# Low dose Docetaxel, Carboplatin and Capecitabine in the treatment of recurrent and/or metastatic Head and Neck Cancer (HNC): Results of a Pilot Phase II study

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## Abstract

> Rationale: Platinum-based treatment is the standard of care for patients having Head and Neck Cancer (HNC). Many combination regimens were investigated adding Taxane or 5-FU to Cisplatin or Carboplatin resulting in response rates of 30% to 40%. Combination of Cetuximab these regimens produced interesting results.
> Objective: The primary objective is to assess the efficacy and toxicity of the combination of Docetaxel, Carboplatin and Capecitabine in the treatment of HNC. Results of this pilot phase II trial will serve as a feasibility study in order to assess the possibility of addition of Cetuximab to this combination.
> Patients and Methods: Between January 2002 and August 2004, patients with recurrent or metastatic HNC received the combination of: Docetaxel 25 mg/m2 on days 1 & 8, Carboplatin AUC 2 on days 1 & 8 and Capecitabine 1350 mg/m2 per day for two consecutive weeks, repeated every 21 days.
> Results: Twenty patients have been enrolled. There were 20 % of complete response (4 pts), 30 % (6 pts) of partial response resulting in an overall response rate of 50 % (IC 95%: 27.20 – 72.80 %). The median overall survival was 5.2 months. The major hematological toxicities were Grade 2 and 3 anemia in 12 patients (60 %) and 2 patients (10 %) respectively and febrile neutropenia in 2 patients (10 %). The non hematological toxicities were mainly nausea, vomiting and stomatitis.
> Conclusion:This combination showed good results with acceptable toxicity profile. It warrants to be studied in addition to Cetuximab in metastatic and recurrent Head and Neck Cancer.

## Rationale

Despite surgical resection and postoperative radiotherapy, advanced carcinomas of the head and neck have a 30% rate of recurrence regionally or locally and 25% rate of distant metastasis.
The five year survival rate of patients with advanced carcinomas of the head and neck is 40 %. Chemotherapy for squamous cell carcinoma of the head and neck cancer (HNC) was initially limited to palliative settings. Since the introduction of Cisplatin, HNC is considered chemosensitive Controlled trials have established the association of 5-FU and Cisplatin as the effective regimen especially in induction therapy for locally advanced HNC [1, 2]. In three meta-analyses of updated individual data reported by the MACH-NC Collaborative Group, the authors concluded that chemotherapy (Platinum and 5-FU combination) showed a small significant survival benefit. Indeed, the main meta-analysis of 63 trials (10,741 patients) of locoregional treatment with or without chemotherapy yielded a pooled hazard ration of 0.9 (95% CI 0.85-0.94, $p < 0.0001$) corresponding to an absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy [3].
Thus, alternative regimens with the potential to improve complete response rate, the durability of locoregional control and survival were being investigated.
Docetaxel, a semisynthetic taxoid antineoplastic, was proved to be more effective than Cisplatin in inhibiting the growth of Xenografts of HNC cell lines. In preclinical models, potential synergy was noticed when adding Docetaxel to Cisplatin [4]. Single agent Docetaxel was prospectively evaluated in four phase II trials. The dose of 100 mg/m2 IV every 3 weeks was shown to be an active and generally well tolerated single-agent regimen for locally recurrent or metastatic HNC, with overall response rates ranging from 21% to 42%. In vivo, the promising single agent activity and tolerability of Docetaxel in HNC prompted assessment of Docetaxel plus Cisplatin or plus 5-FU. Overall response rates have ranged from 33 to 42% with Cisplatin and from 24 to 27 % with 5 FU. Phase II trials with the triplet Docetaxel, Cisplatin and 5FU were reported. Different schedules were tested [5-22]. Based on the encouraging efficacy of the combination Docetaxel, Cisplatin and 5FU, this study was designed. Cisplatin is replaced by Carboplatin trying to reduce the renal toxicity of Cisplatin. 5-FU was replaced by Capecitabine allowing oral and easier administration schedule. Lower doses were chosen in attempt to reduce the toxicity of the chemotherapy and ensure better compliance to treatment. Indeed, Docetaxel given at 100 mg/m2 or 75 mg/m2, a significant toxicity in terms of neutropenia was reported in the 3-week schedule, while this was not the case with a weekly schedule including docetaxel at 35 mg/m2 and cisplatin at 25 mg/m2.

Based on the above, the study was designed on January 2002. Results of this pilot phase II trial will be used to assess the possibility of adding Cetuximab to this regimen in order to reach the best efficacy and toxicity profile.

