Phase II study of bi-weekly administration of paclitaxel and cisplatin in patients with advanced oesophageal cancer

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In a phase I study we demonstrated the feasibility of a bi-weekly combination of paclitaxel 180 mg m⁻² with cisplatin 60 mg m⁻². In this study we further assessed toxicity and efficacy of this schedule in the treatment of advanced cancer of the oesophagus or the gastro-oesophageal junction. Patients received paclitaxel 180 mg m⁻² administered over 3 h followed by a 3-h infusion of cisplatin 60 mg m⁻². Patients were retreated every 2 weeks unless granulocytes were < 0.75 x 10⁹ or platelets < 75 x 10⁹. Patients were evaluated after three and six cycles and responding patients received a maximum of eight cycles. Fifty-one patients were enrolled into the study. The median age was 56 years (range 32–78). WHO performance status were: 0 (19 patients); 1 (29 patients); 2 (three patients). All patients received at least three cycles of chemotherapy and all were evaluable for toxicity and response. Haematological toxicity consisted of uncomplicated neutropenia grade 3 in 39% and grade 4 in 31% of patients. Five patients (10%) were hospitalised, three patients because of treatment related complications and two patients because of infections without neutropenia. Sensory neurotoxicity was the predominant non-haematological toxicity; grade 1 and 2 neurotoxicity was observed in 43 and 20% of patients, respectively. Response evaluation in 51 patients with measurable disease: complete response 4%, partial response 39%, stable disease 43% and progressive disease in 14% of the patients. The median duration of response was 8 months. The median survival for all patients was 9 (range 2–29+) months and the one-year survival rate was 43%. Four patients who received additional local treatment (two patients surgery and two patients radiotherapy) are still disease free after a follow-up of 20–29 months. This bi-weekly treatment of paclitaxel and cisplatin is well tolerated by patients with advanced oesophageal cancer. The toxicity profile of this regimen compares favourably to that of previously used cisplatin- and paclitaxel-based regimens. Trials are underway evaluating this bi-weekly regimen in a neo-adjuvant setting.

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The incidence of oesophageal cancer is rising in the United States and most Northern European countries, especially due to a rapid increase in the incidence of adenocarcinomas of the distal oesophagus or the gastro-oesophageal junction (Blot and McLaughlin, 1999). Although adenocarcinomas are known to be related to symptoms of gastric reflux (Lagergren et al, 1999) and to specialised columnar (Barrett’s) epithelia (Jankowski et al, 1999) it is questionable whether this totally accounts for the rising incidence.

Many patients who present with symptoms of oesophageal obstruction already have locally advanced or metastatic disease. After surgery the 5-year survival is 20% and the majority of patients relapse both locoregionally as well as at distant sites (Millikan et al, 1995). Multimodality treatment plays an increasingly important role in the treatment of oesophageal cancer. Chemotherapy with concurrent radiotherapy has been shown to be superior to radiotherapy alone in patients with locoregional disease (Herskovic et al, 1992). However, pre-operative treatment with chemotherapy remains still investigational because a number of randomised studies have provided conflicting results (Kok et al, 1997; Kelsen et al, 1998; Clark, 2000). Chemotherapy can also be given for palliation of symptoms and improvement of quality of life in patients with metastatic disease (Spiridonidis et al, 1996; Illson et al, 1999).

Combination chemotherapy with cisplatin and 5-fluorouracil and/or etoposide or with bleomycin and vindesine has predominantly been used in patients with squamous cell carcinoma (Kelsen et al, 1990; Kok et al, 1996; Bleiberg et al, 1997), yielding response rates of 45–75% in patients with locoregional disease and 25–35% in patients (Enzinger et al, 1999).

Single agent paclitaxel has been tested in squamous cell and adenocarcinomas of the oesophagus. Ajani et al (1994) reported a response rate of 31% after treatment with paclitaxel 250 mg m⁻² administered every 3 weeks in combination with granulocyte colony-stimulating factor support. In combination with cisplatin, also in a 3-week schedule, Kelsen et al (1997) reported a response rate of 49% for patients with either locoregional or metastatic oesophageal cancer.

