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ORIGINAL ARTICLE

Capecitabine as salvage treatment in relapsed nasopharyngeal carcinoma: a phase II study

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Summary

Purpose: *To evaluate the efficacy of capecitabine (Xeloda®) as rescue treatment (2nd, 3rd and 4th line) in patients with relapsed nasopharyngeal carcinoma (NPC) in a phase II study.*

Patients and methods: *Between 5/2002-11/2005, 23 relapsed NPC patients (17 locoregional relapse, 3 metastatic, 3 locoregional + metastatic) received capecitabine 2500 mg/m^2/d, days 1-14 every 3 weeks, until progression or for a maximum of 6 cycles.*

Results: *Patient characteristics: 23 patients (14 men, 9 women) with median age 46 years (range 15-59); ECOG performance status 1 n=21, 2 n=2; histology: undifferentiated carcinoma (WHO type III) n=21, non-keratinizing epidermoid carcinoma (WHO type II), n=2. Capecitabine was given as 2nd - (13 patients), 3rd - (7 patients), and 4th - (3 patients) line chemotherapy. Previous chemotherapy regimes were epirubicin+ cisplatin, paclitaxel + carboplatin, paclitaxel + 5-fluorouracil and leucovorin (5-FU/LV) or methotrexate. 104 cycles were given (median 5, range 2-6). Two (9%) patients achieved complete response (CR); 9 (39%) partial response (PR); 9 (39%) stable disease (SD) and 3 (13%) progressed (PD). Toxicity was mild without toxic deaths or grade 4 toxicities. The most frequent toxicities (grades 1-3) were anemia (38%), hand-foot syndrome (23%), leukopenia (13%) and diarrhea (7%). Median follow-up was 10 months (range 2-44). Median overall survival was not reached at 18 months and actuarial one-year survival was 62% (95% confidence interval/CI: 41-80). Median progression-free survival was 14 months.*

Conclusion: *Capecitabine is active in relapsed NPC patients, achieving 48% objective responses, with mild toxicity. It is an attractive therapy to be administered in an outpatient setting.*

Key words: capecitabine, nasopharyngeal carcinoma, salvage chemotherapy

Introduction

Long-term survival was noted in some patients with relapsed/ metastatic NPC treated with chemotherapy. Extensive use of chemotherapy as part of the initial treatment of locally advanced NPC (especially cisplatin concomitantly with radiation therapy, followed by cisplatin + 5FU) creates the need of new efficient second-line chemotherapy regimens for refractory/ relapsed patients [1,2]. The development of a new generation of agents active in head and neck cancers gives hopes of improving prognosis in relapsed, chemotherapy-pretreated NPC patients, as well as in patients previously untreated with chemotherapy.

Several agents have shown promising activity in this setting. Single-agent paclitaxel has been shown to produce response rates in excess of 38% in advanced head and neck cancers [3]. The combination of paclitaxel with cisplatin or carboplatin exhibited antitumor activity in patients with inoperable head and neck cancer, with a wide range (20-70%) of overall response [4-8]. The triplet of paclitaxel, carboplatin, and gemcitabine showed promising efficacy against metastatic NPC but at the expense of considerable toxicity for an overall response rate of 78% [9].

Capecitabine (Xeloda®), an orally available fluoropyrimidine that is activated to 5-FU in the tumor cell by thymidine phosphorylase, is particularly interesting

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due to its ease of administration and favorable toxicity profile. Capecitabine proved active in NPC in phase II studies, with an overall response rate of 23.5%, median time to progression of 4.9 months and median overall survival of 7.6 months [10].

Patients and methods

The aim of this prospective phase II study was to analyse the efficacy of capecitabine in relapsed/metastatic NPC patients (2nd, 3rd or 4th line), and was conducted at the Cancer Institute "Ion Chiricuta" of Cluj-Napoca, Romania.

The main endpoint was response rate and secondary endpoints were progression-free survival, overall survival and toxicity profile.

Eligibility criteria

Patients aged 15-70 years with histologically proven recurrent or metastatic NPC, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and life expectancy of ≥12 weeks were eligible for the study. The patients were refractory or had relapsed after 1-3 previous chemotherapy regimens: 1st line: epirubicin/cisplatin (EC) or bleomycin/epirubicin/cisplatin (BEC); 2nd line: paclitaxel/carboplatin (TC) or paclitaxel/5-FU/leucovorin (TFL); 3rd line: methotrexate.

At least one site of measurable disease outside prior radiotherapy ports was required, unless a subsequent progression of the lesion was documented. Prior radiotherapy or surgery were allowed. All patients had to have adequate bone marrow function (white blood cells >3,500/mm^3, neutrophils >1,500/mm^3, platelets >100,000/mm^3, hemoglobin (Hb) >10 g/dL), liver function (bilirubin <1.25 × upper limit of normal, ASAT and ALAT <2.5 × upper limit of normal) and renal function (creatinine <1.5 mg/dL or creatinine clearance > 60 mL/min). All females of child-bearing potential had to have negative serum or urine pregnancy test results obtained within 2 days prior to treatment initiation. All patients had to be amenable to a regular follow-up.

