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ORIGINAL ARTICLE

Docetaxel, cisplatin and 5-fluorouracil induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy alone in stage III–IV unresectable head and neck cancer

Results of a randomized phase II study

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Abstract
Purpose Concurrent chemoradiotherapy (CRT) is the standard treatment for advanced head and neck squamous cell carcinoma. In this phase II randomized study, the efficacy and toxicity of docetaxel, cisplatin and 5-fluorouracil induction chemotherapy (ICT) followed by concurrent CRT was compared with those after standard CRT alone in patients with locally advanced, unresectable head and neck cancer.
Patients and methods Between January 2007 and June 2009, 66 patients with advanced (stage III or IV) unresectable squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx, and larynx) were randomly assigned to two groups: one receiving two cycles of docetaxel, cisplatin, and 5-fluorouracil ICT followed by CRT with three cycles of cisplatin and one treated by CRT alone. Response rate, local tumor control (LTC), locoregional tumor control (LRTC), overall survival (OS), progression-free survival (PFS), and toxicity results were assessed.
Results Three patients from the ICT + CRT group did not appear at the first treatment, so a total of 63 patients were evaluated in the study (30 ICT + CRT group and 33 CRT group). Three patients died of febrile neutropenia after ICT. The median follow-up time for surviving patients was 63 months (range 53–82 months). The rate of radiologic complete response was 63 % following ICT + CRT, whereas 70 % after CRT alone. There were no significant differences in the 3-year rates of LTC (56 vs. 57 %), LRTC (42 vs. 50 %), OS (43 vs. 55 %), and PFS (41 vs. 50 %) in the ICT + CRT group and in the CRT group, respectively. The rate of grade 3–4 neutropenia was significantly higher in the ICT + CRT group than in the CRT group (37 and 12 %; $p = 0.024$). Late toxicity (grade 2 or 3 xerostomia) developed in 59 and 42 % in the ICT + CRT and CRT groups, respectively.
Conclusion The addition of ICT to CRT did not show any advantage in our phase II trial, while the incidence of adverse events increased. The three deaths as a consequence of ICT call attention to the importance of adequate patient selection if ICT is considered.

Keywords TPF · Induction chemotherapy · Chemoradiotherapy · Head and neck cancer · Randomized trial

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Induktionschemotherapie mit Docetaxel, Cisplatin und 5-Fluorouracil gefolgt von simultaner Chemoradiotherapie oder Chemoradiotherapie allein bei irresekablen Kopf-Hals-Tumoren im Stadium III–IV

Ergebnisse einer randomisierten Phase-II-Studie

Zusammenfassung

Hintergrund Simultane Chemoradiotherapie (CRT) ist eine Standardtherapie beim fortgeschrittenen Plattenepithelkarzinom im Kopf-Hals-Bereich. In dieser randomisierten Phase-II-Studie wurden die Wirksamkeit und Toxizität einer Induktionschemotherapie (ICT) mit Docetaxel, Cisplatin und 5-Fluorouracil gefolgt von simultaner CRT mit der CRT allein bei Patienten mit lokal fortgeschrittenen, irresektablen Kopf-Hals-Tumoren verglichen.

Patienten und Methoden Zwischen Januar 2007 und Juni 2009 wurden 66 Patienten mit fortgeschrittenem (Stadium III oder IV), inoperablem Plattenepithelkarzinom im Kopf-Hals-Bereich (Mundhöhle, Oropharynx, Hypopharynx, Larynx) nach dem Zufallsprinzip in 2 Gruppen eingeteilt. Die eine Gruppe erhielt 2 Zyklen der Docetaxel-, Cisplatin- und 5-Fluorouracil-ICT gefolgt von CRT mit 3 Zyklen Cisplatin, die andere Gruppe erhielt nur CRT. Ansprechrate, lokale Tumorkontrolle (LTC), lokoregionale Tumorkontrolle (LRTC), Gesamtüberleben (OS), progressionsfreies Überleben (PFS) und toxischer Effekt wurden verglichen.