We previously performed a dose finding study with a fixed cisplatin dose (60 mg m⁻²) and increasing doses of paclitaxel...
given every 2 weeks in patients with advanced oesophageal cancer (van der Gaast et al, 1999). The paclitaxel dose could be increased to 200 mg m⁻² without encountering dose limiting haematological toxicity. However sensory neurotoxicity was dose limiting at paclitaxel dose levels ≥ 190 mg m⁻². The recommended dose for further studies was paclitaxel 180 mg m⁻² in combination with cisplatin 60 mg m⁻². In view of the response rate of 52% observed in this dose finding study we performed a phase II study to further confirm the safety and activity of this bi-weekly regimen.

MATERIALS AND METHODS

Patients

Patients with histologically proven metastatic or unresectable adenocarcinoma, undifferentiated- or squamous cell carcinoma of the oesophagus or gastro-oesophageal junction area were eligible for the study. Further eligibility requirements were: a life expectancy of more than 12 weeks; age ≤ 18 years; WHO performance status 0–2; written informed consent; adequate haematological, renal and hepatic functions defined as: granulocytes ≥ 1.5 × 10⁹ l⁻¹, platelets ≥ 100 × 10⁹ l⁻¹, total bilirubin ≤ 1.5 × upper normal limit and creatinine ≤ 120 µmol l⁻¹. Patients were required to have measurable or evaluable disease. Prior radiotherapy was allowed if not involving more than 30% of the bone marrow or was given within the 4 weeks prior to study entry. The study was approved by the institutional ethics committee.

Drug administration

Paclitaxel 180 mg m⁻² and cisplatin 60 mg m⁻² were administered intravenously every 2 weeks. After prehydration with at least 1 l of normal saline, paclitaxel, diluted in 500 ml of normal saline, was infused over 3 h and subsequently cisplatin was administered over 3 h followed by post-hydration over 24 h. All patients received premedication with dexamethasone 20 mg given orally 12 and 6 h prior to the paclitaxel infusion. Thirty minutes before the paclitaxel infusion, the patients received 10 mg dexamethasone, 2 mg clemastine and 50 mg ranitidine, all given i.v. Ondansetron at a dose of 8 mg i.v. was given as anti-emetic prophylaxis. Patients were retreated after 14 days when the granulocytes were ≥ 0.75 × 10⁹ l⁻¹ and the platelets ≥ 75 × 10⁹ l⁻¹. When these criteria were not met, treatment was postponed for 1 week. A dose reduction was only made for patients with neutropenic fever; in that case paclitaxel was reduced to 75% in subsequent courses.

Treatment assessment

Pre-treatment evaluations consisted of a complete medical history, physical examination, complete blood cell count and serum biochemistry, computerised tomography (CT) scan of the chest and upper abdomen and ultrasonography of the supraclavicular nodes when appropriate. Patients with the primary tumour in situ were also evaluated by endoscopy. During treatment blood cell counts were assessed every week and physical examination, toxicity assessment and serum chemistry studies every 2 weeks. Toxicity was graded and reported using NCI–CTC criteria (version 2). For response evaluation the CT-scan, and also a ultrasonography and endoscopy when appropriate, were repeated after the third and sixth cycle and after discontinuation of therapy. Response was evaluated using WHO criteria (World Health Organisation, 1979). A complete response (CR) required the disappearance of all known disease, determined by two observations not less than 4 weeks apart, and for patients with the primary tumour in place an endoscopic confirmation of a complete response with normal endoscopic biopsies. A partial response was defined as a decrease by at least 50% reduction in the sum of the products of the largest perpendicularly diameters in all measurable lesions or at least a 30% reduction of the largest diameters in uni-dimensional disease (evaluable disease) for at least 4 weeks. It is not necessary for all lesions to have regressed to qualify for partial response, but no lesion should have progressed and no new lesion should appear. Stable disease was defined as less than 50% decrease and less than 25% increase in tumour size. Progressive disease was greater than 25% increase of one or more measurable lesions or the development of new lesions.

