Cancer Chemother Pharmacol (2007) 60:399–406
DOI 10.1007/s00280-006-0370-y

ORIGINAL ARTICLE

Comparison of hyperfractionation and conventional fractionation radiotherapy with concurrent docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)

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Received: 26 April 2006 / Accepted: 23 October 2006 / Published online: 10 November 2006

Abstract
Purpose Radiotherapy (RTx) has been considered as the treatment for locally advanced squamous cell carcinoma of the head and neck (SCCHN). However, with only conventional fractionation (Cfx), response rates are relatively low. In this study, we report the results of hyperfractionation (Hfx) RTx with concurrent docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy (CTx) in patients with locally advanced SCCHN and compare Hfx and Cfx RTx with concurrent TPF CTx.
Methods Fifty patients with previously untreated stage III–IV SCCHN were entered into this study. Eligible patients received RTx delivered using arm 1: Hfx at 1.2 Gy/fraction, twice daily, 5 days/week to 76.8 Gy/64 fractions, and arm 2: Cfx at 2 Gy/fraction/day, 5 days/week to 70 Gy/35 fractions. Patients received 2 cycles CTx every 4 weeks. The doses were docetaxel 50 mg/m^2 (day 1), cisplatin 60 mg/m^2 (day 4), and 5-FU 600 mg/m^2/day (days 1–5).
Results The overall clinical response rate and the pathological CR were 100% (25/25) and 84% (21/25) in arm 1, and 100% (25/25) and 80% (20/25) in arm 2. Local–regional control was better significant in arm 1 than arm 2 ($P = 0.048$). There were also trend toward improved disease-free survival ($P = 0.059$) and overall survival ($P = 0.078$) in arm 1. Mucositis was significantly more frequent in arm 1 ($P = 0.048$).
Conclusion There were trend toward improved local–regional control, disease-free survival and overall survival in Hfx RTx with concurrent TPF CTx, compared to Cfx RTx with concurrent TPF CTx.

Keywords Hyperfractionation radiotherapy · Docetaxel · Cisplatin · 5-Fluorouracil · Squamous cell carcinoma of the head and neck (SCCHN)

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Introduction

Radiotherapy (RTx) has been considered the treatment for locally advanced squamous cell carcinoma of the head and neck (SCCHN). However, with only conventional fractionation (Cfx), response rates are relatively low and 2-year survival rates are less than 30% [1]. To overcome the poor locoregional control rates, many approaches have been tested, such as altered fractionated regimens and combined RTx and chemotherapy (CTx) [2–6].

One of the altered fractionated methods is hyperfractionation (Hfx). In Hfx, radiobiologic premises were used as follows: differences in repair capacity between early-reacting normal tissues/tumors and

late-reacting normal tissues, differences in effects of sensitivity between the tumors and late-reacting normal tissues and less profound oxygen effect at lower doses [7–9]. Randomized studies that compared Hfx and Cfx, and significant advantage for Hfx was also found in many studies [2–3].

Another therapeutic option is the use of combined RTx and CTx. Randomized trials have shown that combined RTx and CTx is effective in preserving organ function in a subset of patients by reducing the need for surgery of the primary tumor site and improving survival [4–6, 10, 11]. Taylor et al. [12] reported concurrent chemoradiotherapy (CRTx) with cisplatin and 5-fluorouracil (5-FU) (PF), and complete response (CR) was 52%. But, survival of patients with stage III and IV disease remains poor despite these improvements.

Docetaxel is a new agent that has demonstrated significant activity against SCCHN. A number of studies have explored the combination of docetaxel, cisplatin and 5-FU (TPF) in SCCHN, with promising results. The overall response rate with the three drugs in previously untreated, advanced SCCHN was approximately 64–93% [13–15]. Different investigators also examined the feasibility of combination of docetaxel and RTx. Koukourakis et al. [16] tested in a phase I setting the combination of docetaxel, irinotecan and Cfx RTx.

We had reported Cfx RTx with concurrent TPF CTx. It achieved an overall response rate of 100%, and the pathological CR rate was 84% [17, 18]. The response rate and pathological CR rate of the concurrent TPF CTx were better than those seen with TPF CTx followed by RTx [19].