Ergebnisse Drei Patienten der Gruppe mit ICT + CRT erschienen bei der ersten Behandlung nicht, so dass insgesamt 63 Patienten in der Studie ausgewertet wurden (30 in der Gruppe ICT + CRT, 33 in der CRT-Gruppe). Drei Patienten starben an febriler Neutropenie nach ICT. Die mediane Nachbeobachtungszeit der überlebenden Patienten betrug 63 Monate (Spanne 53–82 Monate). Die Rate des radiologischen vollständigen Ansprechens war 63 % nach ICT + CRT vs. 70 % nach CRT allein. Es gab keinen signifikanten Unterschied in der 3-Jahres-Rate bei LTC (56 vs. 57 %), LRTC (42 vs. 50 %), OS (43 vs. 55 %) und PFS (41 vs. 50 %) zwischen der Gruppe mit ICT + CRT und den mit CRT behandelten Patienten. Die Rate von Neutropenie mit einem Grad 3–4 lag in der Gruppe mit ICT + CRT deutlich höher als in der CRT-Gruppe (37 und 12 %; $p = 0{,}024$). Späte Toxizität (Grad-2- und Grad-3-Xerostomie) ereignete sich in der Gruppe mit ICT + CRT und in der CRT-Gruppe in jeweils 59 vs. 42 %.

Schlussfolgerung Die Kombination von ICT und CRT erbrachte in unserer Phase-II-Studie keine Vorteile, wobei die Gesamtinzidenz der unerwünschten Ereignisse stieg. Die 3 Todesfälle infolge ICT weisen auf die Wichtigkeit der Patientenauswahl im Falle einer ICT-Behandlung hin.

Schlüsselwörter TPF · Induktionschemotherapie · Chemoradiotherapie · Kopf-Hals-Tumoren · Randomisierte Studie

Chemoradiotherapy (CRT) is a highly efficient treatment approach for locally advanced squamous cell carcinoma of the head and neck improving locoregional tumor control (LRTC), overall survival (OS), and reducing the development of distant metastases [1]. Induction chemotherapy (ICT) can also decrease distant failure and cisplatin-based ICT produces high response rates [1, 2]. The rationale for using ICT prior to CRT is to reduce the locoregional tumor volume, minimize the risk of distant metastases, and support organ preservation. The docetaxel–cisplatin–fluorouracil (TPF) regimen provided a significantly higher larynx preservation rate with no difference in OS compared with cisplatin–fluorouracil [3]. The TAX-324 trial compared a sequential plan of ICT with and without docetaxel followed by CRT and showed a significant improvement in survival in patients with resectable and unresectable locally advanced head and neck cancer treated with TPF induction [4]. In a meta-analysis of Blanchard et al. [5], PF induction chemotherapy was compared with TPF in randomized trials in locoregionally advanced head and neck cancers in 1772 patients. Absolute benefit at 5 years was 7.4 % in favor of TPF and it was associated with significant reduction of progression, locoregional failure, and distant failure compared with PF.

However, it has not been proved whether the addition of TPF ICT to CRT improves the results compared with administering CRT alone. Only a limited number of phase II or phase III trials and a retrospective study have investigated the efficacy of ICT + CRT compared with CRT alone, but no significant difference was found favoring ICT + CRT with respect to LRTC and OS, while the rate of adverse effects increased following ICT + CRT [6–10].

In this single institution, phase II randomized clinical trial we studied the toxicity and efficacy of TPF induction followed by CRT comparing it with standard CRT.

