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# A randomized phase III multicenter trial of neoadjuvant docetaxel (Taxotere) plus cisplatin plus 5-fluorouracil (TPF) versus neoadjuvant cisplatin plus 5-fluororuacil (PF) in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN): final analysis of EORTC protocol 24971.


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## BACKGROUND

The combination of cisplatin and infusional 5-fluorouracil (5-FU) (PF) represents the current standard neoadjuvant chemotherapy in locally advanced SCCHN, if so indicated prior to locoregional treatment (Ref 1). It induces high response rates, but overall did not show a major impact on survival. However there are suggestions that it may have an impact in patients with unresectable disease (Ref 2-3). To improve the efficacy of the standard PF treatment, several new agents has been used in combination, most extensively taxanes. Several phase II studies and two randomized phase III trials suggested improved efficacy of neoadjuvant chemotherapy by adding taxanes to the standard regimen. (Ref 4) This report is the final analysis of EORTC 24971 trial comparing the addition of docetaxel (Taxotere®) TPF with the standard PF treatment.

## METHODS

**Study design and treatment** (figure 1)

Eligible patients:

- 18 to 70 years of age
- newly histologically or cytologically proven stage III or IV inoperable squamous cell carcinoma of the head and neck
- WHO performance status ≤1 or less
- no evidence of distant metastases
- primary tumor sites: oral cavity, oropharynx, hypopharynx and larynx.

  (excluded: tumours of the nasopharynx, the nasal and paranasal cavities)

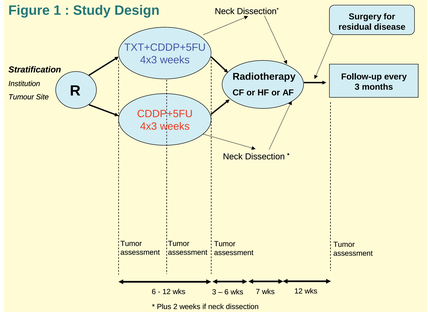
**Randomization: (at the EORTC Data Center)**

- Stratification according to:
  - o primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx)
  - o treatment center

**Statistical design**

The primary endpoint was progression-free survival. Main secondary end points were clinical response rate before and after radiotherapy, overall survival, full toxicity profile and the quality of life. This study had 85 % power at a significance level of 5% to detect a 50 % increase in median PFS (10 mths vs 15 mths, HR= 0.67), assuming that 260 events occurred. All analyses were conducted on an ITT basis.

**Figure 1 : Study Design**




PF : Cisplatin 100 mg/m2 over 1 h on Day 1, 5-FU 1000 mg/m2/day for 5 days, every 3 weeks for 4 cycles. Treatment discontinued in case of progressive disease, unacceptable toxicity, or refusal; dose modifications allowed in case of predefined toxicities.

TPF : Docetaxel 75 mg/m2 over 1 h on Day 1, Cisplatin 75 mg/m2 over 1 h on Day 1, 5-FU 750 mg/m2/day for 5 days, every 3 weeks for 4 cycles.

RT: Locoregional radiotherapy (conventional fractionation or accelerated/ hyperfractionated regimen) over 7 weeks within 4–7 weeks of chemotherapy. cTotal dose: 66–70 Gy (conventional), 70 Gy (accelerated), 74 Gy (hyperfractionated); surgery permitted before (neck dissection) or 3 months after radiotherapy (residual disease), at discretion of investigator.

Docetaxel premedication included dexamethasone and ciprofloxacin; for cisplatin included hydration and antiemetics. Primary prophylaxis with granulocyte colony stimulating factor (G-CSF) was not allowed; secondary G-CSF prophylaxis permitted if indicated.

## RESULTS

From April 1999 until March 2002, 358 patients from 37 institutions in 15 countries were randomly assigned to receive PF (181 patients) or TPF (177 patients). The characteristics of the patients in the two groups were well balanced at baseline (Table 1). Reason of inoperability was the tumor size and/or the infiltration of adjacent structure in 90% of the patients. 42.7% of the cases were T4N2. Lymph nodes and hypopharynx were involved in respectively 44.7% and 31.3% of the cases. The tumor was moderately to poorly differentiated in 68% of the patients.

Chemotherapy was adequately administered (Table 2). The median time between CT and RT was 5,6 weeks (Table 3). At the time of progression, a new therapy was administered to 57.3% of patients (Table 4). The most important severe adverse events are summarized in Table 5. Toxic deaths rate was 7,8% in the PF and 3,7% in the TPF arm. Hearing loss occurred only in the PF group (2,8%). During RT the frequency of the main adverse events was similar in the two groups (Table 6).

