Toxicity of Induction Chemotherapy with Docetaxel, Cisplatin and 5-Fluorouracil for Advanced Head and Neck Cancer

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ABSTRACT: **Background:** The role of induction chemotherapy in advanced squamous cell carcinoma of the head and neck (SCCHN) is under constant debate. Surgery, radiotherapy, chemotherapy, and targeted therapies are part of the treatment strategy in these patients, but their sequence remains to be defined.

Objectives: To evaluate the feasibility of induction chemotherapy with docetaxel-cisplatin-5-flurouracil (TPF) followed by external beam radiotherapy (EBRT) with concomitant chemotherapy or cetuximab (ERT) in the treatment of patients with advanced SCCHN.

Methods: We reviewed the data of all patients with advanced SCCHN, stage III and IV, treated in 2007–2010. Tolerability was assessed and scored according to the proportion of patients completing the planned study protocol. Toxicity was scored using the U.S. National Cancer Institute Common Toxicity Criteria (version 4) for classification of adverse events.

Results: The study included 53 patients. TPF was initiated at a reduced dose in 13 patients (25%). Twenty-two patients (41.5%) received primary prophylaxis with granulocyte colony-stimulating factor (GCSF) and 42 (77%) completed treatment according to schedule. During the induction phase one patient (2%) died and 24 (45%) had one or more grade 3-4 complications. The number of patients who developed neutropenia was lower in the group that received primary GCSF prophylaxis. Secondary dose reductions were required in 21% of the patients.

Conclusions: Induction TPF was associated with grade 3-4 toxicity. Prophylaxis with GCSF should be part of the treatment regimen.

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KEY WORDS: squamous cell carcinoma of the head and neck (SCCHN), chemotherapy, radiotherapy, induction therapy (ICT), docetaxel, cisplatin, 5-fluorouracil (5-FU)

The role of induction chemotherapy in advanced squamous cell carcinoma of the head and neck is under constant debate. Surgery, radiotherapy, chemotherapy, and targeted therapies are part of the treatment strategy in these patients, but their sequence remains to be defined. Organ preservation has become the standard of care for patients with advanced SCCHN [1-3]. However, the organ preservation approach should not compromise loco-regional control and overall survival. The introduction of taxanes to ICT has invigorated attention to the ICT approach. A triplet induction regimen using docetaxel-cisplatin-5-flurouracil was more active than the doublet (cisplatin and 5-FU), which translated to survival benefit [4-6]. A possible explanation for advantage in survival is the early treatment of distant disease in advanced SCCHN. Nevertheless, since published studies comparing TPF-ICT versus concomitant chemoradiotherapy are lacking, CRT is still the standard of care.

A major concern of both treatment strategies is treatment-induced toxicity. Toxicity may become a significant obstacle to achieving loco-regional control and survival. Acute side effects may include pain, dermatitis, mucositis, dysphagia, anorexia, and hematological toxicity [4-7]. Toxicity often leads to treatment interruption, which may result in accelerated repopulation of malignant cells, treatment failure, and/or mortality. Moreover, toxicity due to ICT may prevent the patient from proceeding or completing a full course of subsequent CRT, which is the most important component in the treatment of non-metastatic disease [3].

In recent years, the addition of cetuximab to radiotherapy has become an acceptable treatment [6]. This was possible due to over-expression of epidermal growth factor receptors in patients with SCCHN. The rationale of targeted treatment

SCCHN = squamous cell carcinoma of the head and neck
ICT = induction chemotherapy
5-FU = 5-flurouracil
CRT = concomitant chemoradiotherapy

was to retain activity while reducing toxicity of concurrent chemoradiotherapy [6].

The aim of this study was to evaluate the feasibility of ICT with TPF followed by external beam radiotherapy with concomitant chemotherapy or cetuximab (concomitant cetuximab and external beam radiotherapy, ERT) in the treatment of patients with advanced SCCHN.