Patients and methods

Study design

In 2005 a phase II, single institution, randomized controlled trial was initiated in the National Institute of Oncology, Budapest, Hungary (EUDRACT 2005-001623-11). Recruitment took place between January 2007 and June 2009. The study was approved by the local ethics committee and the National Institute of Pharmacy and was undertaken in accor-

Table 1 Patient and tumor characteristics

Characteristic	ICT + CRT ($n=33$) *n* (%)	CRT ($n=33$) *n* (%)
Mean age[a] (range)	57 (47–68)	56 (39–69)
Gender		
Male	25 (76)	26 (79)
Female	8 (24)	7 (21)
AJCC stage		
III	4 (12)	2 (6)
IV	29 (88)	31 (94)
Tumor size		
T1	0 (0)	1 (3)
T2	4 (12)	2 (6)
T3	6 (18)	5 (15)
T4	23 (70)	25 (76)
Nodal status		
N0	5 (15)	1 (3)
N1	2 (6)	4 (12)
N2	22 (67)	25 (76)
N3	4 (12)	3 (9)
Primary disease site		
Oral cavity	4 (12)	2 (6)
Oropharynx	20 (61)	17 (52)
Larynx	3 (9)	1 (3)
Hypopharynx	6 (18)	13 (39)

ICT induction chemotherapy, *CRT* chemoradiotherapy, *AJCC* American Joint Committee on Cancer [18]

[a]In years.

dance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Sixty-six eligible patients—providing written informed consent—with histologically confirmed stage III and IV (according to the American Joint Committee on Cancer), non-metastatic, unresectable squamous cell carcinoma that arose from the oropharynx ($n=37$), hypopharynx ($n=19$), larynx ($n=4$), or oral cavity ($n=6$) were randomly assigned to receive TPF ICT + CRT ($n=33$) or CRT alone ($n=33$). Randomization was carried out at the weekly oncoteam conference of the National Institute of Oncology with random allocation by blocks. Inclusion criteria included tumors of the oro-, hypopharynx, larynx, and oral cavity with squamous cell carcinoma, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, age between 18 and 70 years, ejection fraction $\geq 50\%$ and adequate laboratory parameters [neutrophils $\geq 2000/mm^3$, platelets $\geq 100000/m^3$, hemoglobin ≥ 10 g/dl, bilirubin upper limit of normal (ULN), Alanine transaminase (ALT)≤ 2.5 ULN, AST ≤ 2.5x ULN, alkaline phosphatase ≤ 5x ULN, serum creatinine ≤ 120 micromol/l]. Exclusion criteria included history of any previous malignant disease, except nonmelanoma skin or in situ tumor of the cervix, as well as peripheral neuropathy $\geq$ grade 2. The diagnosis and staging were established by physical examination, endoscopy, computed tomography (CT) or magnetic resonance imaging (MRI), and histology.

Patients were randomly assigned in a 1:1 ratio to the ICT (TPF) + CRT or CRT groups. Patient and tumor characteristics are shown in Table 1.

The TPF group (2 cycles with a 3-week interval) included docetaxel (75 mg/m^2), cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2) per day, administrated as a continuous 24-h infusion for 4 days before CRT (with 100 mg/m^2 cisplatin), which started 4 weeks after the second TPF course. In the CRT group 100 mg/m^2 cisplatin was administered on days 1, 22, and 43 of radiotherapy. Granulocyte colony-stimulating factor (G-CSF) was administered in febrile and grade 4 neutropenia.

The planned radiation dose to the primary tumor and the involved lymph nodes was 70 Gy (2 Gy per day, 5 days per week) and 50 Gy to the lymph node areas with microscopic disease. All patients were irradiated using the ConPas (Conformal Parotis-sparing) technique [11].

End points

The primary end point was the radiologic response rate evaluated 8–12 weeks after completion of CRT (with or without ICT). Secondary end points included local tumor control (LTC), LRTC, OS, progression-free survival (PFS), and toxicity.

Evaluation and statistical analysis

The originally planned sample size ($n=92$) was calculated to detect 20% difference in complete response (CR) rate between the two treatment groups (70% after ICT + CRT vs. 50% after CRT) with a statistical power of 80% and at a significance level of 5%. Recruitment was stopped prematurely at a sample size of 66 patients in June 2009 because of 3 deaths due to febrile neutropenia after ICT.