At the cut-off date (21/09/2003) 273 patients were progressive or dead (147 in PF group and 126 in TPF group). The unadjusted hazard ratio for progression or death in the TPF group as compared with PF group was 0.74. The log rank test was significant (P=0.015, Figure 2). The treatment effect remained significant after adjustment Cox model including the stratification factors (Table 7). An updated survival analysis showed an overall survival (OS) benefit with TPF (p=0,0052, Figure 3). Figure 4 present the comparison of the best overall response rates to chemotherapy (ORR-CT), the complete response rates to chemotherapy (CR-CT), the best overall response rates to chemotherapy and radiotherapy (ORR-CTRT) and the complete response rates to chemotherapy and radiotherapy (CR-CTRT).

**Table 1: Patient's characteristics**

| Characteristic | PF (n=181) | TPF (n=177) |
|---|---|---|
| **Male, n (%)** | 162 (89.5) | 159 (89.8) |
| **Median age (range), years** | 52 (30 - 70) | 53 (30 - 69) |
| **WHO performance status, n (%)** | | |
| 0 | 91 (50.3) | 90 (50.8) |
| 1 | 90 (49.7) | 86 (48.6) |
| 2 | 0 | 1 (0.6) |
| **Site of primary tumour, n (%)** | | |
| Hypopharynx | 52 (28.7) | 53 (29.9) |
| Larynx | 13 (7.2) | 12 (6.8) |
| Oral cavity | 32 (17.7) | 31 (17.5) |
| Oropharynx | 84 (46.4) | 81 (45.8) |
| **Number of organs involved, n (%)** | | |
| 1 | 23 (12.7) | 18 (10.2) |
| 2 | 143 (79.0) | 153 (86.4) |
| ≥3 | 12 (6.6) | 5 (2.8) |

WHO = World Health Organization

**Table 2: Chemotherapy delivery**

| Variable | Randomized Treatment | |
|---|---|---|
| | PF (N=181) | TPF (N=177) |
| **Total number of cycles** | 601 | 613 |
| **Never started CT - no (%)** | 2 (1.1) | 4 (2.3) |
| **4 cycles administered - no (%)** | 118 (66) | 136 (78.6) |
| **Median duration of CT - wk** | 12.1 | 12.0 |
| **Median DI Docetaxel (mg/m²/wk)** | - | 24.3 |
| **Median DI CDDP (mg/m²/wk)** | 30.6 | 24.3 |
| **Median DI 5-FU (mg/m²/wk)** | 1517 | 1215 |
| **No dose reduction - no (%)** | 151 (84) | 155 (90) |
| Reduction due to toxicity - no (%) | 17 (10) | 6 (3.5) |
| **No delay - no (%)** | 61 (34) | 116 (67) |
| Delay due to toxicity - no (%) | 68 (38) | 4 (2) |
| Delay for administrative failure - no (%) | 31 (17) | 39 (23) |
| Delay > 7 days - no (%) | 37 (21) | 14 (8) |
| **Main reasons for stopping CT** | | |
| Adverse events | 21 (12) | 11 (6) |
| Death | 12 (7) | 6 (3) |
| Progression | 13 (7) | 14 (8) |

Note: CT= Chemotherapy, DI = Dose Intensity

**Table 3: Radiotherapy delivery**

| Variable | Randomized Treatment | |
|---|---|---|
| | PF (N=181) | TPF (N=177) |
| **No RT given - no (%)** | 59 (33) | 44 (25) |
| **Median duration of RT - wk** | 7.1 | 7.1 |
| **Median duration of RT+CT - wk** | 19.9 | 21.0 |
| **Conventional RT only - no (%)** | 91 (51) | 100 (58) |
| **Total dose of RT - Gy †** | 70.0 | 70.0 |
| **RT not per protocol - no (%)** | 27 (15) | 27 (16) |
| **Neck dissection - no (%)** | 4 (2) | 7 (4) |
| **Before RT - no (%)** | 1 (<1) | 1 (<1) |
| **Salvage - no (%)** | 8 (4) | 16 (9) |

Notes: CT= Chemotherapy, DI = Dose Intensity

**Table 4: New treatment after disease progression**

| Variable | Randomized Treatment | |
|---|---|---|
| | PF (N=181) | TPF (N=177) |
| **Surgery for progression - no (%)** | 15 (8) | 27 (15) |
| **(Re)-irradiation - no (%)** | 31 (17) | 36 (20) |
| **Chemotherapy - no (%)** | 36 (20) | 37 (21) |
| **All therapies for progression - no (%)** | 64 (35) | 61 (34) |

