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ORIGINAL ARTICLE

Phase II study of rubitecan in recurrent or metastatic head and neck cancer

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Abstract
Purpose Rubitecan is an oral camptothecin analogue that has shown activity against a broad spectrum of human tumor xenografts and has been tested in several diseases.
Patients and methods In the present study, 19 patients with incurable, recurrent or metastatic head and neck cancer were treated with rubitecan at the initial dose of 1.5 mg/m^2 × 5 days per week. An appropriate dose modification program was set up according to the observed toxicities.
Results Thirteen out of the 19 treated patients were formally evaluable for tumor response. Ten patients had a disease progression and three patients had a stabilization of disease as their best response. The mean duration of stable disease was 141 days. Median survival was 16 weeks (range 2–22 weeks). Three patients died during the study or less than a month after their last dose of study medication. Hematologic toxicity was serious in this study since four patients discontinued their participation because of severe anemia. The drug was also associated with grade 1–4 neutropenia, and with 1–3 thrombocytopenia.
Conclusion We conclude that rubitecan is not effective as a single-agent in recurrent or metastatic head and neck cancer with the doses and schedule used in this study.

Keywords Head and neck cancer · Oral camptothecin · Phase II study · Rubitecan

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Introduction

Head and neck cancer (HNC) represent the sixth most common type of cancer diagnosed worldwide. Nearly 600,000 new cases are diagnosed every year, and the risk of mortality is considerably high. Around 60% of HNC involve the oral cavity and the pharynx, the remaining arising mainly in the larynx [4]. Platinum-based chemotherapy is generally used as a palliative therapy for patients with recurrent or metastatic disease. Methotrexate, taxanes, gemcitabine and vinorelbine are other slightly active drugs; in general, tumor response rates rarely exceed 30% and responses are of short duration. One-year survival rate is below 30% in this group of patients and the search for new active drugs is strongly pursued [4]. Topotecan has shown activity in recurrent or metastatic HNC as well, and this justifies the trials with other topoisomerase (topo) I inhibitors [15].

Rubitecan (RFS 2000, 9-nitro-camptothecin) is an oral camptothecin analogue that exists in equilibrium as 9-nitro-camptothecin and 9-amino-camptothecin (9-AC), a supposedly active metabolite, which, however, failed in clinical trials [5]. Rubitecan has shown activity against a broad spectrum of tumor types in vitro and in vivo human tumor xenograft models [5]. Disappointingly, objective responses were low in the clinical setting, since rubitecan has undergone a number of phase I–II clinical trials, both alone and

in combination, which have shown a low-activity level, perhaps with the only exception of pancreatic cancer [5].

Based upon the wide spectrum of rubitecan activity in preclinical models, the present phase II study in incurable, recurrent or metastatic HNC was carried out with the main aim of having a reliable estimate of the activity of the drug in this patient population.

Patients and methods

Patient selection

Eligibility criteria for study entry included histologically or cytologically verified, incurable locally advanced, unresectable or metastatic squamous cell carcinoma of the head and neck with at least one target lesion bidimensionally measurable by computed tomography (CT) scan; age >18 years; WHO performance status 0–2; adequate bone marrow, liver, renal, cardiac function; life expectancy of at least 3 months. One prior chemotherapy regimen was allowed. Patients were ineligible in presence of brain metastases, previous or current malignancies at other sites, with the exception of adequately treated cone-biopsed in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin. Patients with undifferentiated and non-cheratinizing carcinomas, including lymphoepitheliomas or tumors of the nasal and paranasal cavities and of the nasopharynx were also ineligible. Pregnancy, lactation, uncontrolled infections, unstable systemic diseases were also exclusion criteria. A minimum of 4 weeks had to have elapsed between the end of prior radiotherapy or chemotherapy and entry into the protocol. The study was approved by the Investigational Review Board and the Ethics Committee of each participating center. Written informed consent was obtained from each patient before registration.

