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Phase I study of a weekly schedule of a fixed dose of cisplatin and escalating doses of paclitaxel in patients with advanced oesophageal cancer

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Abstract

The objective of this study was to determine the toxicities and maximum tolerated dose (MTD) of a dose-dense schedule with a fixed dose of cisplatin and escalating doses of paclitaxel in patients with metastatic or irresectable squamous cell-, adeno-, or undifferentiated carcinoma of the oesophagus. Patients received paclitaxel over 3 h followed by a 3-h infusion of a fixed dose of cisplatin of 70 mg/m^2 on days 1, 8, 15, 29, 36 and 43. The starting dose of paclitaxel was 80 mg/m^2. Patients were re-treated if white blood cell count (WBC) was $\geqslant 1\times10^9$ cells/l, except for day 29 when the WBC had to be $\geqslant 3\times10^9$ cells/l. Six patients were treated at each dose level. The dose of paclitaxel was increased by 10 mg/m^2 per level. Of the 24 patients enrolled, 13 had adenocarcinoma, 10 had squamous cell carcinoma and one had an undifferentiated carcinoma. All patients were evaluable for toxicity and 22 of 24 patients were evaluable for response. The paclitaxel dose could be escalated to 110 mg/m^2. At this dose, 3 out of 6 patients developed dose-limiting toxicity (DLT) including neutropenic enterocolitis with sepsis, vomiting and diarrhoea. Diarrhoea grades 3 and 4 was seen in 4 (17%) patients. Two of these patients died of neutropenic enterocolitis. Neutropenia grades 3 or 4 was seen in 20 (83%) patients, but apart from the two patients with neutropenic enterocolitis no other infectious complications were seen. Mild to moderate sensory neurotoxicity was seen in 11 (46%) patients (grade 1 in 8 patients and grade 2 in 3 patients). Other toxicities were mild and easily manageable. Of the 22 evaluable patients, 11 (50%) patients achieved a partial or complete response with a median duration of 13 months. Ten patients with either locally advanced disease or supraclavicular or celiac lymph nodes received additional local treatment after response to chemotherapy, seven patients are still without evidence of disease after a median follow-up of 32 months. Paclitaxel at a dose 100 mg/m^2 infused over 3 h followed by a 3-h infusion of 70 mg/m^2 cisplatin can be recommended for further studies in patients with metastatic or unresectable oesophageal cancer. Occurring diarrhoea should be handled with caution because it may be a sign of neutropenic enterocolitis. The response rate of this dose-dense schedule seems encouraging.

Keywords: Advanced oesophageal cancer; Chemotherapy; Cisplatin; Paclitaxel; Weekly

1. Introduction

The majority of patients with squamous cell- or adenocarcinoma of the oesophagus either present with systemic disease or will relapse after prior surgery and the prognosis of these patients remains poor [1,2]. Response rates achieved with single agent chemotherapy are usually modest, although with combination chemotherapy response rates of 35% in metastatic and 45–55% in locoregional disease can be obtained [3]. In most trials, the reported median duration of response is short. Moreover, the impact of chemotherapy on survival is unclear also because of a lack of randomised phase III studies on chemotherapy versus best supportive care.

Cisplatin is one of the most extensively studied drugs in oesophageal cancer yielding an overall response rate of 24% [4]. The combination of cisplatin and 5-fluoro-

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uracil (5-FU), mainly studied as preoperative treatment, yielded response rates from 37–65% [5–7]. This combination is considered standard therapy by some authors, although this can be questioned as the premise is based upon the results of a small randomised study [6].

Paclitaxel is a new agent in the treatment of patients with oesophageal cancer. Ajani and colleagues reported a response rate of 31% using 250 mg/m^2 paclitaxel every 3 weeks [8]. By adding cisplatin to paclitaxel response rates of 49% [9] and 52% [10] have been reported. The latter study involved a bi-weekly drug administration.

