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Phase I/II dose escalation study of docetaxel and carboplatin combination supported with amifostine and GM-CSF in patients with incomplete response following docetaxel chemo-radiotherapy: additional chemotherapy enhances regression of residual cancer

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Taxanes have been shown to interact with anti-apoptotic proteins. In the present study we investigated whether the addition of taxane in combination with DNA damaging drugs can further enhance tumor shrinkage in cases with incomplete response to radiotherapy. Since the dose of docetaxel in combination with carboplatin is not known, the above hypothesis was tested in the context of a dose escalation phase I study.

Twenty-eight patients with locally advanced chest or pelvic tumors, showing residual disease on CT scans performed 40 d following docetaxel radio-chemotherapy, were recruited in a dose escalation protocol of docetaxel/carboplatin supported with amifostine and GM-CSF. The starting dose of docetaxel was 40 mg/m^2 every 2 weeks. Carboplatin dose was calculated using the Calvert formula and was escalated in cohorts of 4 patients (starting dose AUC2 every two weeks; AUC0.5 increments up to AUC3). Thereafter the docetaxel dose was increased to 50 and 60 mg/m^2, while carboplatin was escalated (by AUC0.5 increments) starting from AUC3 and AUC4 respectively. Amifostine (600 mg/m^2) was administered i.v. before carboplatin and GM-CSF (480 μg) was injected s.c. on days 5, 6 and 10, 11 of each cycle. Six cycles were given and response was assessed 2 weeks after the end of chemotherapy.

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None out of four patients treated in the 6th dose level cohort (50 mg/m^2 of docetaxel and AUC4 of carboplatin every 2 weeks) showed any grade 2–4 hematologic toxicity. Mild non-hematologic toxicity such as neuropathy, leg edema, pleural effusion, pyrexia, alopecia grade 2 and hypersensitivity was observed in 4–12% of patients. Out of four patients treated in a 7th cohort (docetaxel 60 mg/m^2 and carboplatin AUC4), one developed grade IV neutropenia and two developed grade 3 severe asthenia requiring treatment delay for 2 weeks. Out of 11 patients with PR following docetaxel radio-chemotherapy, 7 (63%) showed CR after docetaxel/carboplatin additional chemotherapy. Eight out of 17 patients with MR following docetaxel radio-chemotherapy showed PR (47%) and one showed CR (6%) after additional chemotherapy.

High dose combined docetaxel (50 mg/m^2) and carboplatin (AUC4) chemotherapy can be safely administered on a two-weekly basis if supported with amifostine and GM-CSF. Such an additional therapy may be important in patients with incomplete response after chemo-RT. Broad spectrum cytoprotection with amifostine and GM-CSF may also contribute to the reduction of incidence of neurosensory reactions and asthenia in patients treated with taxanes. *Medical Oncology* (2000) **17,** 135–143.

Keywords: docetaxel; carboplatin; amifostine; GM-CSF; radiotherapy; non-small cell lung cancer

Introduction

Docetaxel as a single agent has shown a remarkable activity in a variety of human cancers such as non-small cell lung,[1] ovarian[2] and breast cancer.[3] Carboplatin has also been shown to be one of the most active drugs in ovarian carcinoma[4] as well as in non-small cell lung cancer.[5] It has therefore been suggested that docetaxel in combination with carboplatin could be much more effective than single agent therapy, at least in ovarian and lung carcinomas where the efficacy patterns of the two drugs seem to coincide. Although paclitaxel and carboplatin combinations have been thoroughly investigated,[6–8] phase I/II combination trials of docetaxel with carboplatin are rare.[9]

