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A Phase II Trial of Concurrent Paclitaxel, Carboplatin and Radiotherapy in Stage III/IV Resectable Cancer of the Oral Cavity and Oropharynx

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Introduction

In the treatment of head and neck cancer chemotherapy used to be limited to metastatic or recurrent settings. During the last twenty years the addition of chemotherapy to aggressive local treatment has been investigated to overcome high local relapse rates. Recent meta-analysis have confirmed data of randomized trials of combined modality treatment concepts and identified the advantage in treatment outcome for patients with concomitant chemoradiotherapy (Munro 1995, El-Sayid et al. 1996, Bourhis et al. 1998). Many chemotherapeutic agents have been used as radiation sensitizers, including platinum compounds, bleomycin, mitomycin, and antimetabolites such as methotrexate and 5-fluoro-uracil. Taxane have been the focus of several multi-modality studies combining chemotherapy and radiotherapy (Aisner et al. 1995, Hoffmann et al. 1996, Chougule et al 1997, Vogt et al. 1998). The efficacy and feasibility of a Paclitaxel/Carboplatin combination with simultaneous radiotherapy could be demonstrated in phase I-II trials (Tab.1).

	pts	operability	Regimen	Response
Chougule (1997)	34	operable	Paclitaxel 60mg/m ^{2} Carboplatin AUC 1 Radiation 45Gy	CR 73% PR 23% pCR 71% (PT) pCR 85% (LN)
Chougule (1997)	16	inoperable	Paclitaxel 60mg/m ^{2} Carboplatin AUC 1 Radiation 72Gy	CR 57% PR33%
Haas (1999)	60	inoperable	Paclitaxel 45mg/m ^{2} Carboplatin 100mg/m2 Radiation 72Gy	CR 82% PR 11%

Tab. 1

Both Paclitaxel and Carboplatin have demonstrated high single agent activity in head and cancer as well as radiosenzitizing effects (Hoffmann et al.1996, Leonard et al.1997). Paclitaxel causes a enhancement of the rate and yield of microtubular assembly and prevents microtubular depolimerisation, therefore acting as a mitotic inhibitor in the radiation-sensitive G2/M-phase. Based on documented excellent radiosensitization effects, a prospective phase II trial was initiated using Paclitaxel (P) and Carboplatin (C) with concurrent conventional fractionated radiotherapy followed by surgery of the primary tumor and regional neck nodes.

Methods

Patients were eligible for this study if they met the following criteria: histologically confirmed squamous cell carcinoma of the oral cavtiy or oropharynx; resectable stage III and IV disease; ECOG performance status <2; no tumor-specific pretreatment; no major impairment of liver, kidney, bone marrow, lung, or cardiovascular functions. Staging procedures consisted of careful clinical investigation with tattoowing of the resection margins under general anesthesia, neck sonography, computed tomography of the primary lesion and the neck, chest x-ray. The extent of the disease was defined according to the TNM system.
Radiotherapy was applied using a conventional fractionated protocol of 5 x 2,0 Gy/week to a total dose of 40Gy with 6-MeV photons. Using standard premedication Paclitaxel 40mg/m2 was administered as a weekly continous 1-hour infusion in weeks 1-5, followed by Carboplatin AUC 1,5 continous infusion over 30 minutes. Colony-stimulating factors were given only in instances of severe neutropenia with documented infection. Toxicity was grade according to the NCI Common Toxicity Criteria (CTC); and response was assessed according to WHO standards.
Surgery of the primary tumor followed within four weeks after completion of chemoradiation. Resection of the tumor, a suprahyoidal or complete functional neck dissection was performed according to DÖSAK criteria. The mucosal defects were reconstructed in most cases using a fasciocutaneous radial forearm flap.
This study was approved by the ethics committee of our institution. Written informed consent was required from all patients. All patients underwent repeated clinical examination during treatment for identification of response and acute reactions.

Results

From 5/98 to 10/99 twenty-eight patients (23 males, 5 females) with stage III (6 pts.) and stage IV (22 pts.) desease were enrolled. The mean age was 54 years (range 40-71). Six patients had squamous cell carcimona of the oropharynx and twenty-two patients of the oral cavity.
A total of 115 cycles of chemotherapy was administered to the patient population. Patients data of this ongoing trial are summarized in Tab. 2.

Patient characteristics	
Treatment period:	5/98 - 10/99
	No of pts
Total	28
Female	5
Male	23
Tumor site:	
Oral cavity	22
Oropharynx	6
Median age	54 yrs (range 40-71)
T-Stage:	
T1	0
T2	6
T3	9
T4	13
N-Stage:	
N0	5
N1	10
N2	13
N3	0
Stage III	6
Stage IV	22

Tab. 2

Twenty-seven patients were evaluable for toxicity and response (Tab.3). One early death was reported due to septic neutropenia. Clinical response was as follows: CR (14/27 52%); PR (13/27 48%).