The duration of response was defined as lasting from the start of treatment to documentation of the disease progression. Patients with stable disease received up to a maximum of six cycles of treatment. In patients achieving a partial or complete response, an additional two cycles were allowed. Patients were followed for survival and disease progression every 3 months until death.

Statistical considerations

Patient enrolment followed a five-step sequential design. If no response was seen in the first eight patients further accrual had to be halted. Otherwise an additional six patients could be entered and if at least two patients responded again six patients had to be entered. In the fourth step 10 more patients were entered if at least four responses were observed in the 20 patients that were treated. Finally when 30 patients were treated the trial was continued with an additional 20 patients if the observed number of responses was at least 50%. Under this design there is only an 18% chance of continuing the trial while the true response percentage is below 40%.

Actuarial survival was calculated using the method of Kaplan and Meier.

RESULTS

Fifty-one patients were entered in this study. Patient characteristics are listed in Table 1. All patients received at least three cycles of chemotherapy and all were evaluable for toxicity and response. A total of 286 cycles were administered (median six, range 3–8). Nine patients received only three cycles. Three of these nine patients had progressive disease and in five patients with stable disease who had persistent dysphagia treatment was stopped and these patients were palliated by oesophageal stenting. One patient refused further treatment. Five of the remaining 42 patients did not complete six cycles of therapy. Two patients were not able to continue treatment after four cycles for reasons of toxicity mainly consisting of fatigue; one patient developed a cerebrovascular accident and two patients had progressive disease after the fourth and fifth cycle, respectively. Seven patients who had achieved a partial response received eight cycles of treatment.

Seventy-one chemotherapy cycles (25%) were delayed. In 19 (37%) patients there was no treatment delay; one, two or more delays were required in respectively seven (14%), 11 (22%) and 14 (27%) patients. Sixty-five cycles in 25 (49%) patients were delayed for 1 week because of a granulocyte count < 0.75 × 10⁹ l⁻¹. Four cycles were delayed for 1 week because of infections without neutropenia, one cycle was delayed for 1 week because of elevated liver-enzymes due to co-medication and one cycle was delayed for 3 weeks in a patient who developed a broncho-oesophageal fistula 4 days after the start of chemotherapy. The planned and achieved dose intensity were for cisplatin 30 and 26.4 mg m⁻² per week, respectively, and for paclitaxel 90 and 79.3 mg m⁻² per week, respectively.

Haematological toxicity

Neutropenia grade 2 or 3 were observed in 39 and 31% of patients and in 23 and 10% of cycles, respectively. The nadir for granulocytes usually occurred after the fourth or fifth cycle of treatment. Neutropenic infections were not observed. No
apy on the primary tumour and supraclavicular region and is still
patient who had a complete response received additional radiother-
apy. The duration of complete response was 7 months in a patient
with a local recurrence and lymph node metastases. The second
response was already documented after three courses of chemother-
dimensionally evaluable disease. In 15 of 22 responding patients the
had bi-dimensionally measurable lesions and one patient had uni-
PD in eight patients (16%). Twenty-one of 22 responding patients
was 43%; 20 patients (39%) had a PR and two patients (4%)
All 51 patients had measurable disease. The overall response rate
Responses

Non-haematological toxicity

Grade 1 sensory neurotoxicity was observed in 22 patients (43%) and
grade 2 in 10 patients (20%). Six of these in total 32 patients
had a complete resolution of sensory neurotoxicity and in 11
patients neurotoxicity partially subsided. Five patients developed
infections without neutropenia. Three of these patients were
admitted because of pneumonia, an urinary tract infection and
an infected subcutaneously implanted intravenous access device,
respectively. All patients recovered after treatment with antibiotics.
Two patients were admitted for gastro-intestinal toxicity. In total
five patients (10%) were hospitalised, three patients because of
treatment-related complications and two patients because of infec-
tions without neutropenia. There were no treatment-related deaths.
Other toxicities were usually mild and are listed in Table 2.