Taxanes are shown to be potent radiosensitizers, their activity being related to G2/M cell cycle synchronisation but also to bcl-2 anti-apoptotic protein phosphorylation.[10–13] Moreover, the activity of taxanes seems to be enhanced in cells with wild type p53 functional loss.[14] It has been suggested that intact p53 function may be important for the induction of apoptosis by a variety of cytotoxic agents.[15] Although the process of reproductive cell death induced by radiation is not well clarified,[16] it may be that radiotherapy interferes with the normal cell death process, enforcing cancer cells to abandon their infinite growth transformation and undergo apoptosis.[17,18] It is well known that radiotherapy-induced cancer cell damage leads, at least in some cases, to slow tumor burden reduction, the complete tumor disappearence been awaited even 2–4 months following the end of radiation treatment.[19,20] It has therefore been suggested that this period is important as far as the outcome of therapy is concerned. Whether the addition of chemotherapy during this period would further enhance the radiation-induced apoptotic death of residual cancer cells is unknown.

We propose the hypothesis that patients with residual tumor after radiotherapy may benefit from additional therapy with docetaxel combined with a DNA-damaging drug. The phosphorylation of bcl-2 anti-apoptotic protein expected by docetaxel may well contribute to the elimination of cancer cell reparatory mechanisms that would allow effective DNA recovery and inhibition of apoptosis. Combination of docetaxel with a DNA damaging agent, such as carboplatin, could further increase the apoptotic potential of docetaxel. The aims of the present study are to establish a well tolerated corboplatin/docetaxel combination regimen that could be used for the treatment of advanced

cancers and to investigate whether patients with residual disease following docetaxel radio-chemotherapy could benefit from an apoptosis-enhancing regimen.

Patients and methods

Recruitment criteria

Twenty eight patients with histologically confirmed locally advanced chest or pelvic cancer with residual or stable disease, confirmed on CT scan 40 d after docetaxel radio-chemotherapy, entered this phase I/II study. Patients with progressive disease after radiotherapy or with performance status > 2 were excluded. Written informed consent was obtained from all patients and the study was approved by the hospital ethical committee. The study was an 'in-house' and not a company sponsored trial. The exclusion criteria, also valid for the recruitment of patients in the radio-chemotherapy protocol, were the following: white blood cells (WBC) < 2500/μl, platelets (Pt) < 120,000/μl and creatinine clearance < 55 ml/min. Patients with hemoglobin (Hb) < 10 g/dl were transfused till Hb levels were raised > 11 g/dl. Pregnant women or patients with major heart, lung, liver, renal dysfunction, psychiatric disease or hematologic malignancies were excluded. Patients with known episodes of collapsus as a result of allergic response to any drug or substance were also excluded. The median age of our patients was 62 y (range 42–74). Patient characteristics recruited in the study are shown in Table 1.

Table 1 Patient characteristics

Total no. of patients	28
Male : female	23 : 5
Age, y	
median	62
range	42–74
WHO performance status	
median	1
range	0–2
Prior treatment	
radiotherapy/Docetaxel*	28
platinum chemotherapy	13
Tumor type	
non-small cell lung cancer	19
endometrial cancer	4
cervical cancer	2
prostate cancer	1
rectal cancer	2

* Docetaxel: 30 mg/m^2/week x 6 weeks.

Pretreatment and treatment evaluation

Baseline studies included physical examination, chest X-rays, whole blood count (WBC) with differential and platelet count, complete biochemical profile, creatinine clearance calculation, bone scan and computed tomography of the chest, upper abdomen and pelvis. Patients were followed with WBC, serum urea and creatinine and liver enzymes once a week. Electrocardiogram (ECG) was performed every 2 weeks. The WHO scale[21] was used to assess chemotherapy toxicity. A study nurse was engaged to monitor side-effects once a week.

Response to treatment was assessed with CT scan performed 2 weeks following the delivery of 6 cycles (3 months) of the regimen. CR was defined as disappearance of the measurable lesion, whilst partial and minimal response refers to 50–95% and 25–49% reduction of tumor dimensions, respectively. Small reductions of tumor dimensions between 0–24% lasting for at least 2 months after response documentation were considered as stable disease. All other cases were considered as progressive disease, regardless of the initial response.