Treatment plan

Patients were treated with a single daily dose of rubitecan taken orally for five consecutive days, followed by two treatment-free days, repeated every week for 4 weeks. A period of 4 weeks was considered a cycle. Rubitecan was provided as crystalline powder in gelatine capsules containing 0.5 or 1.25 mg of active drug. Capsules had to be stored at 2–8°C in an opaque or amber container until use. Antiemetic coverage was used at discretion of the investigator. Rubitecan was to be taken 1 h prior to breakfast after an overnight fast. Patients were asked to increase their fluid intake up to 3 l per day during treatment to reduce the risk of chemical cystitis. The starting dose of rubitecan for all patients was 1.5 mg/m^2 daily × 5 days per week (dose level 0). The maximum dose was 2.0 mg/m^2 daily × 5 days per week (dose level +2) and the minimum 0.75 mg/m^2 daily × 5 days per week (dose level −3) (Table 1). All patients started at dose level 0. Thereafter, dose levels were determined on the basis of weekly blood counts and assessment of toxicities. Once reduced, a dose could not then be increased. Patients experiencing a >2 week treatment delay had their dose reduced by one level. A >3-week delay caused the patient to be taken off study. The dose of rubitecan could be increased by one level if granulocytes were >2,000 and platelets were >150,000 at each measurement, no other drug-related toxicity except alopecia was observed. If these criteria were met for a further 4 weeks at level +1, the dose could be increased to dose level +2. The dose of rubitecan was to be reduced for signs of hematologic toxicity: in case of granulocyte nadir 500–1,000 and/or platelet nadir 50,000–100,000 dose was decreased by one level; in case of granulocyte nadir <500 and/or platelet nadir <50,000 dose was decreased by two levels. All cycles were to be held pending hematologic recovery to a neutrophil count >1,500 μl^{-1} and platelet count >100,000 μl^{-1} Dose reductions were to be performed also for non-hematologic toxicities, except alopecia. In particular, in case of grade 2–3 toxicity the investigator had to either decrease one dose level or withhold the treatment; in case of grade 4 toxicity treatments had to be withheld until recovery and decreased two dose levels.

Patient evaluation

At enrolment, patients were evaluated by a complete history and physical examinations, performance status recording, complete blood cell (CBC) count, serum chemistries, urinalysis, ECG, chest X-ray, total body CT-scan. Other exams were performed only in the presence of clinical indication. Patients were monitored weekly throughout treatment by clinical examination, toxicity assessment, CBC count and urinalysis. Biochemistries were repeated every 4 weeks, along with the recording of performance status and tumor measurement by physical examination. Evaluation for tumor response was performed every two courses

Table 1 Rubitecan dose levels

Level	Rubitecan (mg/m^2 day)	Treatment days	Treatment-free days
+2	2.0	1–5	6–7
+1	1.75	1–5	6–7
0	1.5	1–5	6–7
−1	1.25	1–5	6–7
−2	1.0	1–5	6–7
−3	0.75	1–5	6–7

of chemotherapy with repetition of all tests which were abnormal at baseline. Response was assessed according to RECIST criteria. A follow-up scan obtained at least 4 weeks later was required to confirm complete response (CR) or partial response (PR). Responding or stable patients received additional treatment until progression or unacceptable toxicities. National Cancer Institute (NCI) Common Toxicities Criteria (CTC) were used to grade toxicity.

Statistical methods

The sample size calculation was based on the standard two-stage Gehan's rule. In the first stage, 14 evaluable patients were required. If no response was observed in this cohort of patients, the study was to be closed. In case of one or more responses in the first 14 patients, additional patients would be added up to a maximum of 25. This design ensures that, if the drug is active in 20% or more of patients, the chance of erroneously rejecting the drug after the first 14 patients is 0.044. Although it was stipulated in the protocol that the study would not be closed until 14 evaluable patients had been assessed, none of the centres managed to further recruit a patient in the year following the last inclusion. The duration of CR or PR was measured from the time these criteria were met until the first date that recurrent or progressive disease was documented. The duration of stable disease was measured from the start of the treatment until the criteria for progression were met. Overall survival was measured from the start of treatment until death or last follow-up.

Results

Patient characteristics

Between April 2001 and July 2004, 19 patients were enrolled in the study. All of the patients had squamous cell carcinoma, differentiation grade was 2 in the majority of patients, and larynx was the most frequent site of primary tumor. Thirteen patients had received prior chemotherapy, which included cisplatin in all cases. All but one patient had previously undergone surgery. The characteristics of the eligible patients are detailed in Table 2.

