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Short Communication

Phase II study on gemcitabine in recurrent and/or metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982)

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ARTICLE INFO

Article history:
Received 16 July 2008
Received in revised form 11 August 2008
Accepted 13 August 2008
Available online 24 September 2008

Keywords:
Adenoid cystic carcinoma
Gemcitabine
Salivary gland tumours
Head and neck cancer

ABSTRACT

Background: This phase II study was conducted to determine the antitumour activity of gemcitabine in adenoid cystic carcinoma (ACC).

Patients and methods: Patients with progressive and/or symptomatic, recurrent and/or metastatic ACC were treated with gemcitabine 1250 mg/m^2 intravenous (i.v.) on days 1 and 8 of each 21-day cycle. Each cycle was repeated every 3 weeks in the absence of disease progression for a minimum of four cycles and a maximum of 12 cycles.

Results: Among 21 ACC patients, there were no objective responses. Eleven patients had a stable disease, of which ten patients for more than 6 months, and eight had a progressive disease after 4 cycles. Gemcitabine was well tolerated by most patients.

Conclusion: We conclude that gemcitabine is not an active drug in ACC.

1. Introduction

Adenoid cystic carcinoma (ACC) of salivary origin in the head and neck region comprises only 7% of all head and neck cancers. It is characterised by slow growth, the frequent occurrence of infiltration into surrounding soft tissues (perivascular and perineural) and bone, a high local recurrence rate after standard local treatment of the primary tumour and late onset of distant metastases. The occurrence of regional lymph node metastases is rather uncommon.[1]

Primary treatment includes extensive local resection of the tumour, radical neck dissection when cervical lymph node metastases are present, and in the great majority of cases surgical resections combined with radiation therapy

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.08.014

postoperatively. During the first five years of follow-up, these local treatments suggest a high success rate, with 50–75% remaining disease-free. However, subsequent follow-up periods show a steady rise in the number of patients with local recurrence and/or metastases with only 10–20% remaining disease-free at 15 years. Fifty percent of patients will develop haematogenous metastases, most frequently in lungs, bone and liver. The majority of those patients will die within three years. However, some patients with metastases live for many years.[2] Therefore, in general, chemotherapy is only started when patients have a rapidly progressive disease or are symptomatic. The response rates of ACC to conventional cytotoxic chemotherapy have been modest, both for single-agent and for combination therapies. Objective response rates to 5-fluorouracil, doxorubicin, cisplatin and cyclophosphamide or combinations of these drugs vary between 15 and 30% with a median duration of 5–40 months.[3] However, these are all small studies and the figures are difficult to interpret because of the varying clinical course of metastatic ACC. In view of these disappointing results, new drugs are needed.

Gemcitabine is a pyrimidine antimetabolite with antitumour activity in non-small cell lung cancer, pancreatic cancer, bladder cancer, breast cancer and ovarian cancer. Gemcitabine is generally well tolerated.[4] The principal objective of this phase II study was to evaluate the activity and the safety of gemcitabine in patients with recurrent or metastatic ACC of the head and neck.

2. Patients and methods

This was a multinational, multicentre, open non-randomized phase II study. Patients were eligible with the histologically documented evidence of measurable metastatic or recurrent adenoid cystic carcinoma of the head and neck not amenable to curative surgery and with symptomatic and/or progressive disease, no bone metastases as only metastatic site, age >18 years, WHO performance status <2, no prior chemotherapy, no prior radiotherapy $\leqslant$3 months prior to study entry except palliative radiotherapy to painful bone lesions, no symptoms or signs of central nervous system metastases, no second malignancy in the last five years except for adequately treated basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, no uncontrolled infections, no pregnancy and/or breastfeeding, normal haematological, renal and hepatic functions. Participants gave informed consent before they entered onto the study, and the local research ethics committees of the participating centres approved the study.

Treatment consisted of gemcitabine 1250 mg/m^2 i.v. over 30–60 min on days 1 and 8 of each 21-day cycle. Each cycle was repeated every 3 weeks in the absence of a disease progression for a minimum of four cycles and a maximum of 12 cycles.

Evaluation of the disease was performed every four cycles, according to the RECIST criteria.[5] Evaluation was planned after 4 instead of, more frequently used, 2 cycles, because of the often slow evolution of these tumours. In case of clinical benefit, defined as stable disease (SD), partial (PR) or complete response (CR), treatment was continued for a maximum of 12 cycles. Dose reductions and delays were specified as per the protocol. Toxicity was scored according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 2.0).[6]

The primary objective of this study was to assess the activity documented by the objective response rate to gemcitabine in patients with recurrent and/or metastatic ACC of the head and neck. Secondary end-points were response duration and toxicity experienced with the use of gemcitabine in this clinical setting.