In vitro studies and clinical studies have suggested that a dose-response relationship for cisplatin may exist for solid tumours [11–13]. Therefore, a further dose intensity increase might be attractive. Further shortening the interval between chemotherapy cycles is a possibility to increase this dose-intensity. Our group has previously demonstrated that single agent cisplatin at a dose of 80 mg/m^2/week was tolerated by most chemotherapy-naive patients [14,15]. Cisplatin at a dose of 70 mg/m^2/week could be combined with etoposide 50 mg administered orally on days 1–15 and 29–43 [16]. Finally, in patients with ovarian cancer weekly cisplatin at a dose of 70 mg/m^2 could safely be combined with weekly paclitaxel at a dose of 90 mg/m^2 [17]. In the latter study, there was no apparent difference in tolerance between pre-treated and non-pretreated patients. The dose-limiting toxicity was fatigue and the level of myelosuppression was remarkably low. The latter study confirms the observation of minimal haematological toxicity in studies using single agent weekly paclitaxel [18–22], in which the schedule dose is limited by reversible neurotoxicity [21].

We now report the results of a dose-finding study with a weekly schedule of a fixed dose of cisplatin and escalating doses of paclitaxel in patients with metastatic or unresectable cancer of the oesophagus or the oesophageal-gastric junction.

2. Patients and methods

2.1. Patient selection

Eligibility included patients with metastatic or unresectable histologically-proven squamous cell-, adeno-, or undifferentiated carcinoma of the oesophagus or oesophageal-gastric junction area, a Performance Status (World Health Organisation (WHO)) of 0–2, a life expectancy of more than 12 weeks, adequate haematological, renal and hepatic function defined as white blood cell count (WBC) $\geqslant 3.0\times10^9$ cells/l, platelets $\geqslant 100\times10^9$ cells/l, creatinine $\leqslant 120$ μmol/l and total bilirubin $\leqslant 1.5\times$upper normal limit. Patients with neurotoxicity $>$Common Toxicity Criteria (CTC) grade 1 were not eligible. Prior radiation for primary or metastatic disease was allowed, but not in the 4 weeks prior to study entry and not involving more than 30% of the bone marrow. Patients previously treated with chemotherapy were not eligible. The study was approved by the institutional ethics committee. All patients gave written informed consent.

2.2. Dose and dose escalation

Treatment consisted of weekly intravenous (i.v.) administrations of paclitaxel and cisplatin on days 1, 8, 15, 29, 36 and 43. Further treatment was left to the discretion of the treating physician. The cisplatin dose was fixed at 70 mg/m^2/administration and the starting dose of paclitaxel was 80 mg/m^2/administration. Six patients were to be treated at each dose-level. The paclitaxel dose was increased by 10 mg/m^2/administration per cohort. Treatment comprised of pre-hydration with one litre of normal saline administered over 3 h followed by the calculated dose of paclitaxel diluted in 500 ml of normal saline infused over 3 h. This was followed directly by the infusion of cisplatin diluted in 1000 ml of a mixture of 5% dextrose and 0.9% saline in 3 h. This contrasted with our previous use of 250 ml of 3% saline. Post-hydration comprised the infusion of 3 litres normal saline with the addition of 20 mmol/l potassium chloride and 2 g/l magnesium sulphate over 24 h. All patients were pre-medicated with dexamethasone 20 mg orally 12 and 6 h prior to paclitaxel treatment and clemastine 2 mg and ranitidine 50 mg i.v. 30 min before the paclitaxel infusion. Ondansetron 8 mg was administered i.v. before the cisplatin infusion and was repeated twice daily if necessary. Patients were re-treated on days 8 and 15 provided the WBC was $\geqslant 1.0\times10^9$ cells/l and platelets were $\geqslant 50\times10^9$ cells/l, while prior to the start of the day 29 course the WBC had to be $\geqslant 3.0\times10^9$ cells/l and platelets $\geqslant 100\times10^9$ cells/l. When these criteria were not met, treatment was postponed for 1 week. If bone marrow recovery was insufficient after a 1 week delay the patient was taken off study.

Toxicity was graded using National Cancer Institute (NCI)-CTC criteria. Dose-limiting toxicity (DLT) was defined as any of the following events occurring during the first 4 weeks of treatment: grades 3–4 leucocytopenia with infection or fever requiring parenteral antibiotics, grades 3–4 thrombocytopenia requiring 2 or more platelet transfusions, or resulting in $\geqslant$grade 2 haemorrhage, or $\geqslant$grade 3 non-haematological toxicity, with the exception of acute nausea and/or vomiting. Maximum tolerated dose (MTD) was defined as the dose level below the dose that induced DLT in three patients out of six during the first 4 weeks.