Table 2 Characteristics of eligible patients (total $n = 19$)

Median age	
Years	56
Range	41–69
Sex (M/F)	17/2
Perfomance status	
0	8
1	9
2	2
Primary site	
Larynx	8
Tongue	6
Mouth floor	1
Left piriform sinus	1
Left maxillary sinus	1
Oropharynx	1
Unknown	1
Tumor grading	
Well differentiated	2
Moderately differentiated	12
Poorly differentiated	4
Unknown	1
Previous surgery	
Yes	18
No	1
Prior radiotherapy	
Yes	12
No	7
Prior chemotherapy	
Yes	13
No	6

Response

A total of 47 cycles of rubitecan were administered to all registered patients, for a median number of two courses per patient (range 1–6). Thirty-three cycles were started at dose level 0, seven at +1, two at +2, three at −1, and two at −2. Thirteen out of 19 treated patients were formally evaluable for tumor response. Reasons for non-evaluability included lack of full tumor evaluation (five patients) and source data not verifiable (one patient). No objective responses were observed. Ten patients had a disease progression and three patients had a stable disease as their best response. The mean duration of stable disease in these three patients was 141 days (range 113–181). Median survival was 16 weeks (range 2–22 weeks).

Toxicity

Three patients died during the study or less than a month after their last dose of study medication. Two of these patients left the study at second course of chemotherapy due to general deterioration and died shortly later. In one of these two cases, the serious adverse event was reported as possibly related to rubitecan administration, although the patient showed clinical signs of disease progression, such as deterioration of general

condition, performance status 4, hypercalcemia. The third patient experienced grade 3 anemia, and broke his femur at the end of his first cycle. He left the study because of his deteriorating general conditions and died 2 weeks later; his death was judged as unrelated to rubitecan.

Hematologic toxicity was significant. Grade 3 anemia was observed in four cycles; grade 4 anemia occurred in three cycles requiring red blood cell transfusion; overall, grade 3–4 anemia led to treatment discontinuation in four patients. Grade 3 and 4 leukopenia occurred in three cycles each. Grade 3 neutropenia occurred in two cycles, and grade 4 neutropenia in four cycles. However, no overwhelming infections occurred. Grade 3 thrombocytopenia was observed in one course, but was never complicated by bleeding, nor did it require platelet transfusion. Hematologic toxicity is detailed in Table 3. Non-hematologic toxicities were in general mild to moderate. Nausea was observed in six patients and reached grade 3 in one patient; vomiting and diarrhea occurred in five and nine patients, respectively, but they never reached grade 3. Fatigue was also frequently encountered and reached grade 3 in two cases. Grade 3 anorexia was observed in one case. Cystitis/hematuria revealed less heavy than expected, since it occurred in ten patients, but was grade 1 in the vast majority of them. Biochemical abnormalities suggestive of liver or kidney dysfunction were rarely observed. Non-hematologic toxicities are detailed in Table 4.

Table 3 Hematologic toxicities (worst grade per cycle)

Hematological abnormalities	Cycle	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hemoglobin	1	8	4	2	0	14
	2	6	5	2	2	15
	3	3	2	0	0	5
	4	1	1	0	1	3
Platelets	1	3	0	0	0	3
	2	3	0	1	0	4
	4	1	0	0	0	1
White blood cells	1	4	1	2	2	9
	2	2	4	0	1	7
	3	1	1	0	0	2
	4	0	0	1	0	1
Neutrophils	1	0	1	0	3	4
	2	2	2	1	1	6
	4	0	0	1	0	1

Table 4 Main non-hematologic toxicities (worst grade per patient; $n = 19$)

Non-hematological abnormalities	Grade 1	Grade 2	Grade 3	Grade 4	Total
Nausea	3	2	1	0	6
Vomiting	2	3	0	0	5
Stomatitis	0	2	0	0	2
Diarrhea	6	3	0	0	9
Fatigue	1	6	2	0	9
Cystitis/hematuria	8	2	0	0	10
Anorexia	0	1	1	0	2
General health deterioration	0	0	0	1	1
Dyspnoea	0	0	1	0	1
Alopecia	5	0	0	0	5
Renal toxicity	1	0	0	0	1
Liver toxicity	4	1	0	0	5

Discussion

Topoisomerase I inhibitors represent an important class of anticancer drugs, with notable activity especially in colorectal cancer, in ovarian cancer, and in small-cell lung cancer. Rubitecan is an orally active topoisomerase I inhibitor that has undergone a wide evaluation within phases I–II clinical trials.