**Table 5: Safety chemotherapy**

| Grade 3 or 4 | Randomized Treatment | |
|---|---|---|
| | PF (N=179) | TPF (N=173) |
| **Leukopenia - no (%)** | 41 (23) | 72 (42) |
| **Neutropenia - no (%)** | 94 (53) | 133 (77) |
| **Thrombopenia - no (%)** | 32 (18) | 6 (3) |
| **Hemoglobin - no (%)** | 23 (13) | 16 (9) |
| **Alopecia (including grade 2)** | 20 (12) | 96 (55) |
| **Nausea** | 12 (7) | 1 (<1) |
| **Vomiting** | 8 (4) | 1 (<1) |
| **Stomatitis / oral** | 20 (11) | 8 (5) |
| **Anorexia** | 6 (3) | 1 (<1) |
| **Diarrhea** | 6 (3) | 5 (3) |
| **Infection** | 11 (6) | 12 (7) |
| **Febrile neutropenia †** | 5 (3) | 9 (5) |

Notes: Related toxicities only / in the safety population / † Grade ≥ 2 fever concomitant with Grade 4 neutropenia

**Table 6: Safety radiotherapy**

| Grade 3 or 4 | Randomized Treatment | |
|---|---|---|
| | PF (N=179) | TPF (N=173) |
| Esophagitis / dysphagia | 28 (16) | 25 (14) |
| Stomatitis | 48 (27) | 46 (27) |

Note: in the safety population

**Figure 2: Kaplan-Meier estimates of Progression-Free Survival**

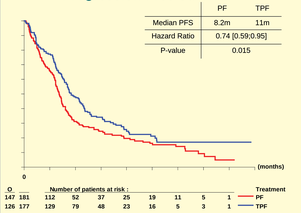



**Figure 3: Kaplan-Meier estimates of Overall Survival**

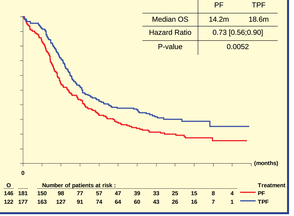



**Figure 4: Overall Response Rates**

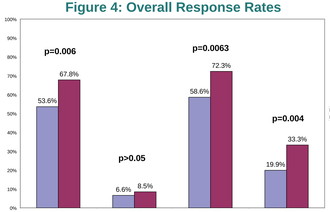



**Table 7: Cox Proportional Hazard Model for Progression-free Survival**

| Variable | p-value | Hazard Ratio 95% CI |
|---|---|---|
| **Arm (TPF/PF)** | 0.0071 | 0.72 [0.57-0.91] |
| **Hypopharynx primary (y/n)[a]** | 0.0120 | 1.03 [0.60-1.76] |
| **Oral cavity primary (y/n) Oropharynx primary (y/n)** | - | 1.20 [0.68-2.15] |
| **Oropharynx primary (y/n)** | - | 0.73 [0.43-1.22] |
| **T stage: T4/T2-T3-T1** | 0.9122 | 1.02 [0.76-1.36] |
| **N stage: N2-3/N0-N1-NX** | 0.1123 | 1.25 [0.95-1.66] |
| **WHO performance scores: PS=0/ PS ≥1** | 0.0127 | 0.73 [0.58-0.94] |


**References**

**Ref 1.** Posner MR. The Oncologist 2005;10(Suppl. 3):11–19.- **Ref 2.** Paccagnella A, et al. J Natl Cancer Inst 1994:86:265–272. **Ref 3.** Zorat PL, et al. J Natl Cancer Inst 2004;96:1714–1717. - **Ref 4.** Schrijvers D, et al. Ann Oncol 2004;15:638–645.


## CONCLUSION

In this Phase III multicenter randomized trial TPF treatment plus radiotherapy proved to be superior to the conventional PF treatment plus radiotherapy for PFS, long term OS and RR. Toxicity profile and tolerability was also better than that of the standard treatment. This results encourage further investigations using this regimen regarding the still questionnable role of neoadjuvant chemotherapy in the treatment of locally advanced head and neck cancer and in the organ preservation trials. The present results approximate the ideal goals of neoadjuvant chemotherapy: increase locoregional control, reduce the occurence of distant metastases, and improve disease free and overall survival. Due to the favourable toxicity profile it is suitable to use in furter combinations with monoclonal antibodies or other therapy modalities, especially with concurrent chemoradiation.