Docetaxel and carboplatin dose escalation and administration

The extrapolated starting dose of docetaxel was 40% lower than the recommended dose (100 mg/m^2 every 3 weeks); thus 40 mg/m^2 every 2 weeks for 6 consecutive cycles. Carboplatin was escalated in cohorts of 4 patients. The starting dose level was AUC2 every two weeks, which is similarly reduced by 40% as compared to the usually recommended dose (AUC7). Such a dose reduction was thought to be necessary, since no previous experience had ever been reported in the literature using the combination of these two drugs. The carboplatin dose was increased to AUC2.5 and AUC3 in subsequent cohorts. Thereafter the docetaxel dose would be increased to 50 mg/m^2 and 60 mg/m^2 while carboplatin would be escalated by AUC0.5 increments, starting from AUC3 to AUC4 and from AUC4 to AUC5, respectively (Table 2). Any grade 3/4 toxicity related to chemotherapy was followed by treatment interruption for one week or more if necessary. Grade 3–4 toxicity in 3/4 patients in any cohort was required to define the dose limiting toxicity (DLT) of the combination. In case of grade 3–4 toxicity in 2/4

Table 2 Schedule and dose levels

Cycles of 2 weeks (d1 to d14)			
Chemotherapy	*Supportive treatment*		
docetaxel: day 1	amifostine 600 mg/m^2 i.v.: day 1		
carboplatin: day 1	GM-CSF 480 μg s.c.: day 5, 6 and 10, 11		
Dose level	*Docetaxel (mg/m^2)*	*Carboplatin (AUC)*	*No. patients*
1	40	2	4
2	40	2.5	4
3	40	3	4
4	50	3	4
5	50	3.5	4
6	50	4	4
7	60	4	4

patients in a cohort, one more patient would be recruited. The dose level immediately before the DLT was defined as the maximum tolerated dose (MTD).

12 h and 30 min before chemotherapy, patients received 32 mg p.o. and 125 mg i.v. bolus methyl-prednisolone respectively. Tropisetron (10 mg i.v.) was given as antiemetic treatment. Twenty minutes later, Amifostine (Ethyol®) 600 mg/m^2 diluted in 50 ml normal saline (NS) was rapidly infused within 5 min, the patient being in a supine posititon and under continuous monitoring of his/her blood pressure. Carboplatin diluted in 500 mg NS was administrated as a 30 min infusion, within 10 min following amifostine. The recommended dose of amifostine before carboplatin, given in cycles of 4 weeks, is between 750–900 mg/m^2.[22] In the present study, the total carboplatin dose administered every 4 weeks was supported by 1200 mg/m^2 of amifostine, as the carboplatin dose was split into two (cycles of 2 weeks).

Docetaxel was diluted in 250 ml NS and infused within 30 min. Blood pressure and symptomatology assessment was monitored every 5 min during infusion and every 10–15 min for the following hour. No steroids were used thereafter if no allergic reaction occurred. Whenever allergic reactions were observed, patients were given methyl-prednisolone 250 mg i.v. and 32 mg p.o. 12 h after chemotherapy. GM-CSF (Mielogene®) was given prophylactically from the beginning of treatment. 480 μg was injected subcutaneously on days 5–6 and 10–11 of each cycle. The effectiveness of such a supportive schedule has been reported in a previous study of ours.[23] The choice of GM-CSF instead of G-CSF was based on two previous studies, where docetaxel chemo-radiotherapy resulted in a dramatic decrease of monocyte counts.[24,25]

Results

Non-hematologic toxicity

Amifostine administration was followed by symptomatic hypotension in 3/28 patients. Infusion was immediately stopped and restarted some minutes later after blood pressure was fully restored. Nausea and vomiting grade 1 (simple nausea) or grade 2 (transient vomiting) occurred in 18/28 patients. In 10/24 patients nausea persisted for 12–48 h. Hypersensitivity reactions (back pain and subjective feeling of asphyxia) during docetaxel infusion were seen in 1/28 patients leading to the interruption of the infusion. Methyl-prednisolone 250 mg i.v. were immediately given. Treatment was safely resumed 20 min later with no further complications.