Responses

All 51 patients had measurable disease. The overall response rate
was 43%; 20 patients (39%) had a PR and two patients (4%) had
a CR. Stable disease was observed in 21 patients (41%) and
PD in eight patients (16%). Twenty-one of 22 responding patients
had bi-dimensionally measurable lesions and one patient had uni-
dimensionally evaluable disease. In 15 of 22 responding patients the
response was already documented after three courses of chemother-
apy. The duration of complete response was 7 months in a patient
with a local recurrence and lymph node metastases. The second
patient who had a complete response received additional radiother-
apy on the primary tumour and supraclavicular region and is still
disease free 29 months after start of treatment. The median dura-
tion of response (measured from start of treatment) in the patients
with a PR was 8 months (range 5 – 29+ months). Twenty-one
patients (41%) had stable disease with a median duration of 6.5
months. After a response to chemotherapy definitive local therapy
using either radiotherapy or surgery was attempted in nine patients
with either locally advanced disease or lymph node metastases
confined to the celiac or supraclavicular region (M1a disease). Two
patients with an irreplaceable tumour underwent an oesopha-
geal resection, pathologic examination of the resected specimen
showed tumour free margins and these patients are disease free
20 and 28 months, respectively, after surgery. Seven patients with
M1a disease received radiotherapy at a dose of 50 Gy at the
primary tumour and involved lymph nodes; two of these patients
are disease free after 24 and 29 months, respectively. The overall
response rates for patients with adenocarcinoma, and squamous
cell carcinoma were 39 and 44%, respectively, and three of the four
patients with an undifferentiated carcinoma achieved an objective
response.

Survival

After a median follow-up of 32 months (range 1 – 32 months) 12
patients (24%) are still alive. The median actuarial survival in all
patients was 9 months (range 2 – 29+ months), with a one-year
survival rate of 43%. The median actuarial survival for responding
patients is 12 months (range 6 – 29+ months), compared to 7
months (range 2 – 31+ months) in non-responding patients.

DISCUSSION

Chemotherapy either alone or in combination with radiotherapy is
frequently used preoperatively in patients with resectable disease.
For patients with irresectable and/or metastatic disease chemother-
apy may offer a chance of both tumour regression and palliation
of symptoms. The effect of chemotherapy on survival in this group of
patients is unclear due to a lack of randomised phase III studies
comparing chemotherapy to best supportive care.

The combination cisplatin and 5-fluorouracil is probably the
most frequently used combination in the treatment of oesophageal
cancer. Pre-operative treatment with this combination was toler-
ated well by patients with resectable disease in two large
randomised trials (Kelsen et al, 1998; Clark, 2000). However in
one of the few randomised studies performed in patients with
metastatic disease, the toxicity of this regimen appeared to be
severe (Bleiberg et al, 1997). In that trial 88 patients with meta-
static oesophageal cancer received either cisplatin in combination
with 5-fluorouracil or cisplatin alone. In the cisplatin/5-fluorouracil
arm there were 16% treatment related deaths, mostly due to
neutropenic sepsis, versus 0% in the cisplatin arm. Because of this
high incidence of treatment-related deaths the higher response rates
observed in the cisplatin/5-fluorouracil arm most likely did not
translate in a significant survival benefit compared to treatment
with cisplatin alone. The difference in tolerability of chemotherapy