Patients were excluded from the study if they had past or current malignant neoplasms other than NPC, except curatively treated non-melanoma skin cancer or cervical carcinoma *in situ*; a history of atrial or ventricular arrhythmia and/or history of congestive heart failure (even if medically controlled), or myocardial infarction during the previous 6 months; a history of preexisting grade ≥2 motor or sensory neurotoxicity according to NCI common toxicity criteria (CTC), version 3; or active infection or other serious underlying medical conditions which would impair the ability of the patient to receive treatment, including prior intolerance to 5FU (cardiac toxicity or hand-foot syndrome). Menstruating female patients without use of contraceptives, pregnant or breast-feeding were also excluded. Administration of other chemotherapeutic drugs or hormonal therapy was not allowed. The protocol was approved by the ethical institutional committee and patients gave signed informed consent before study entry.

Chemotherapy

Chemotherapy consisted of capecitabine 2500 mg/m^2/day given orally and divided in 2 doses, without premedication, from day 1 to 14. Chemotherapy was repeated on day 21 (every 3 weeks) for a maximum of 6 cycles.

Dosage was reduced to 2000 mg/m^2/day if grade 4 neutropenia or thrombocytopenia persisted for ≥ 7 days or in case of febrile neutropenia or if grade ≥ 3 non-hematological toxicities developed. Dose re-escalation was not allowed in this study. The absolute neutrophil count was required to be ≥1,500/mm^3 and the platelet count ≥100,000/mm^3 before beginning the next cycle. If hematological recovery was not achieved on day 35 of the cycle, the patient was taken off study. Treatment was discontinued in case of grade >2 non-hematological toxicities with the exception of nausea/vomiting. Toxicity criteria were those adopted by the NCI CTC, version 3. Standard RECIST criteria were used for evaluation of tumor response.

Statistical considerations

Statistical analysis was carried out on an "intention-to-treat" basis. The Kaplan-Meier method was used for estimating time to event curves. Survival was calculated from treatment initiation until death from any cause. Time to progression was determined by the interval between initiation of treatment and disease progression. Patients who died of causes probably related to chemotherapy or disease, or who discontinued their treatment for any reason other than tumor progression were considered as having disease progression at that time. Patients who were progression-free or alive on the day of the last update were censored. Reported confidence intervals for response to treatment were exact.

Results

Between May 2002 and November 2005, 23 pa-

tients entered this study. Their pretreatment characteristics are shown in Table 1. Median age was 46 years (range 15-59). Sixty-one percent were males. ECOG performance status was 1 in 21, and only 2 patients had a performance status 2. The vast majority (21 patients) had undifferentiated carcinoma of nasopharyngeal type (UCNT) histology. Seventeen (74%) patients had locoregional relapse, 3 (13%) distant metastases and 3 (13%) had both locoregional and metastatic disease.

Compliance with treatment and toxicity

Capecitabine was administered as 2nd line treatment in 13, as 3rd line in 7 and as 4th line in 3 patients. Table 2 depicts the chemotherapy line in relation with the site of relapse. Selected treatment characteristics are depicted in Table 3. As of September 2006, a total of 104 (75%) cycles, out of 138 cycles theoretically planned, were administered. The median number of cycles delivered was 5, with a range between 2 and 6 cycles.

Fifteen (65%) patients completed all 6 cycles of treatment. Reasons for treatment discontinuation were disease progression in 3 patients, grade 3 hand-foot syndrome in 2, grade 3 diarrhea in 2, and patient refusal in 1 case.

Toxicity is described in Table 4. Toxicity was mild; there were no toxic deaths and no unplanned hospitalizations due to complications of treatment with capecitabine. The most frequent toxicities (all grades) were anemia (38% of the cycles), hand-foot syndrome (23%), leukopenia (17%) and diarrhea (3%). No grade 4 toxicities were encountered. Even grade 3 toxicities were reported in only 8% of the treatment cycles: hand-foot syndrome (3%), diarrhea (2%), leukopenia (2%) and anaemia (1%).

Response and survival

Two patients (9%, 95% CI: 0-20) achieved CR and 9 (39%, 95% CI: 19-59) PR, for an overall response rate (ORR) of 48% (95% CI: 27-68) (Table 5). Furthermore, 9 patients (39%, 95% CI: 19-59) demonstrated disease stabilisation. Three patients (13%, 95% CI: 0-27) progressed during treatment with capecitabine.