## Patients and Methods

To be included, patients had to meet all the following eligibility criteria: histologically confirmed squamous cell carcinoma of the head and neck, clinically or radiologically bidimensionnally measurable disease. In locally recurrent or metastatic disease previous chemotherapy (excluding Taxanes) as induction or as concurrent to radiotherapy for the primary tumor is allowed after a free interval of more than two years. Patients had to have a life expectancy of more than 3 months, with an Eastern Cooperative Oncology Group of 0 to 2. Additional criteria included adequate bone marrow reserve (white blood cell count [WBC]> 3500/µl, neutrophil count > 1500/µl, and platelet count > 100000/µl), adequate hepatic function (bilirubine and liver enzymes < 2 times the upper limit of normal) and a serum creatinine level < 2 times the upper limit of normal. Were excluded all the patients with prior chemotherapy for primary tumor within 2 year free interval, or

with other prior malignancies than prostatic adenocarcinoma, non melanotic skin cancers and in situ cervical cancer. Additional exclusion criteria were an active cardiac disease necessitating continuous therapy renal dysfunction with creatinine clearance less than 40 ml/min, liver dysfunction defined as conjugated bilirubin > upper limit of normal and liver enzymes > 2 times upper limit of normal . Patients included should not present any evidence of neurological disturbance or cerebral metastases.

Patients were evaluated in a multidisciplinary clinic for confirmation of eligibility, staging and treatment planning. Patients were staged by physical examination according to the criteria established by the American Joint committee on Cancer. Radiologic evaluation was used to document baseline disease and response to therapy in sites not fully assessable by clinical examination. The local ethics committee approved the protocol, and all patients signed informed consent.

## Chemotherapy

Docetaxel (25 mg/m2) given weekly for two consecutive weeks followed by one week rest and delivered as an intravenous infusion over 60 minutes in 250 ml of normal saline. Premedication with 16 mg dexamethasone IV was given before each infusion. Followed the administration of Carboplatin at AUC=2 also given weekly for 2 consecutive weeks followed by one week rest. The AUC is calculated according to Calvert Formula and the GFR calculated or estimated according to Cockroft and Gault formula. Carboplatin is delivered as an intravenous infusion over 60 minutes in 250 ml of normal saline. The patients received also Capecitabine at a dose of 1350mg/m2 given orally on a daily basis for two consecutive weeks followed by one week rest. Day 8 of chemotherapy was omitted in case of grade 4 hematologic toxicity (according to National Common Institute Common Toxicity Criteria). If hematologic toxicity does not recover at D21, the D1 will be held for one week. Subsequent dosages in these cases will be reduced of 20%. If toxicities reappear after the dose reduction patient will be withdrawn from the study. The first evaluation was planned after 3 cycles of treatment. Stable or responding patients continued treatment to complete 6 cycles. Additional chemotherapy cycles for stable or responding patients were left to the physician's discretion. However the treatment was discontinued in case of unexpected toxicity, persistent hematologic toxicity despite dosage reduction and progressive disease as measured according to the World Health Organization.

## Baseline and treatment evaluations

The following tests were evaluated before entry into the study : medical history, physical examination, performance status (ECOG), blood cell count and blood chemistry including bilirubin, aspartate aminotransferase, alkaline phosphatase, creatinine, ECG, CT scanners of the Head and Neck and the chest, abdominal sonography and radionuclide bone scan if indicated.

The blood cell count was repeated before each cycle of chemotherapy. An imaging study of the relevant regions was performed after every three courses of treatment. Standard WHO response criteria were used in the evaluation of tumor response. All Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria.

## Statistical Analysis

The primary endpoint was objective tumor response and the secondary endpoints were Progression free survival (PFS), overall survival (OS). Patients were accrued according to Simon's two-stage Optimal trial design, with an assumption of P0=0.1(the level of no interest), P1=0.3 (the target activity level of interest) and both type I and type II errors of 0.1. The PFS and OS curves were analyzed according to Kaplan –Meier method. OS was measured from start of treatment to the time of death from any cause. PFS was measured from the start of treatment to the first observation of disease progression or death.

## Results

> Patient Characteristics: A total of 20 patients were enrolled in this study. Patient Characteristics: A total of 20 patients were enrolled in this study. Demography and clinical characteristics are summarized in Table 1. The median age was 59 years (range, 46-80). The sex ratio was 17 / 3. Eight patients had locoregional recurrence (40%), 6 had distant metastasis (30 %) and 6 had both (30 %).

> Chemotherapy administration: A total of 82 cycles of chemotherapy was administered. The median number of chemotherapy cycles for the 20 patients was four, with a range of one to 9.

> Toxicity: Maximum hematologic toxicities per person are listed in Table 2. The major hematological toxicity was anemia with 80 % of patients experience it at some grade. One episode of febrile neutropenia was observed. Severe neutropenia (grade 3) was observed in 10 % of the patients. The maximum nonhematologic toxicities are listed in Table 3. These adverse effects were mainly grade 1 or 2 and did not cause any treatment delay or withdrawal. 90% of the patients experienced fatigue and 40 % nausea and vomiting. One patient presented a grade 3 stomatitis. Surprisingly, no hand and foot toxicity was reported.

