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Phase I study of concomitant chemoradiation with raltitrexed in locally advanced head and neck cancer

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Abstract

In patients with non-resectable head and neck cancer concomitant chemoradiotherapy is increasingly used, especially in cases of oropharyngeal and hypopharyngeal tumours. Most chemoradiotherapy regimens contain cisplatin as a single agent or in combination with fluorouracil. However, not all patients are fit enough for a cisplatin-containing regimen or they refuse hospital admission. Raltitrexed is a specific thymidylate synthase inhibitor that has been studied as a radiosensitiser in rectal cancer. Raltitrexed can be administered easily in an outpatient setting and has few short-term side-effects. We studied raltitrexed at escalating doses combined with standard radiotherapy in advanced head and neck cancer patients. Seventeen patients with locally advanced head and neck cancer were enrolled in the study. Raltitrexed was administered at dose levels of 1.5, 2.0, 2.5 and 3.0 mg/m^2 intravenously (i.v.), once every 3 weeks, for two doses. Radiotherapy consisted of 70 Gy given over 7 weeks in five fractions of 2 Gy per week. In general, treatment was well tolerated. Toxicity consisted mainly of locoregional radiation toxicity (mucositis and skin toxicity). Systemic dose-limiting toxicity (DLT), complicated febrile neutropenia, was observed at 3.0 mg/m^2 in two of four patients. The dose of 2.5 mg/m^2 was extended thereafter with 3 additional patients without major toxicity. Radiotherapy had to be interrupted in one patient. Five patients had a clinical complete response (CR) and eleven a partial response (PR) six weeks after the last fraction of radiotherapy. Twelve out of 17 patients remained free of locoregional recurrence after a median follow-up of 24$^+$ months (range 3–60+ months). Raltitrexed, at a dose of 2.5 mg/m^2 given twice 3 weeks apart, can be administered in combination with 70 Gy of radiotherapy in locally advanced head and neck cancer patients with a manageable tolerability profile. The clinical results and convenience of the schedule make raltitrexed an attractive drug to explore further in patients considered unfit for cisplatin-containing chemoradiation regimens.

Keywords: Head and neck cancer; Phase 1 study; Radiotherapy; Raltitrexed

1. Introduction

A growing number of patients with head and neck cancer present at diagnosis with a stage III or stage IV tumour. Depending on the site of the primary tumour, the treatment consists of surgery followed by radiotherapy or of radiotherapy followed by salvage surgery. Concomitant chemoradiotherapy is frequently applied in patients considered to have non-resectable disease or when the morbidity of surgery is very high. The most frequently used chemotherapy protocols contain

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cisplatin administered either 3-weekly as a single agent or administered in combination with continuous infusion of fluorouracil during 4–5 days every 4 weeks. [1]. However, not every patient with head and neck cancer is fit enough for treatment with these regimens because of existing comorbidities (e.g. renal function impairment, cardiovascular disease), unfavourable social conditions or patients refusal to be admitted to hospital. For this patient group, a simpler, outpatient-based, treatment regimen is preferable.

Raltitrexed (Tomudex®) is a specific thymidylate synthase inhibitor that is taken up in cells by the reduced folate carrier system in the cell membrane. Inside the cell, raltitrexed is polyglutamated and retained for a long time. The polyglutamates are more potent than the parent compound. The drug can be administered once every 3 weeks as a short infusion on an outpatient basis. Raltitrexed is registered worldwide for the treatment of metastatic colorectal cancer, where it has activity comparable to that of bolus or infusional 5-fluorouracil + leucovorin [2]. Fluorouracil is a potent radiosensitiser and is frequently administered with radiotherapy to locally advanced rectal cancer patients. As an alternative to fluorouracil, raltitrexed has been studied with conventional radiotherapy in locally advanced [3,4] and recurrent rectal cancer [5]. The dose-limiting toxicities (DLTs) in these studies were comparable to those of fluorouracil and consisted of asthenia, diarrhoea and neutropenia [5]. A dose of 2.6–3.0 mg/m^2 was recommended for further studies. In human SCC-25 head and neck squamous cell cancer cell lines raltitrexed showed synergistic activity with radiotherapy with an enhancement ratio in oxygenated cells of up to 19.5 and in hypoxic cells of 2.7 [6]. Given these data, we conducted a phase I study of raltitrexed, in combination with standard radiotherapy, in patients with advanced head and neck cancer who were considered either unfit for standard cisplatin-containing regimens, or who refused hospital admission.