Intention-to-treat (ITT) analysis was performed. The ITT population consisted of all randomized patients, with the exception of 3 patients in the ICT + CRT group who did not appear at the first treatment. Overall response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST/version 1.0/) [12]. Adverse events were determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Late toxicity was graded using the Radiation Therapy Oncology Group (RTOG) Radiation Morbidity Scoring Criteria. CT or MRI scans were made before the beginning of CRT (or 3–4 weeks after TPF induction), 8–12 weeks after CRT (first visit), and every 6 months thereafter. Chest X-ray, abdominal ultrasound examination, and blood tests were performed at least annually.

Local and regional control was defined as freedom from disease—verified with clinical examination and imaging—in the primary site and the neck region. Failure was defined

as local or regional residual or recurrent tumor or distant metastasis. Survival times were calculated from the date of the randomization. OS was calculated as the elapsed time from randomization until death, regardless of the cause. PFS was defined as the time from randomization to either progression or death (regardless of the cause of death). The actuarial rate of LTC, LRTC, OS, and PFS was estimated by the Kaplan–Meier method [13]. The log-rank test was used to compare survival curves. A p-value of ≤ 0.05 was considered to represent statistical significance. The probability of events obtained from the Kaplan–Meier estimates was given with 95% confidence intervals (CI). Differences in response outcome and toxicity between treatment groups were compared using Fisher's exact test. The Solo software (Department of Biometrics, University of California, Los Angeles, USA) was used for statistical analyses.

Results

Patient characteristics

Sixty-three patients were treated and evaluated with 30 assigned to receive TPF + CRT (because 3 patients, who did not appear at the first treatment were excluded from the analysis) and 33 to receive CRT alone. The OS and toxicity were assessed for the 3 patients in the ICT + CRT group who died of febrile neutropenia after ICT. No patient was lost during the follow-up period.

The median dose of radiotherapy was 66 Gy (range 54–70 Gy). Reduced radiation dose (median dose 60 Gy, range 54–62 Gy) was delivered in 19% ($n=5$) in the ICT + CRT group and 9% ($n=3$) in the CRT alone group because of the patients' wish or poor general condition. In the ICT group 12 patients (44%) received 3 cycles, 11 patients (41%) 2 cycles, and 3 patients (11%) 1 cycle of cisplatin during CRT after the 2 cycles of TPF because of biological toxicity. Only 1 patient (4%) was not administered cisplatin because of pancytopenia. In the CRT group, 15 patients (45%) received 3 cycles, 17 patients (52%) 2 cycles, and 1 patient (3%) only 1 cycle of cisplatin chemotherapy because of biological toxicity or treatment refusal.

Efficacy

After induction TPF the rates of radiologic overall response (OR), CR, and stable disease (SD)/progression (P) were 81% (22/27), 11% (3/27), and 19% (5/27), respectively. Following ICT + CRT or CRT the OR, CR, and SD rates were 93% (25/27) vs. 94% (31/33; $p=0.614$), 63% (17/27) vs. 70% (23/33; $p=0.391$), and 7% (2/27) vs. 6% (2/33; $p=0.614$), respectively (Table 2). No patient experienced disease progression during CRT.

Table 2 Response to the treatment

	After ICT ($n=27$)[a] n (%)	ICT + CRT ($n=27$)[a] n (%)	CRT ($n=33$) n (%)
Complete response	3 (11)	17 (63)	23 (70)
Partial response	19 (70)	8 (30)	8 (24)
Stable disease or progression[b]	5 (19)	2 (7)	2 (6)

ICT induction chemotherapy, *CRT* chemoradiotherapy

[a]Three patients were not subjected to chemoradiotherapy because they died of febrile neutropenia after ICT

[b]Progression only during ICT.