Table 1. Patient and tumor characteristics (n=23)

Characteristic	*n*	*%*
Age (years)		
Median	46	
Range	15-59	
Gender		
Male	14	61
Female	9	39
ECOG performance status		
1	21	92
2	2	8
Histology		
Type I - Keratinizing epidermoid carcinoma	1	4
Type II - Non-keratinizing epidermoid carcinoma	1	4
Type III - Undifferentiated carcinoma of nasopharyngeal type	21	92
Pattern of relapse		
Locoregional (T/N)	17	74
Local relapse (T+)	6	26
Regional relapse (N+)	5	22
Locoregional relapse (T+N+)	6	26
Metastases (M +)	3	13
Locoregional + metastases (T+N+M+)	3	13

Table 2. Capecitabine (2nd, 3rd or 4th line) and type of relapse

Type of relapse	*2nd line Patients, n*	*3rd line Patients, n*	*4th line Patients, n*
Locoregional	8	6	3
Distant metastases	3	-	-
Locoregional and metastases	2	1	-
Total patients (n)	13	7	3
Total patients (%)	56	30	14

Table 3. Treatment characteristics

	n
Number of cycles planned	138
Number of cycles given	104
Number of cycles/ patient	
Median	5
Range	2-6
Reasons for early discontinuation	
Disease progression	3
Hand-foot syndrome grade 3	2
Diarrhea grade 3	2
Patient refusal	1

Table 4. Incidence (% of cycles) of various toxicities

Toxicity	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*	*Total*
Anaemia	29	8	1	0	38
Leukopenia	8	7	2	0	17
Hand-foot syndrome	15	5	3	0	23
Diarrhea	0	1	2	0	3

Table 5. Response to capecitabine chemotherapy

Response	*Patients, n*	*%*	*95% CI*
CR	2	9	0-20
PR	9	39	19-59
SD	9	39	19-59
PD	3	13	0-27
Total	23	100	

Overall response rate 48%, 95% CI: 27-68

As of September 2006, the median follow-up time of the surviving patients was 10 months (range 2-44). Median progression-free survival was 14 months (range 0-44). The actuarial one-year progression-free survival was 53% (95% CI: 24-81) (Figure 1).

Median overall survival was not reached at 18 months, its range being 2-44 months. The actuarial one-year survival was 62% (95% CI: 41-80) (Figure 2).

Discussion

This phase II study reports results on the activity and toxicity profile of capecitabine in patients with recurrent or metastatic NPC. Our data suggest that this agent, used at its standard dosage, appears active as monotherapy in this pretreated patient population. The response rate of 48% observed is higher than previously reported [10] and looks very promising in this setting. It is worth noting that complete responses were seen in previously irradiated areas, a rare finding in the head & neck salvage chemotherapy setting, where the relatively high doses of radiotherapy delivered usually impair the access of anticancer drugs to the target tumor. No toxic deaths and no grade 4 adverse events were reported and toxicity (mainly anemia and hand-foot syndrome) was mild, with grade 3 toxicity encountered in only 8% of the cycles. Less toxicity of capecitabine in NPC was noticed in our series compared with literature data [11,12] in colorectal carcinomas: anemia (38 vs. 80%), diarrhea (3 vs. 55%), hand-foot syndrome (23 vs. 54%). Leukopenia/ neutropenia was in the same range in NPC compared with colorectal tumors (17 vs. 13%) [13-16]. Other toxicities reported in colorectal series were not encountered in our NPC patients: vomiting (27%), appetite loss (26%), stomatitis (25%), fever (18%), oedema (15%), constipation (14%), dyspnoea (14%), pain (12%), headache (10%) [13-16]. However, it should be mentioned that in our study toxicity was assessed at 3-week intervals and the nadir of some of the toxicities might have been missed.

In our series 92% of the patients had UCNT histology (WHO type III) and 4% non-keratinizing epidermoid carcinoma (WHO type II) and all of them had already received chemotherapy as part of their primary treatment. The objective response rate of 48% obtained with capecitabine in our series is higher than the 23.5% response rate previously reported by Chua et al. in a single-institution phase II study done in Hong Kong [10] and in the range of the results reported for cisplatin,

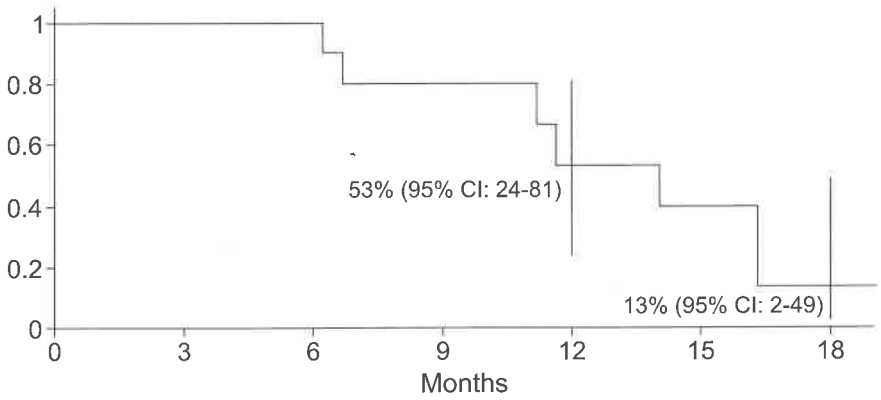


Figure 1. Time to progression with capecitabine in relapsed NPC patients.