2. Patients and methods

Patients were eligible for the study if they had stage III or IV squamous cell carcinoma of the head and neck, if the tumour was considered non-resectable by a team consisting of head and neck surgeons and radiotherapists, or if patients refused hospital admission or were considered unfit for more intensive chemotherapy regimens. Further entry criteria were: age > 18 years, World Health Organisation (WHO) Performance Status of <2, adequate bone marrow function (haemoglobin > 7 mmol/l, white blood cell count (WBC) > 3.0×10^9 cells/l and platelets > 100×10^9 cells/l) adequate renal function (serum creatinine < 1.25 × the upper limit of normal (ULN) and a calculated creatinine clearance >1.08 ml/s) and adequate hepatic function (bilirubin < 1.25 × ULN, aspartate amino-transferase (ASAT)/alanine amino-transferase (ALAT) < 2.5 ULN). Excluded were patients at risk for renal impairment (e.g. patients with known hydronephrosis or with one kidney) as were patients with a systemic or psychiatric disorder considered to have a contraindication to enter the study. Concomitant use of folic acid or folinic acid as a nutrition supplement was not allowed.

All patients gave their written informed consent. The study was approved by the ethical committee of the Erasmus University Medical Center.

Before the start of treatment, all patients had a full medical history taken and a physical examination, full laboratory tests were taken to check the entry criteria and an electrocardiogram was made. In addition before the start of treatment a dental evaluation was done and, if necessary, dental extractions or restorative procedures for superficial caries were carried out and topical fluoride applications were started in dentate patients. During treatment patients were examined in the outpatient department twice a week (alternatively by the radiotherapist and medical oncologist) for the grading of toxicity. Weekly full haematological blood counts, as well as serum creatinine, creatinine clearance and liver function tests were repeated. Toxicity was graded according to the Common Toxicity Criteria (CTC-version 2.0, 1999) for systemic toxicity and the radiotherapy toxicity according to the European Organisation for Research and Treatment of Cancer/Radiation Oncology Group (EORTC/RTOG) Acute Radiation Morbidity Scoring Criteria. Before treatment, a magnetic resonance image (MRI) or computerised tomographic (CT)-scan was made for all patients and an evaluation of these MRI or CT-scans was planned 6 weeks after the last fraction of radiotherapy. All patients were irradiated in a supine position with the use of customised immobilisation masks. Orthogonal laser beams were used to assess the reproducibility of the treatment position. Treatment planning was established with Ct scan investigations taken in the treatment position. Ct scan planning was aimed at obtaining isodose distributions in the central plane of the fields and in at least two off-axis planes, located at a 2–3-cm distance from the field edges. The planning target volume (PTV) included anatomical regions with macroscopic malignant disease, elective target volumes and safety margins for microscopic disease, patients' movements and beam or patient set-up uncertainties. The dose to the spinal cord preferably did not exceed 50 Gy in 5 weeks. Dose variation to the PTV was kept within −5/+7% of the prescribed dose, both in the central and off-axis planes. All patients were treated with 6 MV photon beams and 10–14 MeV electron beams. Portal films were made for all fields, at the start of treatment and, in patients receiving a boost, repeated at the time of the field reduction. All patients were trea-

ted with conventional fractionation (five fractions per week of 2 Gy) up to a dose of 46 Gy for elective volumes and 70 Gy for tumour-bearing sites.