The median follow-up time for surviving patients was 63 months (range 53–82 months). Thirty-three local and/or regional treatment failures occurred: 16 (59%) of the 27 patients who received ICT and 17 (52%) of the 33 patients who did not receive TPF induction therapy. Distant failure was observed in 2 (7%) and 3 patients (9%) in the ICT + CRT and CRT groups, respectively, but they also had locoregional failure. No significant difference was noted between the two groups with respect to the number or site of the failures. Twenty-three of 30 patients (77%) died in the ICT group (3 patients of febrile neutropenia after ICT, 15 due to disease recurrence or progression, 1 in second primary tumor, and 4 due to intercurrent disease) and 20 out of 33 patients (61%) in the CRT group (17 due to disease recurrence or progression, 2 of second primary tumor, and 1 due to intercurrent disease).

The 2- and 3-year actuarial rates of LTC were 62% (95% CI 43–81) and 56% (95% CI 36–76) vs. 60% (95% CI 43–77) and 57% (95% CI 40–74; $p=0.783$), those of LRTC 46% (95% CI 27–65) and 42% (95% CI 23–61) vs. 57% (95% CI 40–74) and 50% (95% CI 33–67; $p=0.452$), while those of OS were 47% (95% CI 29–65) and 43% (95% CI 25–61) vs. 61% (95% CI 44–78) and 55% (95% CI 38–72; $p=0.203$; Fig. 1), and those of PFS 45% (95% CI 25–65) and 41% (95% CI 22–60) vs. 60% (95% CI 46–74) and 50% (95% CI 33–67; $p=0.506$; Fig. 2) in the ICT + CRT and CRT groups, respectively. The median PFS was 15 months (range 5–82 months) in the ICT + CRT group and 26 months (range 4–82 months) in the CRT group.

Adverse events and late toxicity

During TPF induction chemotherapy, 4 patients (13%) had grade 3–4 febrile neutropenia and three of them died of toxic effects. Mucositis, anemia, thrombopenia, neutropenia, febrile neutropenia, and nephropathy were the most frequent grade 3 or 4 adverse events (Table 3). We found no significant differences in these investigated side effects with the exception of neutropenia ($p=0.024$). Forty serious (grade 3 or 4) adverse events were observed in the ICT + CRT group and 30 in the CRT group ($p=0.008$). Ten (37%) patients

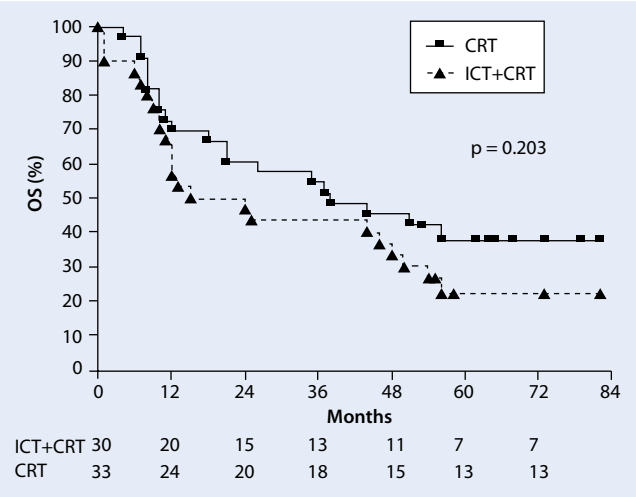

Fig. 1 Overall survival (*OS*) according to treatment. (*CRT* chemoradiotherapy, *ICT* induction chemotherapy)