PATIENTS AND METHODS

We prospectively collected data of all patients with advanced SCCHN, stage III and IV, without evidence of distant metastasis at the time of diagnosis, who were treated at Rambam Health Care Campus in 2007–2010. The study was approved by the institutional review board. Patients were treated with TPF as ICT, followed by either EBRT and chemotherapy or EBRT and cetuximab. Data recorded included patient demographics, gender, age, site of primary disease, stage (according to the American Joint Committee on Cancer TNM staging system), and treatment protocol. Toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria version 4.

Prior to treatment, all patients underwent panendoscopy with numerous biopsies and dental examinations. Systemic evaluation included a computed tomography scan of the neck and chest or FDG-PET/CT (fluorodeoxyglucose-positron emission computed tomography). The therapeutic strategy was decided by a multidisciplinary-multicenter team consultation that included medical and radiation oncologists and head and neck, maxillofacial, and plastic surgeons. When indicated, patients underwent pretreatment evaluation for percutaneous endoscopic gastrostomy insertion by a gastroenterology team. Between ICT cycles the patients were repeatedly evaluated by a dietitian, specialized nurse and dedicated oncologist.

TPF was given during hospitalization as previously reported [5]. In brief, the regimen consisted of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 given intravenously on day 1 and 5-FU 750 mg/m^2/day given as a continuous infusion on days 1–5. Cycles were repeated every 3 weeks.

Premedication with dexamethasone was started 12 hours prior to docetaxel. Antiemetic therapy usually included serotonin with 5-HT$_3$ receptor antagonist and substance P antagonists, and aprepitant and hydration were routinely given.

Primary prophylaxis with granulocyte colony-stimulating factor was given at the discretion of the physician (relating to comorbidity and age, for example). Prophylactic antibiotics (with ciprofloxacin) starting on day 5 of each cycle for 10 days were given as previously suggested [5].

The combined treatment phase included EBRT of the primary tumor and involved lymph nodes as indicated from the disease stage. Radiation was delivered over 7 weeks using conventional fractionation of 5 days a week for a total dose of 66–70 Gy to the gross tumor volume delivered by fractions of 2 Gy per day, and 50 Gy for microscopic disease. Most of the patients received intensity-modulated radiotherapy.

Concomitant treatment of CRT included intravenous cisplatin at a dose of 40 mg/m^2 weekly. Concomitant treatment of ERT was given with an initial loading dose of 400 mg/m^2 of cetuximab before EBRT and 250 mg/m^2 weekly thereafter. Chemotherapy or targeted biologic therapy was given once weekly and was planned for seven to eight cycles (until completion of EBRT). Patients were evaluated for side effects and clinical response before each cycle of chemotherapy (ICT or concomitant treatment). Evaluation included laboratory tests (blood count and biochemistry) performed on day 1 of each chemotherapy cycle and once a week prior to chemotherapy or cetuximab therapy, plus an interview and a physical examination by a nurse and a radiation oncologist. The decision for treatment modification, such as interrupting treatment or reducing the dosage, was dictated by the clinical judgment of the head and neck radiotherapy team.

Clinical and radiological evaluation of response was performed after patients completed ICT and prior to concomitant treatment (CRT or ERT). Response was recorded according to RECIST 1.1 criteria [8].

The primary endpoints of the study were treatment tolerability and toxicity. Tolerability was assessed and scored according to the proportion of patients completing the planned study protocol, and toxicity of the treatment was assessed during the induction chemotherapy by means of the NCI Common Toxicity Criteria (version 4) for classification of adverse events.

RESULTS

Induction TPF was given to 53 patients between March 2007 and June 2010. Patients' characteristics are presented in Table 1. Advanced disease of the primary site (T3-T4) was present in 87% of the patients and advanced nodal metastasis (N2-N3) in 53%.