Anorexia and weight loss of 3–5 kg occurred in 15/28 patients and was independent of the dose level which patients were treated. Mild (grade 1) asthenia was observed in 22/28 patients (78%), but severe asthenia grade 3, enforcing treatment delay was seen in 1/4 and 2/4 patients treated at the two highest dose levels, respectively. Grade 1 alopecia was observed in all patients while grade 2 alopecia was seen in 5/16 (25%) treated at the 50–60 mg/m^2 docetaxel dose levels. Hot flushes were observed in 9/28 (32%) cases. One patient developed peripheral sensory neuropathy (3.5%) and 3/28 (11%) presented with mild bilateral leg edema. Bilateral docetaxel related symptomatic pleural effusion was observed in 3/28 (11%) patients during the 5–6th cycle and regressed within 1–2 months after treatment with furosemide and spirolactone. Steroid-related toxicity was minimal since the high dose methyl-prednisolone administration was restricted to one day every two weeks. Transient increase in blood glucose levels never required the use of insulin. No headache, arthralgia–myalgia, diarrhea, mucositis or nail disorders were observed in any of the three docetaxel dose levels. Table 3 shows the minor nonhematologic and hematologic toxicities.

Hematologic toxicity

Table 3 shows the hematologic toxicity. Hemoglobin reductions were minimal in all cohorts, with a median

Table 3 Hematologic and non-hematologic toxicities

	Dose level						
	1	2	3	4	5	6	7
No. of assessable patients	4	4	4	4	4	4	4
No. of patients with							
grade 1 neutropenia	0	0	0	0	1	1	2
grade 1 anemia	0	0	0	0	0	0	2
grade 1 thrombocytopenia	0	0	0	0	1	1	2
grade 2 alopecia	0	0	0	1	0	2	2
grade 1 asthenia	2	4	3	3	4	4	2
grade 1 hypersensitivity	0	1	0	0	0	0	0
pyrexia	0	0	1	0	1	0	1
nausea–vomiting grade 1/2	4	4	4	4	4	4	4
grade 1 paresthesias	0	0	0	0	1	0	0
leg oedema	0	1	1	0	0	0	1
weight loss (< 5 kg)	2	1	3	1	2	2	4
pleural effusion grade 1/2	0	0	0	1	0	1	1

The only severe toxicity observed was one case with neutropenic sepsis in cohort 7.

drop of 0.8 g/dl. GM-CSF induced neutrophilia or monocytosis has not been observed. Neutrophil toxicity grade II–IV was not observed in any of the 6 cohorts treated at the 40–50 mg/m^2 dose level of docetaxel. Platelet toxicity grade I was observed in 4/12 (34%) patients treated in the AUC3.5–4 carboplatin dose level, but has never been the cause for treatment delay. One out of 4 patients treated at the 7th and final dose level presented with febrile grade IV neuropenia. Figure 1 shows the lymphocyte counts during therapy. Although lymphocyte counts rapidly decreased during the previous combined docetaxel radio-chemotherapy, counts were maintained stable during carboplatin–docetaxel chemotherapy (in the same patients).

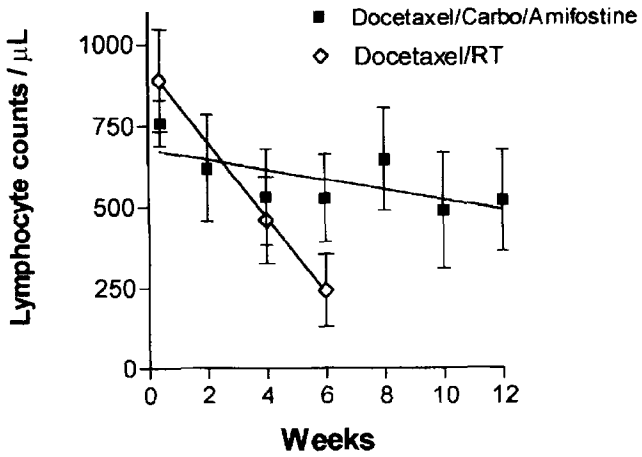

Figure 1 *Lymphocyte counts during docetaxel radio-chemotherapy and docetaxel/carboplatin chemotherapy supported with amifostine and GM-CSF in 24 patients (first six cohorts) with locally advanced chest or pelvic cancer.*

