Feasibility and efficacy of chemotherapy with gemcitabine mono and with paclitaxel/mitoxantron in gynaecological cancers

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Summary

In this prospective study 32 patients with advanced gynaecologic tumours were treated with different schemes of chemotherapy: 15 received a combination of paclitaxel (100 mg/m²/week)/mitoxantron (6 mg/m²/every second week). Seventeen patients were treated with gemcitabine (100 mg/m²) in two different schedules, and the time of infusion was 2,2-3,3 hours or 30 minutes, respectively. Tolerability and efficacy were observed. The most common reason for reduction of the dosage or for cycle delay in the combined scheme was neutropenia. The response rate was 82%. The median overall survival was 30 weeks since beginning of the chemotherapy and 15 weeks after the last infusion. Gemcitabine in the shorter scheme led to a higher median dose rate. Toxic skin effects and hematological adverse events led to dose reduction and cycle delay in 90% of the infusions in the longer scheme. The response rate was 76%. The overall survival was one to 69 weeks with a median survival of 22 weeks. The advantages of the shorter scheme were confirmed.

Key words: Paclitaxel; Mitoxantron; Gemcitabine; Gynaecologic cancers.

Introduction

The first report of a drug-mediated tumour response was noted over 125 years ago using arsenic trioxide in potassium bicarbonate in patients with Hodgkin's disease and leukaemia [1]. Paul Ehrlich developed in vivo models of infection, which encouraged the development of inbred transplantable rodent tumours, thereby establishing a paradigm that has been widely adopted for screening new antitumour agents [2]. After World War II many important chemotherapeutic agents were developed [3]. Between 1965 and 1975 alkylating agents as anthracyclines were discovered and developed, followed by identification of analogs with antitumour activity similar to the parent compound but with a reduction in nonhaematologic toxicity [3]. The 1990s and beyond have brought new agents into clinical practice including the taxanes and nucleoside analogs as gemcitabine. Attention has also been directed at prolonged intravenous infusion and weekly-low-dose therapy with the goal of maximising tumour drug exposure, but with a variable impact on host toxicity and clinical outcomes [4]. Multidrug combinations were tested to minimise toxicity and reduce drug resistance.

Combination of mitoxantron/paclitaxel (Group A)

Paclitaxel is one of the most commonly used drugs in oncology, with approval for salvage therapy for metastatic breast cancer and epithelial ovarian cancer. It is also active against cervical and endometrial cancer [5, 6]. Paclitaxel acts as a mitotic spindle poison.

Early pharmacokinetic studies using standard doses and a 24-hour infusion suggested that paclitaxel pharmacokinetics were linear, however, with short infusions and/or high-dose levels, paclitaxel's nonlinear pharmacokinetics become readily apparent [7]. The nonlinearity is due to saturable distribution, metabolism and elimination. In all Phase I, II and III studies a 24-hour infusion schedule was used from 1987 to 1992. Later clinical studies established that a 3-hour paclitaxel infusion schedule can be administered safely without a significant increase in major hypersensitivity reactions and that the shortened infusion schedule is associated with significantly less grade 4 neutropenia than the 24-hour infusion [8]. Also a 1-hour infusion is feasible and associated with a low rate of adverse events. The response rates are similar to those in the 3-hour schedule [9]. This is why the weekly 1-hour infusion was chosen in this study.

Paclitaxel in metastasised breast cancer after failure of first-line treatment demonstrates response rates of 10-38% [10-12]. No significant differences in response rate or survival could be found in a randomized comparison of paclitaxel 250, 210, or 175 mg/m² over three hours [13]. The results with 1-hour weekly paclitaxel infusions offer good response rates with better tolerability than other schedules [14].

Paclitaxel is also active against endometrial and cervical cancers [15]. A response rate of 43% (95% CI: 6% to 80%) was reported in seven patients with advanced, progressive, or recurrent endometrial cancer following platin analogue treatment [16]. In 19 patients with endometrial

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cancer pretreated with cisplatin, doxorubicin, and cyclophosphamide a response rate of 37% (95% CI: 16% to 62%) was reported [17]. A GOG Study noted a 27.3% response rate (95% CI: 15% to 43%) in 44 persistent or recurrent endometrial cancer patients who failed prior chemotherapy [18].

In advanced cervical cancer paclitaxel mono-therapy shows a response rate of 31% [5].