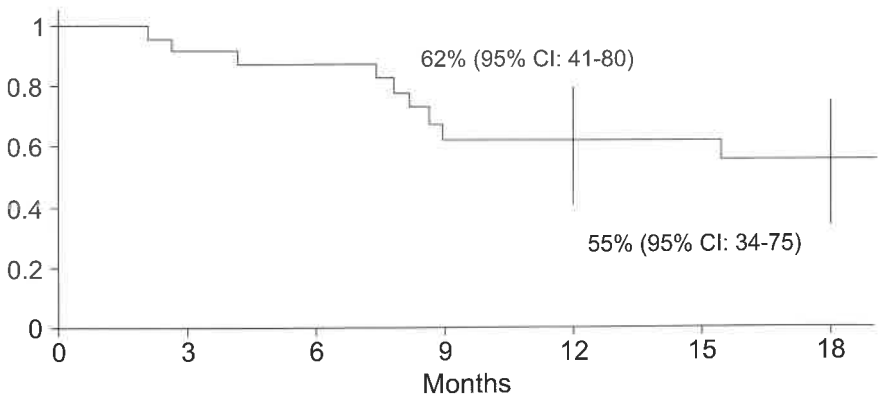


Figure 2. Overall survival with capecitabine in relapsed NPC patients.

5-FU and leucovorin (PFL) combination (56%) and for the paclitaxel/carboplatin combination in various studies (26-75%) [7,8,16-19]. Yeo and coworkers reported a higher response rate (59%) with paclitaxel and carboplatin in a series of 27 patients with undifferentiated (WHO type III) or poorly differentiated (WHO type II) NPC, but only 9 of them (33%) had received prior chemotherapy [18]. Tan et al. [19] reported 75% response rate in metastatic (WHO type III) NPC patients and Leong et al. [9] a response rate of 78% with the triplet paclitaxel/carboplatin/gemcitabine, but in both series all of the patients were chemonaïve. For the paclitaxel/carboplatin combination a better response rate was found with carboplatin at AUC 6 or 7 compared with AUC 5 in various studies in NPC patients [4,5,7,17-19]. Response rate with another combination (paclitaxel, 5-FU and leucovorin) was disappointingly low (12.5%) in a previous series at our institution [20].

The median progression free survival of 14 months with capecitabine in our series compares favorably with the 4.9 months reported by Chua and coworkers [10]. It also compares favorably with the paclitaxel and carboplatin combinations where progression-free survival was 6-7 months and with the 8.1 months reported for the triplet paclitaxel/ carboplatin/ gemcitabine [7-9,18-20].

The actuarial one-year survival of 62% obtained with capecitabine in our series was at least as good as what was reported for paclitaxel and carboplatin (58%) or paclitaxel, 5-FU and leucovorin (48%) in two previous studies at our institution [8,20]. The median overall survival was not reached at 18 months in our series and is superior compared with 7.6 months in a previous capecitabine trial in Hong Kong [10]. It is also superior compared with the median overall survival (11.5-13.9 months) achieved with the paclitaxel/carboplatin combination in studies from Asian centers and from our institution [7,8,17-19], and is probably in the same range with the 18.6 months median overall survival achieved with the triplet paclitaxel/ carboplatin/ gemcitabine in chemonaïve patients [9]. Results with other combinations (paclitaxel, 5-FU and leucovorin; cisplatin and 5-FU; cisplatin, bleomycin and methotrexate or methotrexate alone) were inferior, with a reported median survival of 5.6-7.3 months [20].

It is difficult to interpret the differences between our series and the Hong Kong trial (response rate 48 vs. 23.5%, progression-free survival 14 vs. 4.9 months, median overall survival not reached vs. 7.6 months) [10]. The fact that the median number of cycles administered was 5 in our series compared with only 3 in the Chua et al. trial might be responsible, at least in part, for some differences in results. Racial differences (Caucasian vs. Asian) could also have a role. Finally, the relatively small number of patients in both trials (23 vs. 17) could also explain the dissimilarity in results between the two studies.

We conclude that the use of capecitabine, administered in an outpatient setting, represents a well-tolerated and active treatment option in relapsed or metastatic NPC patients, and deserves further exploration.

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