5522

www.eortc.be

EORTC European Organisation for Research and Treatment of Cancer

Impact on quality of life (QoL) of the addition of docetaxel (T) to neoadjuvant cisplatin plus 5-fluorouracil treatment in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN): EORTC study 24971

[1]Bernier J., [2]Remenar E., [3]van Herpen C., [4]Germa Lluch J., [5]Stewart S., [6]Gorlia T., [7]Degardin M., [6]Desaunois I., [8]Vermorken JB.

1 Clinique de Genolier, Genolier, Switzerland - 2 National Institute of Oncology, Budapest, Hungary - 3 University Medical Centre Nijmegen, Nijmegen, the Netherlands - 4 Institut Catala d'Oncologia, Barcelona, Spain - 5 Charing Cross Hospital, London, United Kingdom - 6 EORTC Data Center, Brussels, Belgium - 7 Centre Oscar Lambret, Lille, France - 8 Universitair Ziekenhuis Antwerpen, Edegem, Belgium

European Organisation for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Group, EORTC, Brussels, Belgium

BACKGROUND

Cisplatin and 5-fluorouracil (5-FU) (PF) in combination is the current standard neoadjuvant chemotherapy for locally advanced SCCH (Ref.1). Although neoadjuvant PF can improve long-term survival in patients with unresectable disease (Ref. 2–4) there is a need for chemotherapy regimens which further improve efficacy outcomes without negatively impacting on patients' quality of life (QoL).

In the EORTC 24971 Phase III trial, the addition of docetaxel (Taxotere®) to cisplatin and 5-FU (TPF) improved progression-free survival (HR 0.74 [95%CI, 0.59 – 0.95], p=0.015; median 11.0 vs 8.2 months) and overall survival (HR 0.72 [95%CI, 0.56 – 0.93], p=0.0052; median 18.6 vs 14.2 months) at a median follow-up of 33.7 months (Ref.5). Results of the QoL assessments are presented.

OBJECTIVES

- The primary aim of the study was to evaluate the efficacy and safety of neoadjuvant TPF versus PF in patients with locally advanced, inoperable SCCHN.
- The secondary objectives were to compare the effects of neoadjuvant TPF versus PF on QoL and clinical benefit.

METHODS

Study design

Phase III, randomized, open-label study, conducted at 37 centers across Europe. The study schema is shown in Figure 1.

Key eligibility criteria

- Histologically or cytologically confirmed nonmetastatic, unresectable Stage III/IV SCCHN, with at least one measurable lesion (uni- or bidimensional)
- Age 18–70 years
- World Health Organization (WHO) performance status ≤1
- No prior chemotherapy or radiotherapy; no prior surgery for SCCHN
- No tumors of the nasopharynx or nasal/paranasal cavities
- Adequate organ function.

Assessments

Five primary QoL domains: Global health status/QoL (EORTC Quality of Life Questionnaire C30 [QLQ-C30], version 3.0), and pain, swallowing, speech, and cough (EORTC QLQ head and neck module [QLQ-H&N35]) self-administered by patients at each study center.

Clinical benefit included 3 subscales (normality of diet, eating in public, and speech disturbance) of the performance status scale (grade 0 [worst] to 100 [best]) for head and neck cancer patients (PSS-HN), and evaluation of changes in WHO performance status as assessed by the physician at scheduled visits.

Assessments were made prior to randomization, during chemotherapy (after cycles 2 and 4), and 6 and 9 months after completion of radiotherapy.