INDUCTION PHASE

The initial 20 patients were treated with two cycles of TPF-ICT for administrative reasons. All other patients were scheduled for three to four cycles of TPF-ICT. The number of cycles ranged from one to four, with a median of two cycles. More than 80% of patients received two or more cycles of TPF. Forty-two patients (77%) completed treatment according to the schedule. Toxicity associated with ICT is summarized in Table 2.

One patient (2%) died during ICT. This patient had severe comorbidities, including hemiparesis due to cerebral

TPF = docetaxel-cisplatin-5-flurouracil
EBRT = external beam radiotherapy
ERT = concomitant cetuximab and external beam radiotherapy
NCI = National Cancer Institute

Table 1. Patient characteristics: induction phase

No. of patients	53
Mean age (range, yrs)	59 (34.5–81)
Gender	
Male	37 (70%)
Female	16 (30%)
Primary tumor site	
Larynx-hypopharynx	20 (38%)
Oral cavity	18 (34%)
Oropharynx	10 (18%)
Other	5 (10%)
T classification	
T1	1 (2%)
T2	5 (10%)
T3	21 (40%)
T4	25 (46%)
Unknown	1 (2%)
N classification	
N0	15 (28.5%)
N1	10 (18%)
N2	24 (45%)
N3	3 (5.5%)

Values are presented as no. (%)

Table 2. Grade 3-4 toxicity associated with induction chemotherapy with TPF

Type of toxicity	No. of patients (%)
Mucositis	14 (26%)
Diarrhea	13 (24.5%)
Nausea/vomiting	5 (10%)
Neutropenia	10 (18.8%)
Neutropenic fever	7 (13%)
Lethargy	12 (22.6%)
Electrolyte imbalance	13 (24.5)
Anemia	8 (15%)
Thrombocytopenia	2 (4%)
Renal failure	2 (4%)

infarction, and severe lung disease. She developed early neutropenia on the third day of the first chemotherapy cycle and died a few days later due to respiratory failure. Another patient developed acute coronary syndrome during 5-FU infusion. Treatment was terminated and the patient was given CRT 2 weeks later. Fatigue was reported by 12 patients; in one case it was severe and prolonged and necessitated treatment delay.

TPF was initiated in reduced doses in 13 patients (25%) considered to be at high risk for toxicity. Dose reductions in subsequent cycles were required in another 11 patients (21%) due to toxicity. The 5-FU dose was reduced in cases of severe diarrhea and/or mucositis. All three chemotherapy drugs were reduced in cases of bone marrow suppression that occurred despite GCSF prophylaxis.

Table 3. Post-induction treatment: patient characteristics

	CRT	ERT	EBRT
No. of patients	24	16	5
Median age (yrs)	58	62	68
T3-T4 classification (%)	90	80	100
N2-N3 classification (%)	65	60	33

CRT = concomitant cisplatin-radiotherapy, ERT = concomitant cetuximab-radiotherapy, EBRT = external beam radiotherapy alone

GCSF PROPHYLAXIS

Neutropenic fever that required intravenous antibiotics developed in 2 of 22 patients (9%) who received primary prophylaxis with GCSF compared to 5 of 31 (17%) who did not receive GCSF. Duration of neutropenic fever was short (2 days) in the former group compared to the latter with an average of 5 days hospital stay. None of these episodes was associated with a documented bacterial infection.

Grade 3-4 neutropenia without fever developed in 10 patients (10/31, 32%) in the non-GCSF group; the next chemotherapy cycle was delayed in five of them. None of the patients in the GCSF group developed grade 3-4 neutropenia.

EARLY-RESPONSE RATE (AFTER ICT)

The overall early response rate (after ICT) was observed in 49 patients as follows: complete response in 19 (38.7%) and partial response in 26 (53%). Two patients (4%) had stable disease and the disease progressed in two (4%).