## Response to treatment

The best overall response rates of the 20 patients are shown in table 4. There was 4 CR (20%), 6 PR (30 %) resulting in an Overall response rate (ORR) of 50 %. The median follow up time of all 20 patients was 50 months. Disease had progressed in 95 % patients with a median PFS of 3.2 months. The median OS was 5.2 months. The Kaplan Meier curves of the PFS and OS are shown in fig 1 and fig 2.

## Discussion

This phase II pilot study was conducted in an attempt to define the safety, the tolerability and effectiveness of the triplet Carboplatin, Capecitabine and Docetaxel in recurrent or metastatic head and neck cancer. This study is published at this moment in order to document scientifically the results of this pilot phase II trial and to serve as a feasibility study in order to assess the possibility of addition of Cetuximab to this combination. The sample size was reduced to 20 patients because of large difficulties of recruitment due to the reluctance of the Lebanese community to treat cancer patients with chemotherapy assuming that their condition is incurable few years ago. Efficacy of this regimen (50% ORR and 10% SD) is favorably comparable to data reported in the literature. It is noticeable that 85 % of patients included in this trial had PS of 0 or 1 which is a good prognosis factor. Toxicity profile is encouraging with specific low rate of Grade 3 / 4 toxicities. Larger conclusion cannot be withdrawn based on the small number of patients with some heterogeneity in the population (PS, previous treatment, etc). However, results are promising and toxicity profile is acceptable especially when palliation is the primary objective of the treatment.

In our study, 12 patients over 20 patients included (60%) had distant metastasis which can explain the lower median overall survival reported in this trial (5.2 months) compared to those reported in Posner et al. and Vermorken et al. trials where patients with distant metastasis were excluded.

In Posner et al. study published in NEJM 2007, a total of 501 patients were randomized to receive either Docetaxel plus Platinum plus 5-FU (TPF) or Platinum and 5-FU (PF) induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin therapy and radiotherapy for 5 days per week. Median overall survival was 70 months vs. 50 months in the TPF arm and PF arm respectively. [23]

In Vermorken et al study published also in NEJM 2007, a total of 358 patients underwent randomization between TPF and PF. Treatment with TPF resulted in a median overall survival of 18.8 months as compared with 14.5 months in the PF group. So as compared with the standard regimen of cisplatin and 5-FU, induction chemotherapy with the addition of Docetaxel significantly improved progression free and overall survival in patients with unresectable squamous-cell carcinoma of the head and neck cancer. [24]

Phase II and III trials adding EGFR inhibition (Cetuximab, Erlotinib, etc) suggest benefit from it. Targeting EGFR in HNC is a rational approach sustained by a large body of evidence that supports the relevance of the target [25 – 33]. Results of a phase III trial comparing Cetuximab plus platinum-based chemotherapy plus 5-FU to platinum-based chemotherapy plus 5-FU alone in Head and Neck Cancer, demonstrated that the introduction of Cetuximab significantly improved survival. Median Overall survival was improved from 7.4 months in the Chemotherapy alone group to 10.1 months in the group that received chemotherapy plus Cetuximab

(hazard ratio for death, 0.80; 95% CU, 0.94 to 0.99; p=0.04). It is noticeable that around 47% of patients had metastatic disease and 38% received prior chemotherapy. [34]

Specific attention should be made to some marker for predicting tumor reponse to anti-EGFR therapy such as EGFR expression, RAS mutation, etc. Thus, the addition of Cetuximab to the combination of Docetaxel, Carboplatin and Capecitabine is a valid option and warrants to be investigated in controlled and randomized trials.

Adding targeted therapy to already consolidated polychemotherapy may display very high toxicity, thus underlining the need not to use these drugs outside clinical trials. Indeed, The National Comprehensive Cancer Network (NCCN) emphasizes in its practice guidelines for the treatment of Head and Neck Cancers that participation in clinical trials is preferred for all patients with advanced Head and Neck cancer. For patients with unresectable disease, such trials testing altered fraction radiotherapy schedules, concurrent chemoradiotherapy, and novel radiosensitizers. For patients with recurrent disease not amenable to curative therapy and patients with metastatic disease, studies include trials of new agents and re-irradiation.