Statistical analysis

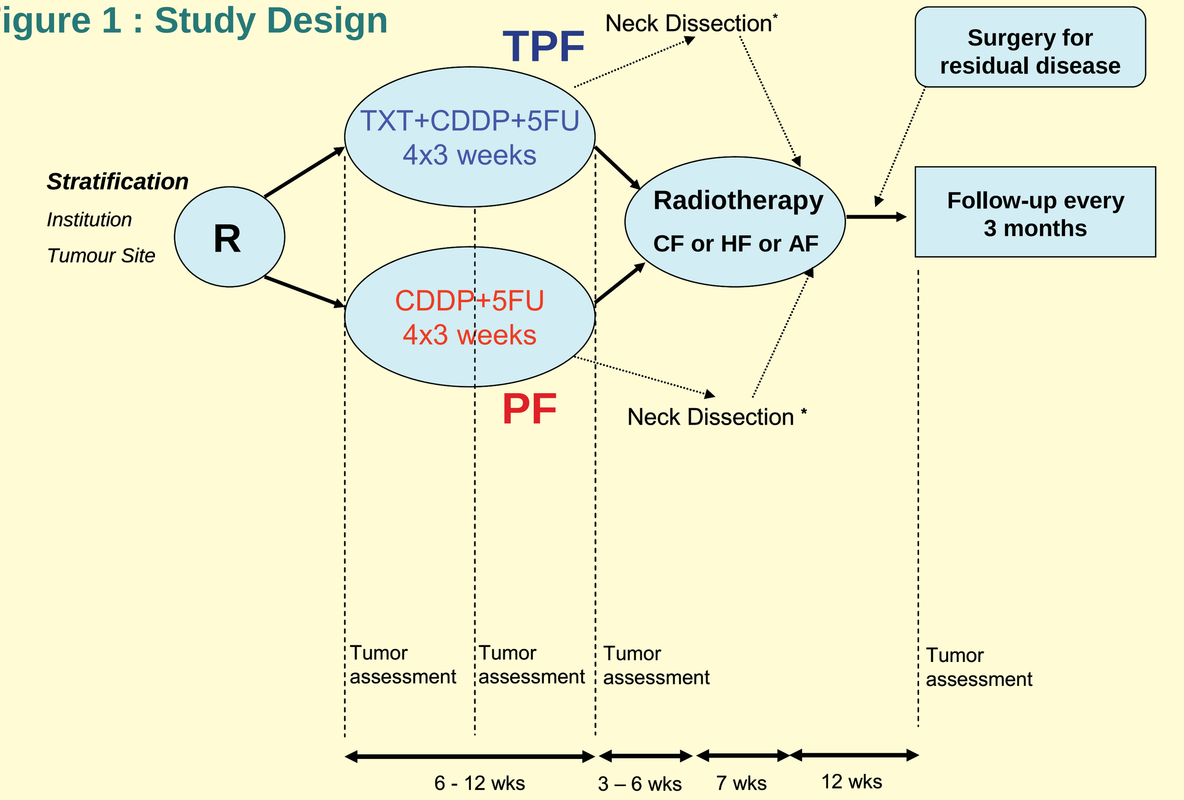
Patients with a baseline assessment and ≥1 post-baseline evaluation were included in the analyses.

Repeated measures, mixed effect, analysis of variance (ANOVA) models were used to analyze the evolution of QLQ-C30, QLQ-H&N35, and PSS-HN scores over time and treatment differences.

Treatment effects on WHO performance status were analyzed using generalized estimating equations methodology. An exploratory Kaplan–Meier analysis was also undertaken to evaluate time to first deterioration of WHO performance status. Deterioration was defined as an increase of ≥1 point at two consecutive evaluations.

Hazard ratios and 95% confidence intervals (CI) were obtained from a proportional hazards Cox regression model, and the log-rank test was used for between-group comparisons. A 2-sided 5% significance level was applied to all tests, unless otherwise indicated.

Figure 1 : Study Design



* Plus 2 weeks if neck dissection

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

Patients

Between April 1999 and March 2002, a total of 358 patients were randomized (177 TPF, 181 PF). Patient characteristics were well balanced (Table 1).

Both groups received a median of four cycles of chemotherapy; the median relative dose intensity was greater than 0.90 for all drugs.

Chemotherapy completion rates (per protocol): 70.1% with TPF and 61.9% with PF; main reason for discontinuation was disease progression (13.6% TPF; 11.0% PF).

Health-related QoL

Overall compliance with the QLQ-C30 was 70% with TPF and 72% with PF (Table 3a). Global health status scores in the two arms were comparable at baseline (61.8 TPF; 60.6 PF) and initially improved in both arms. While scores remained stable with TPF over time, they deteriorated with PF after radiotherapy, resulting in a significant treatment difference (p=0.01) (Figure 2).