| Characteristic | No. of patients (%) |
|---------------|---------------------|
| **Sex**       |                     |
| Male          | 37 (73)             |
| Female        | 14 (27)             |
| **Age (years)** |                   |
| Median        | 56                  |
| Range         | 32–78               |
| **WHO performance status** |   |
| 0             | 19 (37)             |
| 1             | 29 (57)             |
| 2             | 3 (6)               |
| **Weight loss (%)** |               |
| 0–5           | 13 (25)             |
| 5–10          | 15 (29)             |
| >10           | 23 (45)             |
| **Histology** |                     |
| Adenocarcinoma| 31 (61)             |
| Squamous cell carcinoma | 16 (31) |
| Undifferentiated carcinoma | 4 (8) |
| **Prior therapy** |                 |
| Oesophagectomy | 11 (22)            |
| Radiotherapy  | 0 (0)               |
| **Extent of disease** |          |
| Locally advanced/unresectable | 5 (10)  |
| Primary with distant metastases | 35 (69)  |
| Metastases after prior resection | 11 (22)  |
| **Metastatic sites** |                  |
| Celiac/supraclavicular lymph nodes | 38 (75) |
| Liver         | 13 (25)             |
| Other         | 3 (6)               |

| Characteristic | No. of patients (%) |
|---------------|---------------------|
| **CTC grade (%)** |                 |
| Nausea        | 25 (49) 24 (4) 2 (4) |
| Vomiting      | 51 (25) 4 (4) 18 (4) |
| Diarrhoea     | 86 (12) 2 (2)   |
| Mucositis     | 92 (6) 2 (2)   |
| Neurotoxicity | 37 (43) 20 (20) |
| Nephrotoxicity| 96 (4)   |
| Myalgia       | 65 (33) 2 (2)   |
| Fatigue       | 60 (20) 20 (20) |

| **Survival** |       |
| 0            | 1 | 2 | 3 |
| Nausea       | 25 | 49 | 24 | 2 |
| Vomiting     | 51 | 25 | 18 | 4 | 2 |
| Diarrhoea    | 86 | 12 | 2  |   |
| Mucositis    | 92 | 6  | 2  |   |
| Neurotoxicity| 37 | 43 | 20 |   |
| Nephrotoxicity| 96 | 4  |   |   |
| Myalgia      | 65 | 33 | 2  |   |
| Fatigue      | 60 | 20 | 20 |   |

| **Treatment with cisplatin and paclitaxel in oesophageal cancer** |
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Table 1 Patient characteristics (n=51)

Table 2 Worst CTC grade non-haematological toxicities (n=51)
between patients with resectable disease and patients with metastatic disease could be explained by the fact that patients with metstatic disease usually have an impaired performance status, substantial weight loss and co-morbidity.

Recently, several new agents such as the taxanes, irinotecan and vinorelbine, have shown promising activity in the treatment of oesophageal cancer. A further advantage of these new agents is that they cause less mucosal toxicity compared to the combination of 5-fluorouracil and cisplatin with or without leucovorin.

In a previous study we demonstrated the feasibility of cisplatin and paclitaxel administered in a treatment interval of 2 weeks (van der Gaast et al, 1999). We were able to decrease the treatment interval because we retreated the patients when their granulocytes were above 750 $10^9$ l$^{-1}$ instead of the more common used threshold for retreatment of 1500 $10^9$ l$^{-1}$. The safety of this approach was confirmed in the current study. Despite the fact that 70% of patients developed grade 3 or 4 neutrocytopenia, we did not observe any episode of neutropenic fever. The achieved dose intensity was for cisplatin 26.4 and for paclitaxel 79.3 mg m$^{-2}$ per week.

Given the fact that most patients had metastatic disease the treatment was well tolerated. Only five patients (10%) were hospitalised, three patients because of treatment-related complications and two patients because of infections without neutropenia. In general gastro-intestinal toxicity was mild and grade 2 mucositis was observed in only two patients. Sensory neurotoxicity was the predominant non-haematological side-effect: grade 1 and 2 occurred in, respectively, 43 and 20% of patients. In 19% of patients with neurotoxicity we observed a complete resolution and in 34% a partial improvement of neurotoxicity. The neurotoxicity observed with our bi-weekly regimen is comparable to that of previously used cisplatin- and paclitaxel-based regimens. Trials are underway evaluating this bi-weekly cisplatin/paclitaxel regimen.

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