Raltitrexed was dissolved in 100 ml 0.9% NaCl and administered in the outpatient ward as a 15-min intravenous (i.v.) infusion on days 1 and 22 of the treatment, one hour before the radiotherapy fraction. The starting dose of raltitrexed was 1.5 mg/m^2. Three patients were planned per cohort. The second and third patient could start treatment when the first patient had completed the full treatment and was fully evaluable for toxicity. Where a patient experienced DLT, the cohort was to be expanded to 6 patients or until a second patient experienced a DLT. The next lower raltitrexed dose level was considered the dose to be explored further and was expanded to six patients. DLT was defined as neutropenia (ANC) grade 4 lasting for more than 5 days or grade 3 or 4 neutropenia complicated by fever >38.5 °C, thrombocytopenia grade 3 or higher or any non-haematological toxicity grade 3 or higher, with the exception of mucositis or a transient rise in serum transaminases (as this can be a side-effect of raltitrexed).

If on the day of the second raltitrexed administration, the WBC was $<3.0 \times 10^9$ cells/l and/or platelets were $<75 \times 10^9$ cells/l, the administration was withheld until recovery above these values, with a maximum delay of 2 weeks being allowed.

In case of any non-haematological toxicity > grade 2 (with the exception of inadequately treated nausea/vomiting or mucositis), raltitrexed was to be withheld until resolution of the toxicity to CTC-grade 1. For all patients, creatinine clearance was measured or calculated using the Cockcroft formula before the raltitrexed administration. In cases where there was a drop in the clearance to 0.92–1.08 ml/s, the raltitrexed dose was to be reduced to 75%, in cases with clearances of 0.42–0.90 ml/s, the dose was to be lowered to 50%. In cases where the creatinine clearance was <0.42 ml/s, raltitrexed treatment was to be stopped.

Table 1
Patients' characteristics

No. of patients entered	17
Male:female	8:9
Median age in years (range)	58(51–69)
WHO performance status	
0	4
1	13
Tumour localisation	
Oral cavity	1
Oropharynx	7
Hypopharynx	5
Larynx	1
Larynx + hypopharynx	1
Larynx + oropharynx	1
Squamous cell cancer unknown primary	1

WHO, World Health Organisation.

Table 2
Tumour stages

	T3	T4	Tx
N0		2	
N1		2	
N2c	1	2	
N3	4	4	1
Nx		1	

3. Results

Seventeen previously untreated patients were enrolled in the study. The patients' characteristics are presented in Tables 1 and 2. Two patients had a double tumour. Most patients refused hospital admission for proposed cisplatin therapy or had cardiovascular co-morbity which made fluid challenge for cisplatin unattractive and were therefore asked to participate in this phase I study.

4. Toxicity

The toxicity data are presented in Table 3. As expected, locoregional toxicity was observed at all dose levels and tended to be worse at the two highest dose levels. Placement of a feeding tube was necessary in four out of six patients at the dose level of 2.5 mg/m^2 and in three out of four patients at 3.0 mg/m^2, in general 3–4 weeks after the treatment start. In five patients, the feeding tube could be removed within 3 months after

Table 3
Dose levels of raltitrexed studied and toxicities observed (worst grade observed per patient)

Raltitrexed dose (mg/m^2)	No. pts/cycles	Haemoglobin					ANC					Platelets					Skin					Oral					Feeding tube
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	
1.5	4/8	3	1	0	0	0	4	0	0	0	0	4	0	0	0	0	0	2	2	0	0	0	1	2	1	0	1 pt
2.0	3/6	3	0	0	0	0	2	1	0	0	0	3	0	0	0	0	0	3	0	0	0	1	1	1	0	0	1 pt
2.5	6/12	3	2	1	0	0	5	0	1	0	0	6	0	0	0	0	0	3	1	2	0	0	1	1	4	0	4 pts
3.0	4/8	0	3	1	0	0	1	1	0	0	2	2	0	2	0	0	0	2	2	0	0	0	0	4	0	0	3 pts

pts, patients; ANC, absolute neutrophil count.

the last radiotherapy fraction. Up to the dose level of 2.5 mg/m^2, systemic toxicity was minimal. However, at the dose level of 3 mg/m^2, two patients developed febrile neutropenia, in one patient complicated by a lung abcess and in the other patient complicated by reversible renal toxicity, hypokalaemia and hypocalcaemia grade 2. Both patients recovered.