Overall compliance rates with the QLQ-H&N35 were 48% for TPF and 46% or PF and therefore, the QLQ-H&N35 analyses were descriptive only. In general, pain, swallowing, speech, and coughing worsened over time in both treatment arms, though TPF-treated patients generally reported better scores than PF-treated patients.

Clinical benefit

Overall compliance with PSS-HN was similar between the TPF and PF arms (79% and 77%, respectively, Table 3b). Speech and eating disturbances were greater in the PF arm (Table 2).

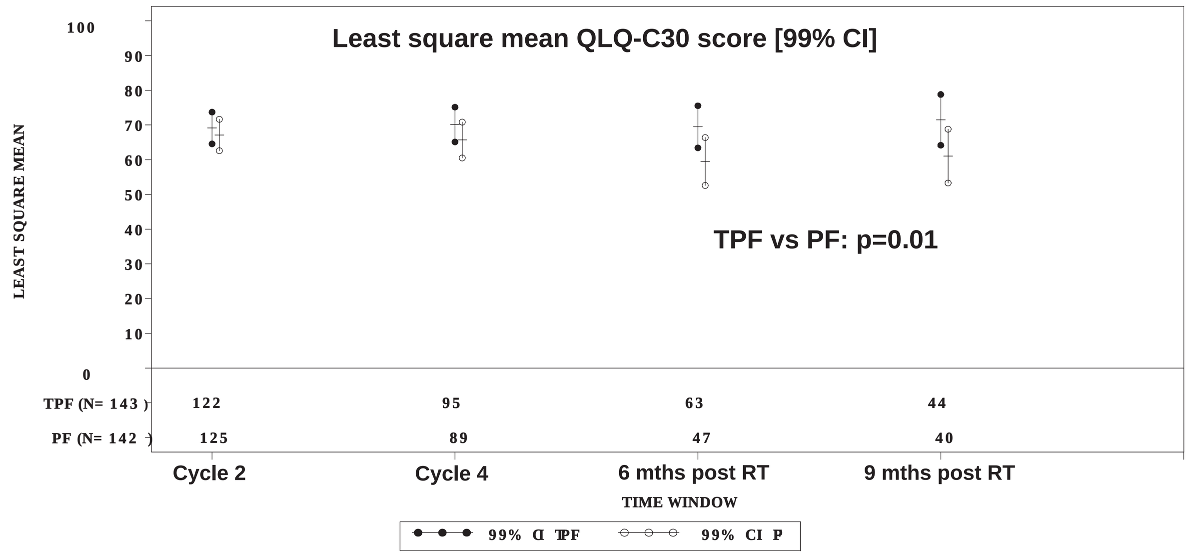
Median time to first deterioration of WHO performance status was significantly longer in the TPF arm than the PF arm (Figure 3).

Table 1 : Patient demographics and characteristics at baseline

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

Figure 2. Effect on quality of life questionnaire C30 (QLQ-C30) score: global health status



CI= confidence interval, RT= Radiotherapy

Table 2 : Clinical benefit assessment by the Perfomance status Scale for Head and Neck (PSS-HN)

Parameter	Treatment	Mean baseline score[a]	Difference in least square mean between treatment arms: End of treatment	Difference in least square mean between treatment arms: End of follow-up	P-Value[b]
Normal diet	TPF	76.0	5.5	16.8	0.0064[c]
	PF	72.0			
Speech	TPF	92.3	3.7	3.9	<0.0001[c]
	PF	89.6			
Public eating	TPF	87.5	6.6	17.3	0.0002[c]
	PF	81.7			

[a] Status scored from 0 (worst) to 100 (best); [b] Mixed model including; [c] Favors TPF