The present study was carried out mainly to evaluate whether objective tumor responses could be achieved in patients with recurrent or metastatic head and neck cancer treated with rubitecan. Thirteen out of the 19 treated patients were formally evaluable for tumor response. Ten patients had disease progression and three patients had disease stabilization as their best response. The mean duration of stable disease was 141 days. Three patients died during the study or less than a month after their last dose of study medication. Hematologic toxicity was serious in this study since four patients discontinued their participation in the study because of severe anemia, always thought to be at least possibly related to rubitecan. The drug was associated with grade 1–4 neutropenia, and with 1–3 thrombocytopenia.

Nausea, fatigue and anorexia were the only extra-hematologic toxicities, which reached grade 3. A single case of grade 4 general health deterioration and grade 3 dyspnoea was reported. Diarrhea, vomiting, hematuria, proteinuria, cystitis, alopecia, and stomatitis were also reported, but they never exceeded grade 2. Due to the likely occurrence of cystitis, increased fluid intake was prescribed. This measure proved successful, since cystitis was experienced only by three patients during the study and there were no dose reductions due to hematuria. Blood chemistry abnormalities were small in this study, and renal and liver functions were never impaired.

Rubitecan has been tested in a number of clinical trials in other solid tumors. Evidence of activity in pancreatic

cancer was observed several years ago. Stehlin et al. [17] treated 107 patients, 60 of whom were evaluable for response. An objective response was achieved in 31.7% of patients. Median survival was 8.7 months, with one patient surviving 44 months. This study also included 33 patients who had failed gemcitabine and a median survival of 4.7 months was observed in this subset of poor prognosis patients. More recently, Burris et al. [3] have carried out a phase II trial of oral rubitecan in previously treated patients with pancreatic cancer. Among 43 patients with measurable disease, 7% achieved a partial response and 16% had stable disease. Median survival in responding patients was 10 months.

Single-agent rubitecan has been tested in a number of phase II studies in pretreated colorectal cancer [11], unpretreated non-small cell lung cancer [2], sensitive and refractory small cell lung cancer [13], hormone refractory prostate cancer [1], cutaneous and uveal melanoma [7], previously treated metastatic breast cancer [10], and advanced glioblastoma multiforme [14]. All these studies turned out to be negative, since no objective responses were observed in any of them. de Jonge et al. [6] carried out a phase II study on rubitecan in patients with pretreated metastatic urothelial cancer; rubitecan did not exert significant activity in this study also, since only 1 patient out of 20 had a partial response. Rubitecan has also been tested in soft tissue sarcoma [12] and three patients (8%) with soft tissue sarcoma histologies other than gastrointestinal leiomyosarcoma had a partial response.

Different treatment schedules of rubitecan have also been tested. Zamboni et al. [19] carried out a phase I pharmacologic study of intermittently administered rubitecan in patients with advanced solid tumors. In particular, on schedule A, rubitecan was given orally daily × 5 days for 2 weeks every 4 weeks; on schedule B, rubitecan was given orally daily × 14 days every 4 weeks. Both schedules were tolerable and the drug showed hints of antitumor activity in gastric and pancreatic cancer.

Given the low single-agent activity of rubitecan, a number of combination studies have been undertaken in solid tumors. In particular, the combination of rubitecan and capecitabine had minimal clinical efficacy in a group of patients with refractory solid tumors [9]. Similarly, the combination of rubitecan and gemcitabine did not induce objective responses in patients with advanced solid tumors [8]. Radiotherapy has also been combined with rubitecan in a small phase I study in locally advanced pancreatic carcinoma, which mainly aimed at evaluating rubitecan maximum tolerated dose, which was 1 mg/m^2 day given concurrently with radiation [18].

Resistance to topoisomerase I inhibitors has been related to down-regulation of nuclear target enzyme, whereas sensitization to topo II inhibitors may result from induction of topo II by topo I inhibitors. Leaving from these assumptions, Simon et al. [16] have recently evaluated a sequence-specific administration of rubitecan followed by etoposide in patients with advanced solid tumors. Despite a median number of four prior regimens, two patients (4%) had an objective response and 13 patients (29%) had stable disease in presence of predictable toxicity. Treatment-induced modulation of topo I and topo II expressions was evaluated in peripheral blood mononuclear cells (PBMC), but it was not consistent with that expected, thus questioning the usefulness of PBMC as an effective biologic surrogate [16].

It can be concluded that RFS-2000 as a single agent, at the dose and schedule used in this study, lacks activity as first-line treatment in incurable, recurrent or metastatic head and neck cancer. Although hematologic toxicity is serious, the drug is otherwise well tolerated.

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