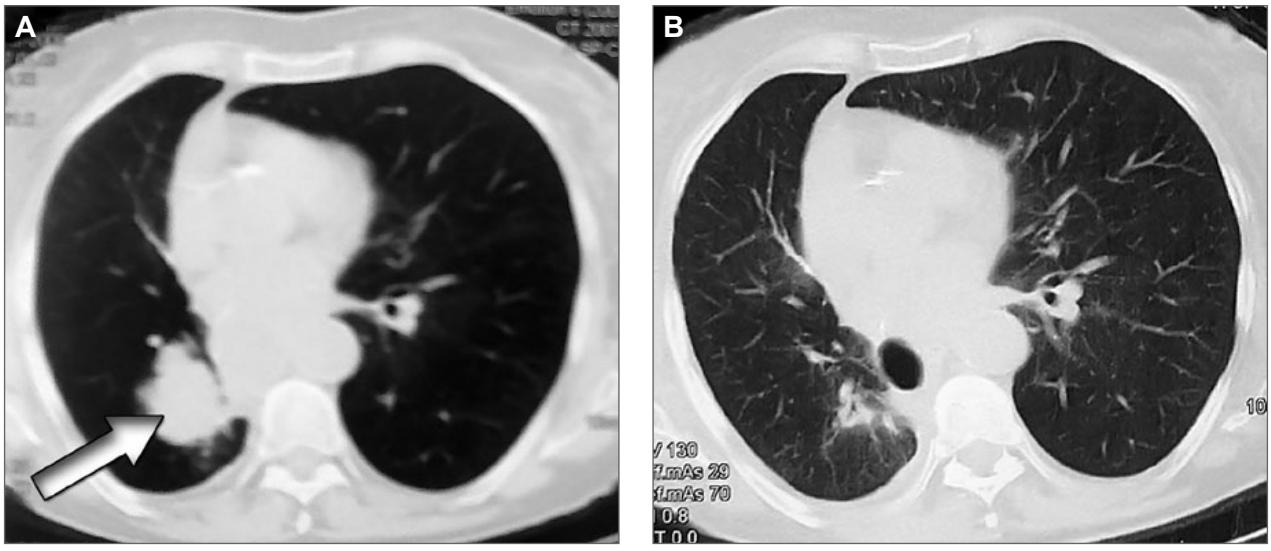


Figure 1. A: Thoracic CT of a patient with primary endometrial adenocarcinoma showing metastatic disease before treatment (arrow). **B:** Complete disease remission after treatment.

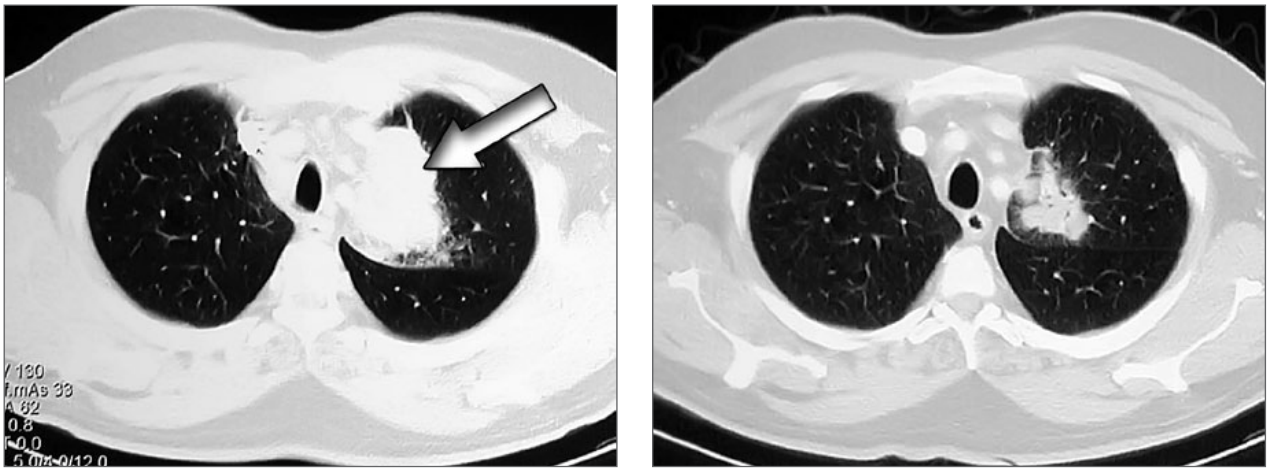
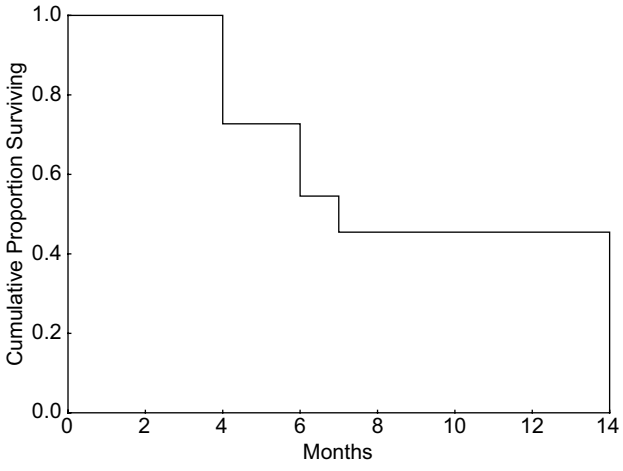


Figure 2. A: Thoracic CT of a patient with primary colorectal cancer showing metastatic lesion before treatment (arrow). **B:** Partial remission after treatment.



	Survival time	Standard error	95% Confidence interval
Mean:	9	1	6 - 12
Median:	7	2	3 - 11

Figure 3. Overall survival.

carcinoembryonic antigen is increased in liver metastases from colorectal cancer (85-90%), but not often in lung metastases. CA 19-9 is mainly increased (85%) in lung metastases but not often in liver deposits (unpublished data); 2) *In vitro* studies [5] have shown that lung metastatic disease from colorectal cancer is sensitive to anthracyclines, an agent not approved for this disease.

Table 3. Treatment toxicity

Toxicity	*Toxicity grades (Number of patients)*			
	1	*2*	*3*	*4*
Nausea-vomiting	1	2	–	–
Fatigue	4	2	–	–
Neutropenia	1	2	1	–
Alopecia	–	6	4	–

Why the choice of pemetrexed-docetaxel? : a) If standard treatment fails, modification is required; b) The combination of pemetrexed-docetaxel is one of the established treatments for lung cancer; c) Since it is an effective combination, why not to administer it since there is no other established solution for patients who have a good PS.

There is quite a number of published data that the treatment of advanced colorectal cancer is based on a limited number of cytotoxic agents. Leucovorin, 5-fluorouracil and irinotecan were only used and studied [6,7]. Capecitabine and then oxaliplatin were added and used over the last 10 years [8-10]. Exceptional was the administration of adriamycin and mitomycin-C presented in a study 15 years ago [11].

The effectiveness of the pemetrexed-docetaxel combination in heavily pretreated patients justifies the selection of these cytotoxic agents, but further investigation is needed.

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