Response

Response to the regimen was re-assessed 2 weeks after the completion of 6 cycles of chemotherapy. Table 4 shows the treatment outcome for each of the 28 patients. Out of 11 partial responders to docetaxel radiochemotherapy, 7 (63%) showed complete response. 8 out of 17 patients with MR following docetaxel radio-chemotherapy showed PR (47%) and one showed CR (6%) after additional chemotherapy. Three out of 17 (17%) patients with MR to radiotherapy progressed after carboplatin/docetaxel chemo-therapy and 5 (29%) did not show any changes in tumor dimensions.

In order to evaluate whether the tumor shrinkage observed following the post-radiotherapy additional chemotherapy was indeed a result of docetaxel/carboplatin combination and not a result of delayed response to radiotherapy, we retrospectively assessed the CT scans of patients with non-small cell lung cancer, previously treated with docetaxel chemo-radiotherapy in a phase I/II study.[22] None out of 15 patients with PR on CT scan performed 2 months after the end of radiotherapy, had a CR on a CT scan done 2–3 months later. One out of four patients with MR (2 months after RT) had a PR 4 months following radiotherapy. Thus, additional chemotherapy induced further tumor shrinkage in 16/28 (57%) patients, which was statistically significant ($P = 0.0009$, t-test with Yate's correction) as compared to the delayed response to radiotherapy observed in patients treated with docetaxel chemo-radiotherapy without further chemotherapy (delayed response observed in 1/19 patients in the control group).

Discussion

Combination of docetaxel with cis-platin has shown interesting results.[26,27] Although paclitaxel combinations with carboplatin have been extensively examined,[6,28] phase I/II trials on docetaxel/carboplatin combinations are missing. We established a well

Table 4 Response to docetaxel radio-chemotherapy and to carboplatin and docetaxel additional chemotherapy (bi-dimensional tumor measurements used for response assessment)

Patient no.	*Disease*	*Stage*	*Response (%) to RT/docetaxel*	*Dose level*	*Response (%) to carbo/docetaxel*
1	SqLC	IIIb	70 (PR)	1	100 (CR)
2	SqLC	IIIb	30 (MR)	1	70 (PR)
3	ULC	IIIb	70 (PR)	1	80 (PR)
4	SqLC	IIIb	40 (MR)	1	60 (PR)
5	SqLC	IIIb	60 (PR)	2	80 (PR)
6	Endometrial C	IVa	80 (PR)	2	100 (CR)
7	Endometrial C	paraortic	80 (PR)	2	100 (CR)
8	SqLC	IIIb	30 (MR)	2	10 (PD)
9	AdLC	IIIb	40 (MR)	3	60 (PR)
10	SqLC	IIIb	60 (PR)	3	100 (CR)
11	Cervical C	IVa	70 (PR)	3	100 (CR)
12	SqLC	IIIb	30 (MR)	3	30 (MR)
13	Prostate C	paraortic	40 (MR)	4	100 (CR)
14	SqLC	IIIb	30 (MR)	4	0 (PD)
15	AdLC	IIIb	40 (MR)	4	80 (PR)
16	SqLC	IIIb	70 (PR)	4	100 (CR)
17	Endometrial C	IVa	30 (MR)	5	30 (MR)
18	SqLC	IIIb	30 (MR)	5	0 (PD)
19	AdLC	IIIb	40 (MR)	5	80 (PR)
20	Cervical C	IIIb	20 (PR)	5	60 (PR)
21	SqLC	IIIb	70 (PR)	6	100 (CR)
22	SqLC	IIIb	50 (PR)	6	90 (PR)
23	AdLC	IIIb	30 (MR)	6	40 (MR)
24	Rectal C	D1	30 (MR)	6	60 (PR)
25	SqLC	IIIb	30 (MR)	7	80 (PR)
26	SqLC	IIIb	30 (MR)	7	0 (PD)
27	Rectal C	D1	30 (MR)	7	30 (MR)
28	Endometrial C	IVa	40 (MR)	7	70 (PR)