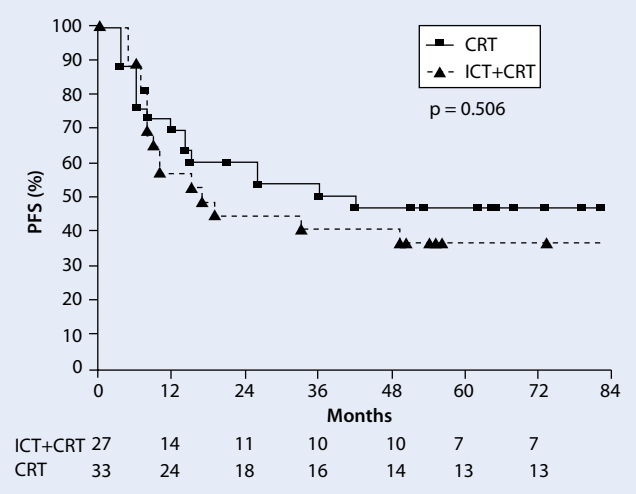

Fig. 2 Progression-free survival (*PFS*) according to treatment. (*CRT* chemoradiotherapy, *ICT* induction chemotherapy)

Table 3 Grade 3 or 4 treatment-related toxicity of induction chemotherapy + concomitant chemoradiotherapy or chemoradiotherapy alone

	ICT ($n=30$) *n* (%)	ICT + CRT ($n=27$)[a] *n* (%)	CRT ($n=33$) *n* (%)
Mucositis	0 (0)	15 (56)	14 (42)
Anemia	2 (7)	4 (15)	3 (9)
Thrombopenia	3 (10)	2 (7)	1 (3)
Neutropenia[b]	9 (30)	10 (37)[b]	4 (12)[b]
Febrile neutropenia	4 (13)	4 (15)	1 (3)
Nephropathy	1 (3)	5 (19)	7 (21)

ICT induction chemotherapy, *CRT* chemoradiotherapy

[a]Three patients were not subjected to chemoradiotherapy because they died of febrile neutropenia after ICT

[b]$p=0.024$.

were hospitalized in the ICT-CRT group and 5 (15%) in the CRT group. A percutaneous endoscopic gastrostoma (PEG) was inserted in 4 (15%) and 2 (6%) patients in the ICT + CRT and CRT groups, respectively.

During follow-up grade 2 or 3 xerostomia developed in 16 (59%) and 14 (42%) patients in the ICT + CRT and CRT groups, respectively ($p=0.150$). Osteoradionecrosis occurred in 1 patient (3%) treated with CRT alone.

Discussion

Concomitant CRT has emerged as a preferred treatment approach on the basis of various studies establishing the efficacy of cisplatin during radiotherapy [14–16]. Nowadays the standard treatment for locally advanced, unresectable, squamous cell carcinoma of the head and neck is 100 mg/m^2 cisplatin every third week during 70 Gy of radiotherapy. The benefit was also shown in a meta-analysis of head and neck cancer (MACH-NC) reporting a 6.5% absolute survival benefit at 5 years for concomitant treatment compared to 2.4% with PF induction followed by radiotherapy alone [1].

The possibility that TPF induction followed by CRT might prove more effective than standard CRT has been analyzed retrospectively or prospectively by some authors (Table 4) [6–10].

In our series the CR, PR, and SD/P rates after IC were 11, 70, and 19%, while in the DeCIDE study they were 8.8, 55.3, and 27.2%, respectively [8]. The rate of CR in our patients was 63 vs. 70% after ICT + CRT or CRT, and were in the study of Paccagnella et al. [7] 50 and 21.3%, respectively. In the latter case, the poorer result with CRT may be explained by the lower dose of cisplatin (80 mg/m^2). Our 2-year rate of LTC was 62% after ICT + CRT vs. 60% following CRT. In the retrospective analysis of Balermpas et al. [6], the 2-year rate of LTC was 47.9 vs. 71.4%, respectively. We found a 3-year LRTC rate of 42% in the ICT + CRT group vs. 50% in the CRT group. In our trial the median time of progression-free survival was 15 vs. 26 months in the ICT + CRT and CRT groups, respectively. In other studies this value was 14.6 and 30.4 months with ICT + CRT and 13.8 and 19.7 months with CRT [7, 10].

Our and the above discussed studies could not prove the advantage of adding ICT to CRT (Table 4).

In the retrospective analysis of Balermpas et al. [6], the OS rate at 2 years was significantly higher for primary CRT compared with the ICT + CRT group (74.8 vs. 54%, $p=0.041$).