Response rates	
evaluable:	27/28 pts
CR	52% (14/27)
PR	48% (13/27)
pCR	44% (10/23)
pPR	56% (13/23)

Tab. 3

CTC grade 2 or 3 mucosistis occured in all patients. Hematologic toxicity was as follows: hemoglobin CTC grade 3 (14%), leukocytes CTC grade 1 (24%), grade 3 (33%), grade 4 (10%), thrombocytes CTC grade 2 (10%), grade 3(14%).

Acute organ toxicity (CTC)		
	Mucosa	
	weeks 1-2	weeks 3-4
grade 0	8%	0%
grade 1	63%	8%
grade2	29%	63%
grade3	0%	29%
	Skin	
	weeks 1-2	weeks 3-4
grade 0	54%	0%
grade 1	42%	63%
grade 2	4%	33%
grade 3	0%	4%

Tab. 4

Major non-hematologic toxicity was mucositis and dermatitis (Tab.4).
Median value of leucocytes, hemoglobin, and thrombocytes are shown in Fig.1a-c. Twenty-three patients were evaluable for pathologic response after surgical resection. Pathological response was as follows: pCR (10/23 44%); pPR(13/23 56%).
With a median follow-up of 10 months the 1-year-survival is 88% (Tab.5)

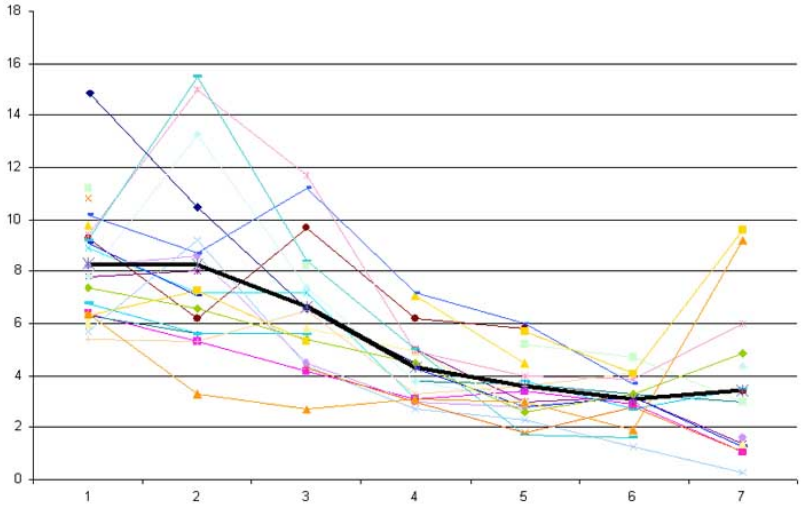

Fig. 1a: Leucocytes

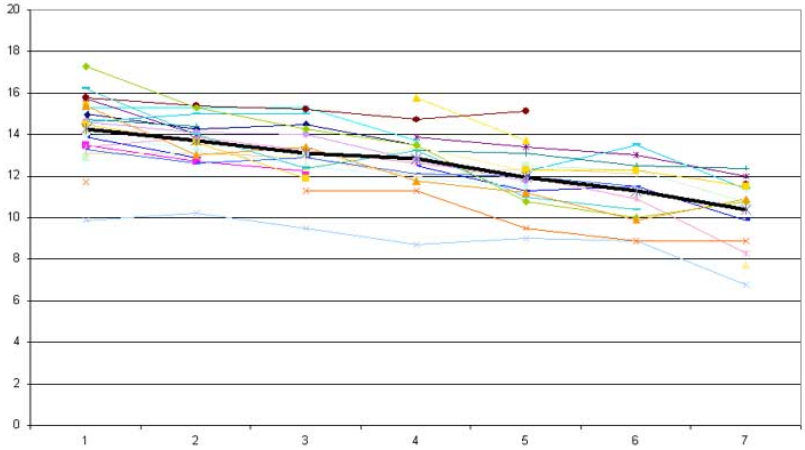

Fig. 1b: Hemoglobin

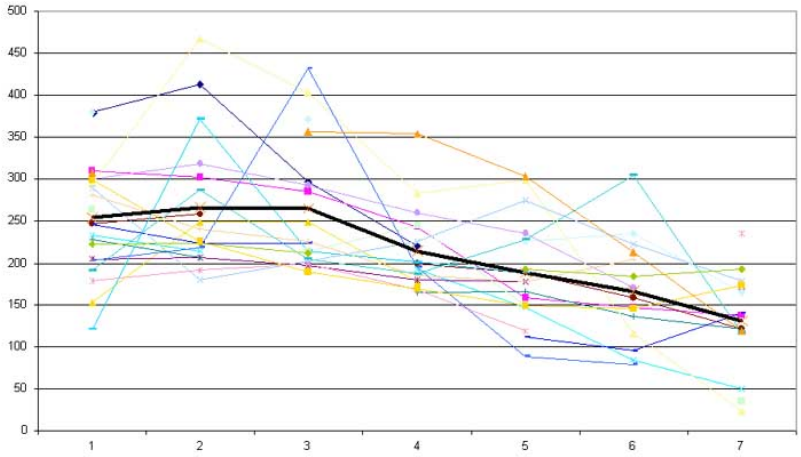

Fig. 1c: Thrombocytes

Follow up		
Median follow-up	10 months	range 5 - 20 Mo