CONCURRENT TREATMENT PHASE

Patients' characteristics are summarized in Table 2. Only 45 (85%) received concurrent treatment. The median number of concurrent cycles was 3.5 (range 1–6) in the CRT arm and 5 (range 1–7) in the ERT arm. With regard to grade 3-4 toxicities during the combined treatment, 50% had mucositis and 45% had dermatitis. No grade 3-4 neutropenia was observed.

TREATMENT INTERRUPTION

Twenty-nine patients (76%) had the initially planned number of TPF-ICT treatments. EBRT was given to 85% (45/53). Of these, 5 patients were treated with EBRT alone, 24 with CRT, and 16 with ERT [Table 3]. Of the patients treated with EBRT, 91% completed the total planned dose and 42% had an interruption during the delivery of the irradiation [Table 4].

GCSF = granulocyte colony-stimulating factor

Table 4. Patients completing treatment protocol

	Initial no. of patients	Completed treatment	Treatment interruption
ERT	16	16	8
CRT	24	22	7
EBRT	5	1	4

CRT concomitant cisplatin-radiotherapy, ERT = concomitant cetuximab-radiotherapy, EBRT = external beam radiotherapy alone

OROPHARYNGEAL FUNCTION

PEG insertions were performed in 16 patients who suffered from carcinomas arising from the oropharynx and hypopharynx. All patients resumed satisfactory function shortly after completion of treatment and the PEG was removed.

DISCUSSION

Locally advanced SCCHN is an aggressive disease with a poor prognosis. After radical surgery and adjuvant CRT, most patients develop loco-regional failure or distant metastasis, with 5 year survival estimated at approximately 33% [9]. Induction chemotherapy with cisplatin and 5-FU was found to significantly improve survival rate at 5 years compared to standard EBRT and surgery in patients with locally advanced disease which enables larynx preservation as an option. However, after the publication of a meta-analysis by Pignon et al. [3], CRT has become the standard of care. The benefit of adding chemotherapy in Pignon's meta-analysis was due to its effect on deaths related to SCCHN, with no effect on non-cancer deaths. The benefit of two types of ICT (TPF versus cisplatin-5-FU) were compared in large phase 3 trials, which demonstrated that adding docetaxel to the induction regimen improved 5 year survival rates and/or organ preservation [4,5,7,10].

A major concern in all induction treatment protocols is the relatively high rates of toxicity. Posner and co-authors [4] reported that neutropenia grade 3-4 was significantly higher in the TPF group in up to 83% of the patients, compared to up to 77% of the patients in the study by Vermorken and team [5]. In two studies [5,7] the ICT doses were similar to those used in our study, but they had higher rates of neutropenia (with or without fever). However, neither study used GSCF for prophylaxis. In our study, neutropenia rates following ICT were lower, 18%; however, 22 patients received primary GCSF. Despite prophylaxis with GCSF and antibiotics, the rate of neutropenic fever was 13%. There were no cases of neutropenic infection.

A retrospective analysis by Buiret et al. [11] reported the results of ICT with TPF and sequential ERT in patients with advanced SCCHN. The study included 46 patients and primary prophylaxis with GCSF. Neutropenia was noted only in the first cycle of ICT in 6.5% of the patients. Both Buiret's results and the present study demonstrate the importance of the prophylactic use of GCSF in these patients.

The number of patients who developed mucositis was higher in our study (4.6%–21%) compared to others [4,5] versus none in Buiret's study [11]. However, our mucositis group included patients with esophagitis and significant dysphagia. Moreover, our study was performed in a single center; all patients were evaluated by the same physician, and all patients were hospitalized during the administration of treatment. This may have contributed to the higher rate of complications in our study.

The rates of diarrhea were significantly higher than reported by other studies, even though the doses of 5-FU were the same. In 25% of our patients the initial TPF doses were reduced due to comorbidities or age. The rates of renal failure were lower in our study than reported by others [11].