Figure 3. Time to first deterioration in WHO performance status

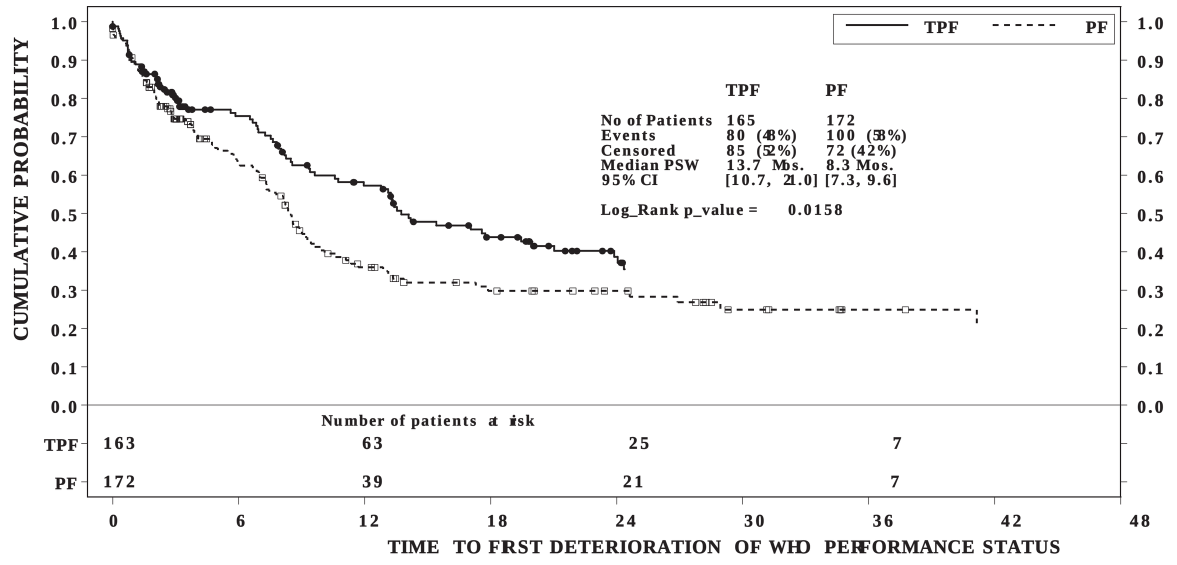


Table 3a: Analysis of compliance EORTC QLQ-C30 questionnaire

Time Window	PF (N=181): N1: in TW	PF (N=181): Compliance: N2/N1(%)	TPF (N=177): N1: in TW (No. of pts)	TPF (N=177): Compliance: N2/N1(%)
	(1)	(2)	(1)	(2)
Baseline	181	96.69	177	94.35
TW 1	167	78.44	164	79.27
TW 2	136	67.65	143	72.73
TW 3	111	45.05	136	50.00
TW 4	90	47.78	113	40.71
Overall	685	71.68	733	70.26

(1) TW: respectively cycle 2 (TW1), cycle 4 (TW2) and during follow-up period (TW3 and TW4).
(2) The compliance corresponds to the number of evaluable questionnaires (1/patient/time window) over the number of expected questionnaires.

Table 3b: Analysis of compliance - Performance status scale for Head and Neck (PSS-HN)

Time Window	PF (N=181): N1: in TW	PF (N=181): Compliance: N2/N1(%)	TPF (N=177): N1: in TW (No. of pts)	TPF (N=177): Compliance: N2/N1(%)
	(1)	(2)	(1)	(2)
Baseline	181	97.24	177	99.44
TW 1	167	83.23	164	88.41
TW 2	136	75.00	143	79.02
TW 3	111	54.05	136	61.76
TW 4	90	52.22	113	55.75
Overall	685	76.50	733	79.26

(1) TW: respectively cycle 2 (TW1), cycle 4 (TW2) and during follow-up period (TW3 and TW4).
(2) The compliance corresponds to the number of evaluable PSS-HN (1/patient/time window) over the number of expected HSS-HN scale.

CONCLUSION

The addition of docetaxel to neoadjuvant cisplatin and 5-FU (TPF) resulted in improved clinical efficacy outcomes compared with PF in patients with locally advanced, inoperable SCCHN. Treatment with TPF was superior to PF in terms of median progression-free survival (primary endpoint; p=0.007) and median overall survival (p=0.013), with manageable toxicity[4].

Health-related QoL and clinical benefit outcomes generally favored TPF over PF.

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.

Ref 5. Remenar E, Van Herpen C, Germa Lluch J, et al. Poster presented at the 2006 ASCO Annual Meeting, June 2–6, 2006, Atlanta, Georgia, USA (abs. 5516).