Combinations of doxorubicin and a taxane have been more effective in metastasised disease than taxane alone; however, the combination increased the frequency of stomatitis, myelo-suppression and cardiotoxicity [19, 20]. Replacement of doxorubicin may lead to even more tolerable combinations, such as taxane plus mitoxantrone. Synergy between taxanes and mitoxantrone was observed, and similar or better response rates in comparison to doxorubicin were found with a lower rate of side-effects [21-23]. In this prospective study tolerability and efficacy of the combined chemotherapy were observed.

Gemcitabine mono (Group B)

Gemcitabine is a nucleoside analogue with broad activity against solid tumours [24]. As a single agent, gemcitabine is usually delivered at 1000 mg/m^2 on days 1, 8 and 15 of a 22-day schedule. Gemcitabine pharmacokinetics were evaluated in 353 patients with varied solid tumours using short (< 70 minutes) and long infusions (70 to 285 minutes). There is a three- to fourfold interpatient variability in pharmacokinetics. Gemcitabine is metabolised intracellularly by deoxycytidine kinase to form the active diphosphate and triphophate metabolites. The drug is inactivated both intracellularly and extracellularly [25].

Toxicity is highly schedule dependent: Infusion durations of greater than 60 minutes are associated with increased myelosuppression and hepatic toxicity, whereas the administration of small daily doses results in dose-limiting flu-like symptoms [26, 27].

Analysis of safety data from 22 completed clinical trials in which gemcitabine was administered on a weekly basis to 979 patients revealed that neutropenia was the most significant haematologic side-effect. Decreases in white blood cell counts were noncumulative, short-lived, and rarely resulted in complications. Nonhematologic toxicities were nausea/vomiting (17% grade 3, 1% grade 4), cutaneous reactions (25%, 0.2% severe), mucositis (8.4%, 0.2% severe), diarrhoea (12%, 1% severe), constipation (8%, 1% severe), fever (0.7% grade 4) and flu-like symptoms (19%, 1% severe) [28].

We explored the effects of the speed of infusion on toxicity and efficacy in a highly palliative setting.

Materials and Methods

Patients

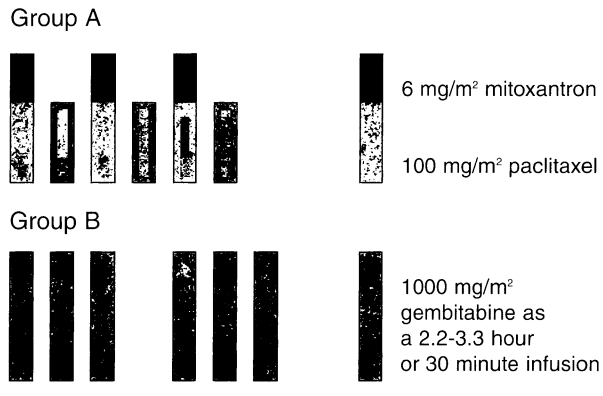
Eligible patients had a progressive disease of a gynaecological malignant tumour, which could not be cured by operation or chemotherapy. Participants were 18-75 years of age, had a life expectancy of more than three months, normal blood counts, adequate renal and hepatic function, a measurable lesion, at least one pretreatment and for the schedule with mitoxantron/paclitaxel a World Health Organization performance status of 0-2, and for the therapy with gemcitabine a performance status of 0-3. All patients gave written informed consent before enrolment.

Criteria for exclusion were disease of the central nervous system, calcaemia, infections, severe organic dysfunction, and severe cardiac failure.

At registration the physician decided – in consideration of the general condition and symptoms – whether the patient would receive mitoxantron/paclitaxel or gemcitabine and at which speed the chemotherapy would be given. At study entry a physical examination was performed and medical history was taken; ECG and chest radiography were done, and the expanse of the disease was measured by computed tomography (CT) scan or magnetic resonance imaging (MRT). The staging workup included isotope bone scanning for patients with breast cancer. Adverse effects of therapy were recorded before every infusion. Blood pressure, temperature, complete blood count and blood chemistry measurements were carried out after registration and before each treatment. The measurement of the tumour markers (CA12-5, CEA and CA15-3) was done every third week. To evaluate the side effects and the response at least two infusions had to be given. Evaluation of the tumour was repeated in both groups after the 6th infusion.