The rates of mucositis rose during concomitant treatment in up to 50% of our patients, leading to treatment interruptions, whereas others reported lower rates of mucositis during CRT [4,5] or ERT [11]. We failed to record in which group the mucositis was more significant (CRT or ERT) in our study. However, the number of ERT cycles was greater than CRT cycles, indicating that ERT is better tolerated after TPF-ICT. The EBRT-only group comprised patients who had barely managed the ICT and most patients did not complete the planned EBRT [Table 4]. This subgroup of patients may be managed best with EBRT without ICT.

When cetuximab was first introduced into the treatment regimen of SCCHN, there were great hopes that the rates of mucositis in concomitant treatment would be lower. However, later studies indicated that mucositis was not trivial when ERT was applied [12]. Argiris and colleagues [13] reported that up to 54% of patients suffered from oral mucositis when cetuximab, cisplatin and EBRT were given concomitantly.

The addition of ICT may compromise the course of CRT, but a greater concern is whether the addition of docetaxel adds significant toxicity that may result in treatment delay and interruptions. A phase II trial compared PF chemoradiotherapy alone versus three cycles of TPF-ICT before CRT indicated that TPF-ICT improved clinical response and did not compromise subsequent CRT [14]. The incidence of hematological and non-hematological toxicities was similar between the groups [14].

Patients who suffer from locally advanced oropharyngeal, hypopharyngeal or laryngeal cancer are candidates for treatment with TPF-ICT. ICT may serve to reduce tumor load, treat potential distant disease, allow more time for

PEG = percutaneous endoscopic gastrostomy

PF = cisplatin-5-FU

radiotherapy treatment planning, and enable "observation" of the aggressiveness of the disease as a "chemoselection" (progressive, stable or responsive disease during ICT).The current study shows a high overall response rate to the ICT phase, with a rapid resolution of symptoms in some patients after the first cycle of ICT. However, the role (if any) of ICT in the treatment of advanced SCCHN is not established as ICT-related toxicity leads to interruption of the subsequent CRT, which is currently considered the most important component in the treatment of non-metastatic disease.

The aim of the current study was to evaluate the toxicity of ICT. Recurrence and survival were not part of the primary endpoints of the study. Recurrence rate and survival will be evaluated in a later work.

There are several flaws to the study: the patient group was small and this was a retrospective unicenter study. Our results were less favorable (except for neutropenia) than those of previous studies, even though most of the patients received antibiotics and GCSF as prophylaxis. All patients in this study were evaluated by the same investigator and received treatment by the same team. Although our results were less favorable, TPF-ICT is a reasonable treatment option in advanced SCCHN and its toxicity is relatively manageable. The patients should be selected carefully: they should have a good performance status, no contraindication to chemotherapy, and a high tumor load. A poor selection of patients may lead to suboptimal treatment and toxicity and compromise the feasibility of CRT. It is imperative that this treatment is given by a multidisciplinary team in a tertiary medical center. Reassessment of these patients between cycles is an integral part of the treatment to avoid severe toxicity and compromising the course of CRT. More studies are needed to evaluate long-term survival and toxicity of TPF-ICT.

CONCLUSIONS

Concurrent chemoradiation is still considered the standard approach for the treatment of locally advanced SCCHN. However, ICT with TPF may be an effective alternative in selected patients with locally advanced SCCHN. Prophylaxis with GCSF should be part of the treatment regimen.

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"An imbalance between rich and poor is the oldest and most fatal ailment of all republics"

Plutarch (46-120 AD), Greek historian, biographer and essayist

"Moral certainty is always a sign of cultural inferiority. The more uncivilized the man, the surer he is that he knows precisely what is right and what is wrong. All human progress, even in morals, has been the work of men who have doubted the current moral values, not of men who have whooped them up and tried to enforce them. The truly civilized man is always skeptical and tolerant, in this field as in all others. His culture is based on 'I am not too sure'"

H.L. Mencken (1880-1956), American journalist, essayist, magazine editor, satirist and critic of American life and culture