2.3. Treatment assessment

Before therapy, a complete medical history was obtained and a physical examination was performed. A

Table 1
Patient characteristics

Characteristic (%)	No. of patients
Total patients	24
Sex	
Female	8 (33)
Male	16 (67)
Age (years) median (range)	55 (30–71)
Performance status (Karnofsky)	
70%	5 (21)
80%	6 (25)
90%	8 (33)
100%	5 (21)
Histology	
Adenocarcinoma	13 (54)
Squamous cell carcinoma	10 (42)
Undifferentiated carcinoma	1 (4)
Extent of disease	
Locally advanced/unresectable	2 (8)
Primary with distant metastases	15 (63)
Metastases after primary resection	7 (29)
Metastatic sites	
Supraclavicular lymph nodes	7 (29)
Celiac lymph nodes	13 (54)
Liver	6 (25)
Retroperitoneum	4 (17)
Other	6 (25)

complete blood cell count (including WBC and differential counts) and serum biochemistry (including sodium, potassium, calcium, phosphorus, urea, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, asparate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase) were assessed. Weekly evaluations included history, physical examination, toxicity assessment, complete blood cell counts and serum chemistry studies. Tumour evaluation was performed after 6 administrations by a Computed Tomography (CT)-scan of the chest and upper abdomen. Patients with the primary tumour *in situ* were also evaluated by endoscopy. Response was assessed using WHO criteria for response [23]. The duration of response was calculated from the start of treatment.

3. Results

Twenty-four patients entered the study. All patients were eligible and all were evaluable for toxicity. Patient characteristics are listed in Table 1. Nineteen (79%) patients received all scheduled six drug administrations.

The paclitaxel dose was increased from 80–110 mg/m^2. At the latter dose level, one patient developed neutropenic enterocolitis and sepsis after the third administration of cisplatin and paclitaxel and, died despite intensive treatment. In addition, two other patients had dose-limiting vomiting and diarrhoea, respectively. Because of this, this dose level could be classified as the DLT. Cisplatin at a dose of 70 mg/m^2 with paclitaxel 100 mg/m^2 for each administration was therefore considered to be the MTD. In addition, the achieved dose intensity at this dose level was higher than with paclitaxel scheduled at 110 mg/m^2. The median dose intensity at the paclitaxel dose level of 100 mg/m^2 was 52 mg/m^2/week for cisplatin and 86 mg/m^2/week for paclitaxel versus 46 mg/m^2/week and 85 mg/m^2/week, respectively, at the paclitaxel dose level of 110 mg/m^2.

A total of 134 cisplatin/paclitaxel administrations were given with a median number of 6 (range 2–6). Nine (6.7%) administrations were delayed for a maximum of one week in 7 (29%) patients. Three administrations (administration numbers 4, 4 and 5, respectively) had to be delayed due to unresolved leucocytopenia. Five patients had a treatment delay because of incomplete recovery of mostly gastrointestinal toxicity resulting from the preceding administration. The other delay was related to required intercurrent other treatment. Treatment delays were seen at paclitaxel doses of 80 mg/m^2 (2 patients), 90 mg/m^2 (4 patients) and 110 mg/m^2 (3 patients).

3.1. Toxicity

Haematological toxicity could be assessed in 133 of the 134 cisplatin/paclitaxel administrations. Neutrocytopenia and thrombocytopenia did not appear to be related to the paclitaxel dose (Table 2). Neutrocytopenia mainly occurred one week after the last drug administration, while mild to moderate thrombo-

Table 2
Haematological toxicity, worst grade per patient

Paclitaxel dose level	No. of pts	Neutropenia Grade					Thrombocytopenia Grade				
		0	1	2	3	4	0	1	2	3	4
80 mg/m^2	6	–	1	–	2	3	5	1	–	–	–
90 mg/m^2	6	–	–	1	3	2	4	1	1	–	–
100 mg/m^2	6	1	1	–	2	2	3	1	1	1	–
110 mg/m^2	6	–	–	–	2	4	5	1	–	–	–

No., Number; pts, patients.