1-year-survival	88%	
local recurrence (neck node)	1	after 4 months
treatment-related death	1	septic neutropenia
post-operative death	1	pneumonia

Tab. 5

Conclusion

The prognosis of advanced squamous cell carcinoma of the head and neck remains poor. Concurrent P/C and radiotherapy resulted in excellent clinical and pathological response rates in advanced stage disease (pCR 44%, pPR 56%). Mucositis was the most common and significant toxicity. The treatment can be performed on outpatient basis. The present phase II trial preceeds a randomized study of the DÖSAK Cooperative Group.

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This poster was submitted by Christian Küttner MD DDS.

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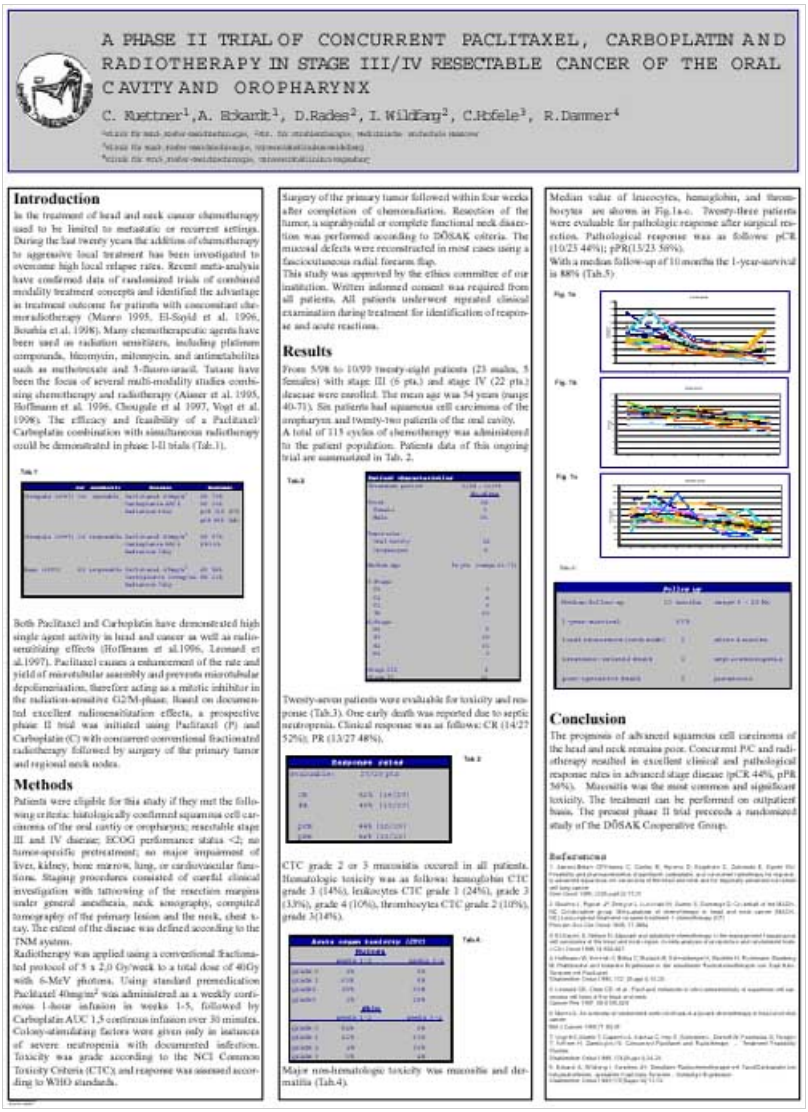

A PHASE II TRIAL OF CONCURRENT PACLITAXEL, CARBOPLATIN AND RADIOTHERAPY IN STAGE III/IV RESECTABLE CANCER OF THE ORAL CAVITY AND OROPHARYNX

C. Kuettner[1], A. Eckardt[1], D. Rades[2], I. Wildfang[2], C. Hofele[3], R. Dammer[4]

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Fig. 1a

Fig. 1b

Fig. 1c

Tab.5

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