Treatment plan

Two different chemotherapeutic schemes were given in a palliative situation. Figure 1 shows the design of the two different trials.



In Group A paclitaxel was given at a dose of 100 mg/m^2 as a 1-hour IV infusion every week. Every other week patients received 6 mg/m^2 of mitoxantron followed by 100 mg/m^2 of paclitaxel. After the completion of six weeks no chemotherapy was given on day 43. On day 50 the second cycle started.

Standard premedication was given to prevent hypersensitivity reactions to paclitaxel; also patients were admininistered standard hydration and antiemetic agents. Treatment modifications for haematological effects (leucopoenia < 2000/mm^3, thrombocytopenia < 5000/mm^3) included the addition of granulocyte colony-stimulating factor on day 2-5, dose reduction of 20-50%

and cycle delay. Patients with nonhaematological side-effects grade 3 or 4 or progression were removed from the study.

In Group B gemcitabine was given at a dose of 1000 mg/m^2 as a 30-minute IV infusion on days 1, 8 and 15 of a 21-day cycle. In the experimental arm gemcitabine was given as a 2.2- to 3.3-hour infusion. Patients assigned to the longer treatment received 20 mg dexamethasone orally six hours before chemotherapy and 30 minutes before beginning 2 mg clemastine and 50 mg ranitidine IV. If required, patients also received clemastine and/or metoclopramid on day 2 and 3. In case of dermatological or gastrointestinal toxic effects the doses of dexamethasone and ranitidine were doubled, and the dose of clemastine was raised to 8 mg. In case of haematological or nonhaematological grade 2 toxic effects the dose was reduced by 20-50%, and in case of grade 3 toxic effects the next cycle was delayed. Patients in the longer infusion-time could be converted to the shorter scheme. Patients with neurological toxicity, stomatitis or hypersensitivity grade 3 or 4 side-effects or progression were removed from the study.

Statistical analysis

Frequencies were only described by median and mean value; the data were registered by Excel and evaluated by SPSS. Survival between groups was compared with use of the Kaplan-Meier life-table method. The log-rank test was used to confirm the robustness of the analysis.

Results

Patients

Between June and November 1996, 15 patients (ovarian cancer n = 5, breast cancer n = 7, cervical cancer n = 2, endometrial cancer n = 1) were treated with mitoxantron and paclitaxel (Group A). Between September 1995 and January 1997, 17 patients (ovarian cancer n = 8, breast cancer n = 8, endometrial cancer n = 1) were treated with gemcitabine (Group B). Table 1 shows the characteristics of the patients.

Group A: Mitoxantron/paclitaxel

Table 2 shows the localisations of the tumours in the different histological groups.

Three patients were ineligible: they were treated only once or twice and died within two to eight weeks. One patient had a hypersensitivity reaction after the 6th infusion and was lost to follow-up after this adverse event.

Treatment

Ten of the 12 eligible patients completed at least one cycle, and four completed two cycles of chemotherapy. The full dose of paclitaxel was administered in three patients, and the full dose of mitoxantron in six patients. In three patients a reduced dose (94%, 88% and 66%) was given from the beginning: in one case for economic reasons (150 mg instead of 160 mg), in one patient because of fear of reduced bone marrow reserve after six preceding chemotherapies and in the third, a 73-year-old patient, because of a Karnofsky index of 60%. In five patients secondarily a reduced dose was given because of toxic effects; four of them needed cycle delay. The most common reason for reduction in the dose was neutropenia. Nine patients received granulocyte colony-stimulating factor one to five times. The observed adverse effects are shown in Table 3.

Table 1. — *Characteristics of the patients in Groups A and B.*

	Mitoxantron/Paclitaxel (A)	Gemcitabine (B)
Age at diagnosis		
Median	59	55
Range	35-76	35-76
Age at the beginning of study treatment		
Median	61	60
Range	39-76	38-80
Stage of disease at first diagnosis		
Stage I	2 (1 cervix, 1 endometrial)	0
Stage II	7 (5 breast, 2 ovary)	3 (2 breast, 1 ovary)
Stage III	3 (1 cervix, 1 breast, 1 ovary)	5 (2 breast, 3 ovary)
Stage IV	2 (1 breast, 1 ovary)	9 (4 breast, 4 ovary, 1 endometrial)
Unknown	1 (1 ovary)	0
Pretreatment		
Chemotherapy	18	40
with platin	5	13
with anthracyclines	3	6
other, e.g. CMF	10	21
Radiation	12	10
Endocrine	9	6
ECOG Performance status		
0	1	0
1	7	1
2	5	8
3	2	8