Table 3
Non-haematological toxicity, worst grade per patient

Paclitaxel dose level	No. of pts	Nausea Grade					Vomiting Grade					Diarrhoea Grade					Neurotoxicity grade				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
80 mg/m^2	6	1	1	3	1	–	1	2	3	–	–	2	3	1	–	–	4	1	1	–	–
90 mg/m^2	6	–	1	5	–	–	–	3	–	2	1	2	2	1	–	1	3	3	–	–	–
100 mg/m^2	6	1	1	4	–	–	1	1	4	–	–	1	3	1	–	1	3	2	1	–	–
110 mg/m^2	6	–	2	2	2	–	1	2	1	1	1	4	–	–	1	1	3	2	1	–	–

No., Number; pts, patients.

cytopenia was only observed after the fifth and sixth administrations. Haematological growth factors were not used. Grade 2 anaemia was seen in 11 patients and 3 patients received red blood cell transfusions.

Diarrhoea was a frequent finding and was dose-limiting in 4 patients (Table 3). Unfortunately, 2 of them died due to neutrocytopenic enterocolitis, 1 after completion of the full treatment at the paclitaxel dose of 90 mg/m^2, and 1 after the third administration of paclitaxel at the dose of 110 mg/m^2. The latter patient experienced a grade 2 diarrhoea after the second administration and he was prophylactically treated with loperamide after the third administration of chemotherapy. The other 3 patients with a grade 3 or 4 diarrhoea did not report a previous episode of diarrhoea. Apart from the sepsis coinciding enterocolitis in 2 patients, no other infectious complications were observed.

Mild to moderate neurotoxicity, mostly characterised by paraesthesias and sensory loss, was seen in 11 patients (46%), and did not appear to be dose related. Only 5 patients with sensory neurotoxicity had a follow-up of more than 6 months, the neurotoxicity was reversible in 1 of these 5 patients. Two patients had reversible tinnitus. Three patients reported short lasting and reversible myalgia/arthralgia grade 1 and 6 reported grade 2. Three of the latter patients were treated at the highest paclitaxel dose level. Renal toxicity grade 1 was seen in 3 patients treated at paclitaxel dose levels of 80, 90 and 100 mg/m^2, respectively, being reversible in 2 of 3. Alopecia was seen in all of the patients who completed at least 3 administrations.

3.2. Response and survival

Twenty-two of the 24 entered patients were evaluable for response. Two patients (9%) achieved a complete response. Both patients are still disease-free after a follow-up of 32 and 27 months, respectively. Nine patients (41%) achieved a partial response with a median duration of 10 months (range 2–34+ months). Ten of the 11 responding patients had bidimensionally measurable lesions and one patient had unidimensionally evaluable disease. All of the other 11 (50%) patients had stable disease with a median duration of 6 months (range 4–34 months). Five patients underwent an oesophageal resection after response to chemotherapy and five patients received radiotherapy (50 Gy) on the primary tumour and/or supraclavicular or celiac lymph nodes. Of the 10 patients who received additional treatment, 7 patients are alive and disease-free (median follow-up: 32 months). The overall response rate for patients with adenocarcinomas was 58% and for patients with squamous cell carcinomas 33%. The median survival for all 24 patients was 16 months (range 2–34+ months) with an one-year survival of 58%.

4. Discussion

Most patients who are diagnosed with oesophageal cancer will die of their disease. In addition, more than half of these patients have locally advanced or metastatic disease at first presentation and their median survival is only between 4 and 8 months. Conventional chemotherapy may offer these patients a chance of tumour regression and palliation of symptoms, but in most cases only for a limited period of time. The efficacy of chemotherapy might potentially be improved by decreasing the time interval between consecutive treatments. Theoretically, such dose-dense schedules yield a more continuous exposure to cytotoxic agents and may herewith permanently impair growth-promoting intracellular signalling and DNA repair [24].

Our group has extensive experience with weekly scheduling of cisplatin, with or without the addition of oral etoposide [14–16,25]. However, paclitaxel may be a more attractive agent to combine with cisplatin in this respect. Frasci and colleagues treated 30 chemotherapy-naive patients with advanced solid tumours with a weekly schedule of escalating doses of cisplatin and paclitaxel [26]. The MTD found in this study was cisplatin 30 mg/m^2/week in combination with paclitaxel 65 mg/m^2/week. When granulocyte-colony-stimulating factor (G-CSF) support was given, the cisplatin dose could be increased to 40 mg/m^2/week and the paclitaxel dose to 85 mg/m^2/week. The encountered DLT consisted of neutropenia, conservatively defined as grade >1 neutropenia on the day of re-treatment. In a subsequent phase II study with the latter regimen, 43 women with advanced breast cancer were treated, and

the observed toxicity was moderate and consisted predominantly of haematological and neurological toxicity, especially in pre-treated patients [27]. Van de Burg and colleagues treated 24 patients with advanced ovarian cancer, mostly pre-treated, with cisplatin 70 mg/m^2/week on days 1, 8, 15, 29, 36 and 43 and escalating doses of paclitaxel [17]. At paclitaxel 100 mg/m^2/week, the DLT consisted of fatigue. Neutropenia grades 3–4 was only seen in 19% of treatment cycles, but no infectious complications occurred.