Interruption of radiotherapy was necessary in only one patient at a cumulative dose of 40 Gy, not because of toxicity, but because of an impedent carotid artery blow out. However, the patient did not develop the blow out, but developed a clinical complete response (CR). All other patients, including the two patients with febrile neutropenia, completed the planned radiotherapy without interruption.

5. Response

The evaluation of clinical response was done in all patients by a radiotherapist and head and neck surgeon. The radiological evaluation was not done according to the protocol in all of the patients so the clinical response is reported. Five patients had a clinical CR and 11 a clinical partial response (PR). In one patient with a PR, a neck dissection was performed and only a small nest of vital tumour cells was found on pathological examination. With a median follow up of 24+ months (range 3–60+ months), five patients remain clinically free of disease, five patients had a recurrence in the irradiated field as the first site of recurrence after a median of 7 months (range 2–11 months), six patients developed distant metastases without locoregional recurrence and one patient developed a second primary tumour in the lung without locoregional recurrence.

6. Discussion

In the Netherlands, an increasing number of patients with head and neck cancer present with stage III or stage IV disease. In previous years, many patients with locally advanced tumours were treated upfront with chemotherapy to downstage the tumour before radical local treatment. Despite high response rates with neoadjuvant chemotherapy, the treatment outcome is considered inferior compared with that of concomitant chemoradiotherapy [7]. Concomitant chemoradiotherapy schedules using cisplatin show superior results compared with non-cisplatin-containing regimens. Unfortunately, not all head and neck cancer patients are good candidates for cisplatin treatment as it necessitates a hospital admission, fluid challenge, etc. A regimen that can be given on an outpatient basis, without too much systemic toxicity, is therefore attractive. Weekly docetaxel at a dose of 25 mg/m^2 [8] and paclitaxel 30 mg/m^2 [9] have already been explored in combination with radiotherapy, with promising results. Carboplatin also has the advantage of ease of administration without the need of pre- and post-hydration. Prades and colleagues could administer carboplatin area under the concentration curve (AUC) 1 given on days 1–5, every 4 weeks, with radiotherapy twice daily [10]. Airoldi and colleagues treated patients during radiotherapy with carboplatin AUC 0.3–0.5 on days 1–5, every 2 weeks, alternated with docetaxel, every 2 weeks, at a dose of 20 mg/m^2. The systemic side-effects were mainly haematological and manageable [11].

Although raltitrexed is not active as a single agent in recurrent head and neck cancer patients [12,13], the drug was considered attractive to explore in this group given the positive results of raltitrexed as a radiosensitising agent in rectal cancer. In the present study, raltitrexed was very well tolerated up to a dose of 2.5 mg/m^2 and systemic toxicity was observed only at the 3 mg/m^2 dose. Despite locoregional toxicity, all but one patient, could complete the treatment without interruption. This is important as treatment interruptions or missed days of treatment are unfavourable prognostic factors [14]. The high locoregional control rate in our patients is encouraging given the advanced stage of the tumours. Treatment results of more intensive, platinum- and fluorouracil-containing regimens in comparable patients, show locoregional control rates varying between 36% and 88% at 2–3 years [15–18]. Given the ease of administration and good tolerability, further studies with raltitrexed at a dose of 2.5 mg/m^2 in combination with conventional radiotherapy can be considered.

Conflict of interest statement

Financial disclosure: The raltitrexed administered in this study was supplied (free of charge) by Astra Zeneca, The Netherlands. None of the authors have a personal financial interest in the study drug.

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