SqLC: squamous cell lung cancer; AdLC: adenocarcinoma of the lung; ULC: undifferentiated lung cancer C: cancer; paraortic: paraortic lymphnode block with positive symptomatology; RT: radiotherapy.

tolerated scheme of docetaxel and carboplatin combination. 50 mg/m^2 of docetaxel can be safely given together with carboplatin at AUC4 every two weeks. This dose approaches the MTD of each of the drugs used. The regimen was supported with amifostine and GM-CSF. Further increase of the dose of docetaxel (60 mg/m^2 every 2 weeks) resulted in severe asthenia, but hematological toxicity was still low (1/4 grade 4 neutropenia). In another preliminary report by Belani *et al*, the MTD of docetaxel/carboplatin combination without G-CSF was 90 mg/m^2—AUC6 every 3 weeks, while G-CSF was required for higher doses.[29] Recently, Giannakakis *et al* presented a preliminary report, in which first docetaxel (80 mg/m^2) and carboplatin (AUC6) given every 3 weeks resulted in febrile neutropenia in 1/6 patients.[9] The schedules used by Giannakakis *et al* and Belani *et al* deliver a similar dose intensity to ours of the drugs (cohort 7) resulting in low neutropenia even without the use of cytoportective drugs. The studies are still preliminary and no details are provided as far as platelet or non-hematological toxicity is concerned. Moreover, because of the specific aim of our study to investigate the additional role of chemotherapy in enhancing response to radiotherapy, patients were shortly before recruitment heavily pretreated with large field radiotherapy and weekly docetaxel. Half of them also had refractory disease to platinum based chemotherapy. The combined use of GM-CSF with amifostine in our study as well as the reports on the good tolerance of high docetaxel/carboplatin dose without cytoprotection render it impossible to comment on the combined or separate role of amifostine/GM-CSF in the protection against neutropenia.

The excellent platelet tolerance to relatively high doses of docetaxel/carboplatin chemotherapy should

be attributed to the efficacy of amifostine. A significant cytoprotective effect of amifostine against carboplatin induced thrombocytopenia and neutropenia has been reported.[30,31] *In vitro* studies support the idea of a synergistic effect of amifostine with granulocyte colony stimulating factor in bone marrow protection.[32] In a recent study of ours amifostine together with G-CSF allowed the delivery of a high daily dose of carboplatin during radiotherapy.[23] 59 mg/m^2/d were given for 10 consecutive days without neutrophil or platelet toxicity. In the present study, carboplatin at AUC4 every 2 weeks was safely given without thrombocytopenia or other hematologic toxicity. Fractionation of carboplatin in 2 doses (one every 2 weeks instead of one every 4 weeks) allowed the fractionated delivery of amifostine, which could well have increased the cytoportective efficacy of amifostine. However, an important effect of taxanes in reducing the cisplatin accumulation in myeloid progenitor cells, human leucocytes but not in cancer cells has been recently reported.[33] Such a mechanism may also have contributed in the very low hematologic toxicity observed in our study.