Table 2. — *Localisations of the different carcinomas in Group A.*

Localisation	Total	Ovary n = 5	Breast n = 7	Cervix n = 2	Endometrial n = 1
Local recurrence	8	2	6	–	–
Lymph nodes	14	4	7	2	1
Bone	4	–	4	–	–
Liver	10	2	5	2	1
Lung	5	1	3	–	1
Pleura	2	1	1	–	–
Peritoneum	5	1	3	1	–
Ovary	2	1	1	–	–

Table 3. — *Adverse events related to paclitaxel/mitoxantron.*

n = 12	grade 0	1	2	3	4
Neutropenia	0	1	7	3	1
Anaemia	1	7	4	0	0
Thrombocytopenia	12	0	0	0	0
Vomiting	4	4	4	0	0
Alopecia	0	0	0	12	0
Skin	0	10	2	0	0
Neuropathy	4	7	0	1	0
Stomatitis	4	2	6	0	0
Diarrhoea	8	4	0	0	0
Constipation	8	4	0	0	0
Elevated liver enzymes	4	2	6	0	0

Efficacy

The median follow-up was 30 weeks. One patient was lost to follow-up after six weeks. The overall survival was

two to 117 weeks with a median overall survival of 30 weeks from the beginning of the chemotherapy (95% CI 11.06 to 48.94) and 15 weeks after the last infusion (95 % CI 0.0 to 31.41). Two patients were alive after 64 and 70 months, respectively, and then lost to follow-up.

Group B: Gemcitabine mono-therapy

Patients

Seventeen patients were treated with gemcitabine. Table 1 shows the characteristics of the patients.

Two patients with breast cancer had concomitant ovarian cancer; one patient with ovarian cancer also had endometrial cancer. Nine of them were diagnosed in Stage IV. In the other patients the time of recurrence was on median 34 months (range 20-58). Thirteen chemotherapy regimes were given in an adjuvant setting, and 27 in a palliative situation before treatment with gemcitabine. Eleven patients had achieved more than two chemotherapies before. Table 4 shows the localisations of the tumour in the different histological groups.

Table 4. — *Localisations of the different carcinomas in Group B.*

Localisation	Total	Ovary n = 8	Breast n = 8	Endometrial n = 1
Local recurrence	14	5	9	0
Lymph nodes	13	5	8	0
Bone	5	1	4	0
Liver	5	4	1	0
Lung	7	1	6	0
Pleura	7	2	5	0
Peritoneum	9	7	2	0
Ovary	4	2	2	0
Gastrointestinal tract	3	2	0	1

Treatment

Seventeen patients were treated; 13 patients started with the 2.2-3.3-hour scheme, four of them switched to the 30-min scheme. Two patients of the longer scheme got only one infusion, and their data were not included in the evaluation of the efficacy. Four patients achieved only the shorter scheme. Overall 135 infusions were given, 73 in 2.2-3.3 hours in 13 patients and 62 in 30 minutes in eight patients. Ten patients completed at least two cycles of chemotherapy.

The median dose rate overall was 513 mg/m^2 per week (range 155-802). The median dose rate in the longer scheme amounted to 450 mg/m^2 per week (range 155-983), and the one in the shorter scheme to 648 mg/m^2 per week (range 257-1000). In the shorter scheme 87% achieved a dose rate of at least 600 mg/m^2 per week, while in the longer scheme only 27%. The most common reasons for reduction in the dose were toxic skin effects and haematological adverse events which led to cycle delay in 90% of the infusions.

Seven of 17 patients died during treatment. Two of them died after the first infusion. After the 2nd, 4th, 9th, 10th and 14th infusion one patient each time died. In one patient the chemotherapy was converted into another chemotherapy because of tumour progression.

The observed adverse effects in the different schedules are shown in Table 5.