It is difficult to compare our work with other studies, because of the wide variations in the chemotherapy agents and radiotherapy fractionation used. We applied TPF induction chemotherapy and standard chemoradiotherapy with cisplatin and 2 Gy/day fractionation schedule. Haddad

Table 4 Studies evaluating induction chemotherapy (*ICT*) + concurrent chemoradiotherapy (*CRT*) vs. CRT alone

Author (study type)	Patient (*n*)	T4 (%)	Treatment	2*- or 3-year PFS (%)		2*- or 3-year OS (%)	
				ICT + CRT	CRT	ICT + CRT	CRT
Balermpas et al. [6][a] (Retrospective)	83	84 (T3–4)	CRT ± 2–3 cycles ICT	44.6*	60*	54*	74.8* ($p=0.041$)
Paccagnella et al. [7][b] (Phase II)	101	45	CRT ± 3 cycles ICT	55.6*	44.7*	61*	57.1*
Cohen et al. [8][c] (DeCIDE—phase III)	280	22	CRT ± 2 cycles ICT	NR	NR	75	73
Haddad et al. [9][d] (PARARDIGM—phase III)	145	24	CRT ± 3 cycles ICT	67	69	73	78
Hitt et al. [10][e] (Phase III)	439	77	CRT ± 3 cycles ICT	~36[g]	~31[g]	~42[g]	~45[g]
Present study[f]	63	71	CRT ± 2 cycles ICT	45* 41	60* 50	47* 43	61* 55

**PFS* Progression-free survival, *OS* Overall survival

[a]ICT: docetaxel 75 mg/m^2, cisplatin 100 mg/m^2, 5-fluorouracil 1000 mg/m^2 96 h continuous infusion or cisplatin 100 mg/m^2, 5-fluorouracil 1000 mg/m^2 120 h continuous infusion; CRT: 2 cycles of cisplatin 100 mg/m^2, 600 mg/m^2 5-fluorouracil and standard fractionation radiotherapy

[b]ICT: docetaxel 75 mg/m^2, cisplatin 80 mg/m^2 (20 mg/m^2 from day 1–4), 5-fluorouracil 800 mg/m^2; CRT: 2 cycles of cisplatin 80 mg/m^2, 800 mg/m^2 5-fluorouracil continuous infusion and standard fractionation radiotherapy

[c]ICT: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, 5-fluorouracil 750 mg/m^2 (1–5 day); CRT: docetaxel 25 mg/m^2, 5-Fluorouracil 600 mg/m^2, hydroxyurea (500 mg twice daily) and 150 cGy radiotherapy twice daily

[d]ICT: docetaxel 75 mg/m^2, cisplatin 100 mg/m^2, 5-fluorouracil 1000 mg/m^2 on days 1–4 as continuous infusion; CRT: in partial remission, stable disease or progression weekly docetaxel at 20 mg/m^2 for 4 weeks and accelerated concomitant boost radiotherapy (A1 group) or in complete remission conventional radiotherapy with weekly carboplatin area under the curve 1.5 mg/ml/min (A2 group); 2 cycles cisplatin 100 mg/m^2 and accelerated concomitant boost radiotherapy or in the CRT group (B group)

[e]ICT: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, 5-fluorouracil 750 mg/m^2/day or cisplatin 100 mg/m^2, 5-fluorouracil 1000 mg/m^2/day; CRT: 3 cycles of cisplatin 100 mg/m^2 and standard fractionation radiotherapy

[f]ICT: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, 5-fluorouracil 750 mg/m^2; CRT: 3 cycles of cisplatin 100 mg/m^2 and standard fractionation radiotherapy

[g]Data from Kaplan–Meier curve.

et al. [9] in the PARADIGM trial used weekly docetaxel at 20 mg/m^2 for 4 weeks in one group in case of CRT, and radiotherapy was given with accelerated concomitant boost. In the DeCIDE trial conducted by Cohen [8] in the CRT group docetaxel–hydroxyurea–flurouracil was given with a radiotherapy schedule using hyperfractionation without platinum. In other studies, CRT was carried out with cisplatin and 5-fluorouracil [6, 7].