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## Tables

Table 1. Patient characteristics

| Parameters | No. of patients | % of patients |
|---|---|---|
| n | 20 | --- |
| Median age | 59 | --- |
| Age range | 46- 80 | -- |
| Sex Ratio: Male / Female | 17/3 | 85% / 15 % |
| **Performance status** | | |
| PS = 0 | 7 | 35% |
| PS = 1 | 10 | 50% |
| PS = 2 | 3 | 15% |
| **Sites of failure** | | |
| Locoregional relapse | 8 | 40% |
| Distant relapse | 6 | 30% |
| Both | 6 | 30% |
| **Location of primary tumor** | | |
| Larynx | 16 | 80 |
| Oropharynx | 0 | 0 |
| Hippopharynx | 1 | 5 |
| Oral cavity | 1 | 5 |
| Mandibule | 2 | 10 |
| **Previous therapy of the primary tumor** | | |
| None | 4 | 20 |
| Surgery alone | 6 | 30 |
| Surgery and RT | 6 | 30 |
| CT and RT | 2 | 10 |
| CT, RT and surgery | 1 | 5 |
| CT alone | 1 | 5 |

*Abbreviations: ECOG, Eastern Cooperative Group; RT, radiotherapy; CT, Chemotherapy.*

Table 2: Maximum Hematologic toxicities

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Neutropenia | 2 (10%) | 1 (5%) | 2 (10%) | 0 (0%) |
| Thrombocytopenia | 0 (0%) | 2 (10%) | 0 (0%) | 0 (0%) |
| Anemia | 3 (15%) | 12 (60%) | 1 (5%) | 0 (0%) |

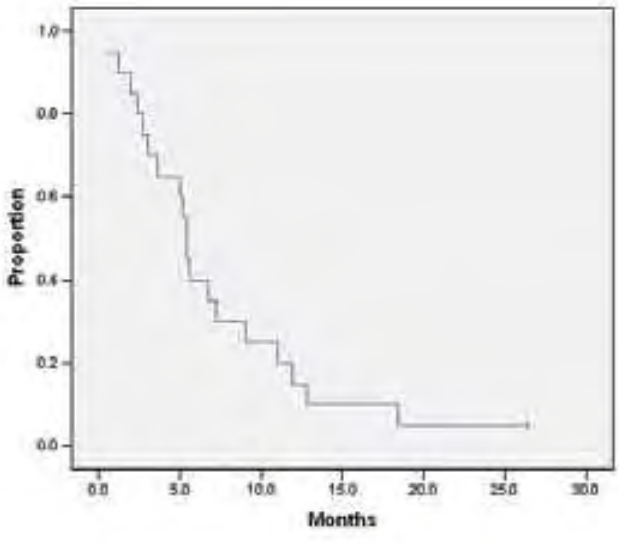
Table 3: Maximum non hematological toxicities

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Nausea | 4 (20%) | 2 (10%) | 2 (10%) | 0 (0%) |
| Vomiting | 4 (20%) | 2 (10%) | 2 (10%) | 0 (0%) |
| Anorexia | 3 (15%) | 4 (20%) | 0 (0%) | 0 (0%) |
| Stomatitis | 5 (25%) | 1 (5%) | 1 (5%) | 0 (0%) |
| Diarrhea | 2 (10%) | 3 (15%) | 1 (5%) | 0 (0%) |
| Fatigue | 10 (50%) | 6 (30%) | 2 (10%) | 0 (0%) |
| Alopecia | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) |
| Hyperglycemia | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Neuropathy | 1 (5%) | 0 (0%) | 0 (0%) | 0 (0%) |

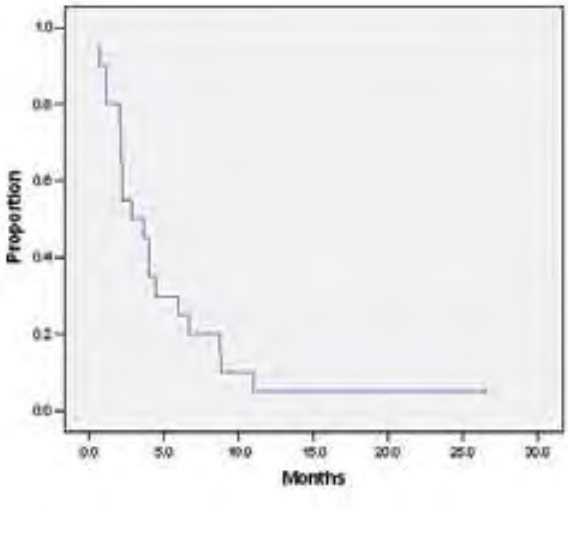
Table 4: Response to treatment

| Best Overall Response | No. of patients | % of patients |
|---|---|---|
| CR | 4 | 20 % |
| PR | 6 | 30 % |
| ORR | 10 | 50 % |
| SD | 2 | 10 % |
| Clinical Benefit | 12 | 60 % |
| PD | 8 | 40 % |

## Figures




Survival (months)
Fig 1: overall survival in all patients




Progression disease free (Months)
Fig 2: progression disease free survival.