In this study using a fixed dose of cisplatin of 70 mg/m^2 and escalating doses of paclitaxel administered on days 1, 8, 15, 29, 36 and 43, we encountered DLT at the paclitaxel dose of 110 mg/m^2. DLT was gastrointestinal.

The difference in MTD between our current study and the study by Frasci and colleagues could be explained by their use of more restrictive haematological criteria. Furthermore, we treated our patients for 3 weeks out of 4 weeks, while Frasci and colleagues treated their patients for 6 consecutive weeks followed by a two week break. The MTD reported by van der Burg and colleagues is also slightly lower compared with the current study, but in that study more than half of the patients had previously received chemotherapy.

The frequency of diarrhoea in the current study was high, and sharply contrasts to other reports. Fifteen patients (63%) reported diarrhoea after one or more administrations, and 3 patients had grade 4 diarrhoea. Diarrhoea was not at all reported in the other phase 1 studies with the weekly combination of cisplatin and paclitaxel [26,27,17]. In patients treated with cisplatin 70 mg/m^2 weekly as a single agent the incidence of diarrhoea was 13%, but mostly grade 1 [25]. Severe diarrhoea is also uncommon in patients treated with weekly paclitaxel at doses up to 200 mg/m^2/week [19,20]. Gordon and colleagues treated patients with advanced ovarian cancer with a fixed dose of cisplatin and escalating doses of paclitaxel repeated every 3 weeks and in that study diarrhoea became the DLT at a paclitaxel dose level of 275 mg/m^2 [28]. So the difference between our study and the one of Frasci in this respect may be explained by differences in dose-intensity. The difference with the study of van der Burg is more difficult to explain. Apart from differences in the patient population, in that study cisplatin was administered using hypertonic saline, while in the current study this was substituted for dextrose-saline. If and how this could explain the difference in diarrhoea frequency remains to be elucidated.

Obviously the 2 cases of neutropenic enterocolitis are a cause for concern. Neutropenic enterocolitis is a necrotising inflammation of the colon, known to occur in patients treated with intensive chemotherapy schedules [29]. It is usually characterised by fever, abdominal pain, diarrhoea and localised tenderness to the right lower abdominal quadrant in combination with severe neutropenia [30]. The cause is probably a direct cytotoxic effect on mucosa, whereas neutropenia itself is a contributing factor since neutropenic enterocolitis can also occur in patients with neutropenia unrelated to chemotherapy [31,32]. Taxane-based chemotherapy is known to be related to the occurrence of neutropenic enterocolitis [33,34], but it remains a relatively infrequent side-effect. Since neutropenic enterocolitis was not seen at all in previous studies with weekly administrations of cisplatin and or paclitaxel, and 1 of the 2 cases observed in our study occurred at a dose intensity explored by others as well, it is quite possible that these 2 cases are incidental observations. Nevertheless, until experience has been expanded, caution is warranted.

The other toxicities observed in this study were usually mild. There were no other infectious complications.

An overall response rate of 50% and a median response duration of 13 months seems to compare favourably with those reported in other studies on advanced oesophageal cancer. Since this regimen is active and can be administered over a short period of time it can be used as an induction treatment as part of multi-modality treatment. Of interest, 10 of our patients initially had irresectable disease or lymph node metastases confined to the celiac or supraclavicular region. They received subsequent local treatment and 7 of them are still alive and disease-free after a median follow-up of 32 months.

In conclusion, cisplatin 70 mg/m^2 in combination with paclitaxel 100 mg/m^2 administered on days 1, 8, 15, 29, 36 and 43 is the recommended dose for untreated patients with advanced oesophageal cancer. Further evaluation of this regimen as an induction treatment for resectable or locoregionally advanced oesophageal cancer and other tumour types is warranted.

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