There were only three trials where there was significant advantage of ICT over standard CRT. Hitt et al. [10] found that the median time to treatment failure was 8.6 months with CRT and 14 months with ICT + CRT ($p=0.0205$) and LRTC is also better in the ICT group ($p=0.02$). The problem with this latter study is that the analysis cohort excluded approximately 25% of the intent-to-treat population randomized to ICT because discontinuation was high in both ICT (TPF or PF) groups, so the observed benefit is questionable. Paccagnella et al. [7] reported a significant difference in the rate of complete remission after ICT + CRT (50 vs. 21.3%, $p=0.004$). In the DeCIDE study, the cumulative incidence of distant metastases was reduced significantly with ICT (19 vs. 10%, $p=0.025$) [8].

It has been well documented that ICT increases the rate of grade 3 and 4 toxicity (Table 3). We detected grade 3–4 mucositis in 56% after ICT + CRT and in 42% following CRT. Other authors reported the incidence of grade 3–4 mucositis in the range of 36.7–73.3% (mean 51%) associated with ICT + CRT and only 16–75% (mean 39%) with CRT [6–10]. The rate of neutropenia and febrile neutropenia was high in studies using ICT [6–10]. We observed a significantly higher rate of neutropenia in the ICT group than in the CRT group (37 vs. 12%; $p=0.024$). In the DeCIDE trial, neutropenia was observed in 25.6% (ICT + CRT) and 11.3% (CRT) and this difference was significant ($p=0.004$) [8]. In the PARADIGM study, febrile neutropenia was found in 23% with and 1% without ICT [9]. Significantly more treatment-related overall grade 4 toxicities were documented by Balermpas et al. [6] in the ICT + CRT group (42.9 vs. 9.8%; $p=0.001$). We experienced the same phenomenon in our patients. The rate of serious (grade 3 or 4) adverse events was significantly higher in the ICT + CRT group than in the CRT group ($n=40$ vs. $n=30$; $p=0.008$). Side effects in our patients were manageable and did not interfere with the treatment course. Unfortunately, 3 patients died after ICT because of febrile neutropenia in spite of administering granulocyte colony-stimulating factor and antibiotics. In the retrospective analysis of Brömme et al. [17], 3 patients out of 40 died due to toxic effect during docetaxel-containing ICT.

Our results seem to be poorer than the results reported in the above mentioned studies. This can be explained by the lower total dose of ICT comparing to the other trials, with the exception of the DeCIDE trial and the relative high incidence of T4 tumors (71 %). The proportion of T4 tumors in three trials (DeCIDE, PARADIGM, and the study of Paccagnella et al. [7–9]) was lower (22–45 %), only in one study [10] was it higher (77 %), while in the retrospective analysis of Balermpas et al. [6] T3 and T4 cases were reported together (84 %; Table 4). Because our institute is the main national oncology center in Hungary, more patients with advanced stage cancer are referred to our department.

Conclusion

The addition of TPF to chemoradiation did not show any advantage in our phase II trial with respect to locoregional response, local and locoregional tumor control, and survival, whereas the rate of adverse events increased. Our results—in spite of the fact that the smaller sample size and the phase II design is the limitation of this study to detect a difference in response rate—are comparable to the results of other studies, while the relatively lower induction chemotherapy dose and the higher proportion of T4 tumors could be responsible for the less favorable results. Our three treatment-related death cases as a consequence of ICT call attention to the importance of adequate patient selection for ICT before CRT.

Compliance with ethical guidelines

Conflict of interest Z. Takácsi-Nagy, E. Hitre, É. Remenár, F. Oberna, C. Polgár, T. Major, M. Gödény, J. Fodor, and M. Kásler state that there are no conflict of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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