The incidence of symptomatic neurosensory reaction following docetaxel chemotherapy (50–750 mg/m^2 cumulative dose) was as high as 11%.[2,34] The incidence of mild peripheral neuropathy was up to 50% after docetaxel/cisplatin combined chemotherapy (600 mg/m^2 cumulative dose).[35] A 6% incidence of Lhermitte's syndrome has been also reported in patients treated with 2 cycles of 100 mg/m^2 of docetaxel.[36] Although severe neurotoxicity is usually associated with cisplatin, carboplatin is relatively free of neurotoxicity if used in conventional doses.[37,38] Whether carboplatin could further worsen the incidence and severity of docetaxel-related neurotoxicity is not known. Amifostine has been shown to protect from platinum related neurotoxicity.[39,40] In the present study, patients received a cumulative docetaxel dose of 240–300 mg/m^2 within 3 months and all were previously treated with 6 weekly cycles of 30 mg/m^2 together with thoracic or pelvic radiotherapy. Half of them were also pretreated with platinum chemotherapy. The very low incidence of transient and mild neuropathy observed in 1/24 (4%) patients seems to be a result of amifostine cytoprotection. However, no specific neurological tests were used to detect a possible higher incidence of subclinical neurotoxicity.

Asthenia was also mild in all but one patient. On the contrary, the same patients recruited in the present study had previously experienced more severe asthenia during their treatment with docetaxel/radiotherapy combination. The onset of severe asthenia correlated with the onset of severe lymphocyte and monocyte toxicity. We also observed that lymphocyte cytotoxicity was accompanied by a dramatic drop of IgG and IgA serum immunoglobulin levels.[25] It was quite striking that patients treated with the present regimen supported with amifostine and GM-CSF did not develop significant asthenia and experienced clinically significant less lymphocyte and monocyte cytotoxicity. These findings further support our previous hypothesis that taxane induced asthenia is related to immunological toxicity[24] and that hematopoietic growth factor and efficient cytoprotective support may increase the tolerability or even the efficacy of docetaxel.

A strong theoretical background supports the concurrent use of taxanes with radiotherapy.[41,42] In a previous study we established a docetaxel scheme that could be administered concurrently with radiotherapy in patients with non-small cell lung cancer.[22] Weekly doses up to 30 mg/m^2 were well tolerated with minimal hematologic toxicity and moderate asthenia. A complete response rate of 27% and an overall RR of 77% was achieved. Our experience in docetaxel radiochemotherapy in pelvic tumors[25] also confirms the efficacy of docetaxel radiosensitization.

Incomplete tumor shrinkage after docetaxel radiochemotherapy is confirmed in about 50–60% of patients with locally advanced disease. It is well known that there is a delay ranging from one to several months before the tumor disappears after radiotherapy.[19,20] The role of additional chemotherapy with DNA damaging agents (such as platinum compounds) or apoptosis-enhancing agents (such as taxanes) in the successful inhibition of clonogenic cell survival and tumor eradication after radiotherapy is not known. We proposed the hypothesis that additional therapy with docetaxel combination and a DNA damaging agent (such as carboplatin) could be important in enhancing the results of radiotherapy. The underlying mechanism could be a modulation of delayed apoptosis-related effects of radiotherapy or even a direct cytotoxic effect on residual cells that may have effectively repaired their radiation-induced DNA damage. Patients responding to docetaxel radio-chemotherapy but with

measurable residual disease 40 d following the end of radiation treatment were recruited in the study. Although delayed tumor removal could have also been observed if no additional therapy was applied, 16/28 (57%) tumors further regressed after the administration of docetaxel/carboplatin additional chemotherapy. Comparison with a control group of patients treated with docetaxel chemo-radiotherapy without additional chemotherapy, showed that such a high rate of further tumor shrinkage is unlikely to be explained just as a 'delayed response to radiotherapy'.

In the present study we established a well tolerated combined regimen of docetaxel and carboplatin. The combination of amifostine and GM-CSF effectively protected the platelet and probably the monocytic and lymphocytic lineage. Such an immunological protection conferred by the broad spectrum cytoprotection Ethyol® and GM-CSF may be important in reducing the incidence of asthenia in patients treated with taxanes. Amifostine also seems to exert an important protective effect against docetaxel-related neurotoxicity. The high additional response rate obtained with docetaxel/carboplatin chemotherapy following radiotherapy suggests a clinically important role of taxanes in modulating the viability of clonogenic residual cells after the end of radiation treatment. Further clinical and *in vitro* studies are required to confirm the above findings.

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