3. Statistical considerations

The Simon one sample two-stage design was used, with a null hypothesis of 5% response rate (not warranting further investigation) and an alternative hypothesis of 25% response rate (leading to further investigation). The statistical error rates of the design were $\alpha = 0.10$, $\beta = 0.05$. The first stage consisted of 16 patients evaluable for response. If 0 responses out of the first 16 evaluable patients were observed, the study was to be stopped with the conclusion that the drug should not be further investigated. In any other situation, the study was to be continued until 29 patients were evaluable for response, and if $\leqslant$3 responses out of these 29 patients were to be observed the study would accept the null hypothesis, with the conclusion that the drug should not be investigated further. If >3 responses out of 29 patients were observed, the null hypothesis would be rejected with the conclusion that the drug should be further investigated.

4. Results

Between April 2001 and April 2003, 21 patients were enrolled (21 patients were enrolled to ensure that at least 16 would be assessable at the first stage). At the first analysis, no response was observed and the study was discontinued.

Patient characteristics are shown in Table 1. All patients were eligible. However, one patient did not have an eligibility review but was eligible per the data provided by the investigator.

4.1. *Adherence to treatment schedule*

The median number of cycles that were administered per patient was 4 (range, 2–11), with a median time of treatment of 12.3 weeks (range, 6–35). In most patients, no dose reductions ($n = 15$, 71.4%) were necessary. The main reason for a dose reduction was haematological toxicity (83.3%). Approximately, half of the patients ($n = 12$, 57.1%) did have a delay of the start of one or more cycles due to non-drug-related issues. One patient was lost to follow-up after 2 cycles.

4.2. *Toxicities*

Gemcitabine was well tolerated by most patients, and most toxicities were grade 1 or 2. The number of grades 3 and 4 toxicities was very low. The main haematological toxicities were leukopaenia (grades 1–4 in 17, grades 3–4 in 5 patients), neutropenia (grades 1–4 in 16, grades 3–4 in 10 patients), thrombopaenia (grade 1–2 in 7 patients) and anaemia (grades 1–2 in 16 patients). The most frequent (at least observed in more

Table 1 – Patient characteristics

	n = 21 (%)
Gender	
Male	7 (33.3)
Female	14 (67.7)
Age, median (range)	53 (36–68)
WHO performance score	
0	4 (19.0)
1	15 (71.4)
2	2 (9.5)
Time since first diagnosis in years, median (range)	9.3 (1.2–24.4)
Histologically proven adenoid cystic carcinoma	
No	1 (4.8)
Only metastases	7 (33.3)
Only local recurrence	5 (23.8)
Both metastases and local recurrence	8 (38.1)
Prior therapy	
Surgery	
Curative	17 (81.0)
Palliative	2 (9.5)
Radiotherapy	
Curative	16 (76.2)
Palliative	2 (9.5)
Both	3 (14.3)

than one patient) and important non-haematological toxicity deemed drug-related was fatigue in 12 patients (grade 1 in 5, grade 2 in 6, grade 3 in 1 patient), dyspnea (grade 2 in 1, grade 3 in 2 patients), grade 2 oedema (in 3 patients) and 2 patients each with grade 2 fever, grade 2 nausea and grade 2 myalgia.

One patient died during cycle 3 due to pneumonia, deemed unrelated to the study drug. She was treated by her general practitioner and was not admitted to hospital and died at home.

4.3. *Efficacy of treatment*

No objective responses were observed in the first 21 patients entered onto the study. Eleven patients had a stable disease and eight had a progressive disease after 4 cycles. One patient was lost to follow-up after 2 cycles and one patient died during the third cycle due to pneumonia. Nine patients received more than 4 cycles. Ten patients (48%) had a stable disease for more than 6 months.

5. Discussion

In this study, we investigated whether gemcitabine was effective in ACC. However, no objective response was observed in 21 patients, and therefore we conclude that gemcitabine is not an active drug in ACC. Ten patients (48%) had a prolonged stable disease of at least 6 months. Although all patients had a progressive disease or complaints at enrolment of the study, it cannot be excluded that the slow natural course of the disease caused the prolonged stable disease instead of the treatment with gemcitabine. Gemcitabine treatment was generally well tolerated. Most important toxicities were haematological toxicities.

To date no treatment has shown any benefit to improving the natural history of ACC. Also targeted therapies such as imatinib mesylate,[7,8] gefitinib,[9] trastuzumab,[10] bortezomib,[11] cetuximab[12] and lapatinib[13] showed no antitumour activity. Responses were seen incidentally. A prolonged tumour stabilisation of more than 6 months was observed in 36% of patients treated with Lapatinib.

We conclude that patients with ACC preferably should be treated within the context of a clinical study and that novel agents with higher efficacy are urgently needed.

Conflict of interest statement

None declared.

Acknowledgements

This publication was supported by grants number 2U10 CA11488-31 through 5U10 CA11488-34 from the National Cancer Institute (Bethesda, Maryland, USA) and by the Kankerbestrijding/KWF from the Netherlands. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI. We acknowledge Eli Lilly Oncology for their grant.

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