Table 5. — *Adverse events per patient related to gemcitabine.*

	Longer scheme n = 11				Shorter scheme n = 8			
	Grade							
	1	2	3	4	1	2	3	4
Neutropenia	4	1	3	0	2	1	1	1
Anaemia	4	2	1	1	3	3	1	0
Thrombocytopenia	3	2	1	0	0	2	0	1
Vomiting	1	2	2	0	1	1	2	0
Skin	1	4	1	0	1	0	0	0
Stomatitis	2	0	0	0	1	0	0	0
Diarrhoea	0	0	0	0	0	1	0	0
Constipation	0	1	0	0	0	1	0	0
Fever	1	2	0	0	0	1	0	0

Efficacy

Two of the 17 eligible patients died after the first infusion and one after two infusions due to cancer progression.

The median follow-up was 22 weeks; during the follow-up all patients died. The overall survival was one to 69 weeks with a median survival of 22 weeks from the beginning of the chemotherapy (95% CI, 18.82 to 37.18) and four weeks after the last infusion (95% CI, 0.0 to 10.72). There were no significant differences between the patients with breast cancer and ovarian cancer.

Discussion

Patients with advanced disease after prior chemotherapy are much less likely to achieve long-term benefits from additional treatment. This is due to drug resistance evolving within the tumour and the impact of prior therapy and/or progressive disease on performance status and vital organ function. As such, treatment goals should be geared to quality of life and control of symptoms. Most patients are treated with endocrine or single-agent chemotherapy; in situations with a need for fast remission combined therapies are selected. An individualized decision for the appropriate regimen mainly depends on vital organ dysfunction, prior treatment and the kind and heaviness of symptoms.

Combination of mitoxantron/paclitaxel (Group A)

In this study 15 patients with advanced gynaecologic tumours were treated with a combination of paclitaxel and mitoxantron. The planned dose rate was 100 mg/m^2 per week for paclitaxel and 6 mg/m^2 every second week for mitoxantron. The median dose rate for paclitaxel was 82.3 mg/m^2 per week, which is higher than the reported dose rates in studies with the 24-hour schedule [29, 30]. The response rate in our scheme was rather high (82%; 9 of 11 patients). However the patients were only observed during the time of chemotherapy; the median time of observation was 13 weeks (range 9-19). There are no data on the follow-up available.

The used regimen was well tolerable. The major side-effect and reason for dose reduction was neutropenia; in 19 of 115 cycles granulocyte colony-stimulating factor was given. In no case did the haematotoxic effects lead to termination of therapy. In one patient polyneuropathy and stomatitis (WHO grade 3) were not tolerable and no further treatment was given. In one patient the therapy was discontinued after six infusions because of a hypersensitivity reaction. This is very uncommon because with standard prophylactic medications the incidence of major hypersensitivity reactions decreases from 30% to less than 2%. The majority can be categorized as grade 1, with symptoms of dyspnoea with bronchospasms, urticaria, and hypotension. Major sensitivity reactions usually occur within the first ten minutes after the first or second dose of paclitaxel [31]. All other adverse events were well tolerable. No fever or cardiotoxicity were documented.

Gemcitabine mono-therapy (Group B)

Two schedules of different velocities were tested: 13 patients started with a 2.2-3.3 hour infusion; in four patients a 30-minute infusion was given. This prospective study confirms the advantages of the shorter scheme. Toxic skin effects and haematological adverse events were especially dose-limiting and led to cycle delay, so that the median dose rate in the longer scheme was less than a third of the median dose rate in the shorter schedule. Only three of 11 patients achieved a dose rate of at least 600 mg/m^2 in comparison with seven of eight in the shorter schedule.

In accordance with the data in the literature [32] vomiting was a fairly frequent toxicity. Cutaneous reactions consisted of erythema in mild cases and desquamation and vesiculation in moderate cases. Ulcerations were seen in one case. In two of five patients a switch to the shorter schedule avoided repeated cutane injuries. Most of the other symptoms were seen as often as described in the literature [33-35], and no patient incurred pulmonary problems, which are documented as an uncommon toxicity.

Regarding response rates gemcitabine ranged from 15-40%, depending on whether patients had received prior chemotherapy [36]. In this study the response rate was 76% though the overall survival was short – all patients died within the median follow-up time of 22 weeks.

Conclusion

The combination of mitoxantron and paclitaxel in a weekly schedule is a well-tolerated regimen with high response rates in heavily pretreated patients. Myelosuppression as the most frequent side-effect is controllable by granulocyte colony-stimulating factor. Gemcitabine in a 30-minute infusion is well tolerated in heavily pretreated patients. The response rate in this study was rather high, but the overall survival was quite short.

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