In this study, we report the results of phase II trial of Hfx RTx with concurrent TPF CTx in patients with locally advanced SCCHN and compare Hfx and Cfx RTx with concurrent TPF CTx.

Patients and methods

Patient population

Patients were selected if they had histologically or cytologically confirmed SCCHN, at least one unidimensionally measurable lesion, and stage III or IV disease without evidence of distant metastases. Patients with primary sites in the nasopharynx, mesopharynx, hypopharynx, larynx, oral cavity or paranasal sinus were eligible. Patients who had received previous CTx, RTx or surgery were excluded. Patients were ineligible if they had another cancer. This study was a randomized prospective study.

Patients were required to be from 20 to 75 years of age and have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, life expectancy of at least 3 months, a WBC count of $\geq$4,000 cells/μl, an absolute neutrophil count (ANC) of $\geq$2,000 cells/μl, a platelet count of $\geq$ 100,000/μl, a hemoglobin level of $\geq$9.5 g/dl, AST, ALT and alkaline phosphatase levels below 2.5 times the upper limit of normal (ULN), total bilirubin and creatinine levels below 1.5 times ULN, a BUN level below the ULN and a 24-h creatinine clearance rate of more than 60 ml/min. Patients with significant cardiac arrhythmia or heart failure were ineligible. All patients provided written informed consent prior to enrollment in the chemoradiotherapy.

Study design

This study was a prospective, randomized phase II trail study and we compare Hfx and Cfx RTx with concurrent TPF CTx.

Radiotherapy schedule

Eligible patients received RTx delivered using arm 1: hyperfractionation (Hfx) at 1.2 Gy/fraction, twice daily, 6 h apart, 5 days/week to 76.8 Gy/64 fractions/6.4 weeks, and arm 2: conventional fractionation (Cfx) at 2 Gy/fraction/day, 5 days/week to 70 Gy/35 fractions/7 weeks. The arms were selected randomly. All patients were irradiated with 6 MV photons by linear accelerator machines with a source-to-surface distance >80 cm. Simulation films and beam verification port films were required for each treatment field.

A combination of lateral opposing fields, anterior and lateral wedged fields or other field arrangements was used to treat the primary tumor and the lymph nodes in the upper neck. A single anterior field was used to treat the neck below the fields for the primary tumor. For patients with nodes >6 cm in diameter, supraclavicular nodes, or pyriform sinus tumors that were T3 or T4 or with clinically positive nodes, the anterior field could extend 5 cm inferiorly to include the upper mediastinum.

At least two field reductions were recommended. The first field reduction off the spinal cord occurred at 48 Gy for arm 1 and 40 Gy for arm 2. The second field reduction occurred at 60 Gy for arm 1 and arm 2. A third field reduction at 69.6 Gy was recommended for arm 1. A minimum 2-cm margin around the initial tumor volume and positive neck node(s) for the first field reduction, a minimum of 1–1.5 cm margin for the second field reduction and a minimum 1 cm margin for

the third field reduction were required. When high-grade (grade 3–4) toxicities were observed frequently, RTx was delayed or reduced.

Chemotherapy schedule

Before this trial, we had performed phase I trial of Cfx RTx with concurrent TPF CTx in patients with locally advanced SCCHN and the overall response rate was 100%, including 84% complete responses (CR) [17, 18]. The recommended dose of the regimen was docetaxel 50 mg/m^2 (day 1), cisplatin 60 mg/m^2 (day 4) and 5-FU 600 mg/m^2/day (days 1–5) and the regimen was safe and generally well tolerated and demonstrated good efficacy in patients with locally advanced SCCHN.

In this study, we used the recommended dose of docetaxel 50 mg/m^2 (day 1), cisplatin 60 mg/m^2 (day 4) and 5-FU 600 mg/m^2/day (days 1–5). The administration schedule is shown in Fig. 1. Docetaxel was administered intravenously over 1 h on day 1. More than 1 h after completion of the docetaxel infusion, 5-FU on days 1 through 5 was delivered by continuous intravenous infusion with 3.5 l of natural saline (NS) per day. Cisplatin was administered intravenously on day 4. Patients received ramosetron 0.3 mg and dexamethasone 8 mg intravenously on days 4 through 8 of CTx. Two cycles of CTx repeated every 4 weeks. If the ANC was less than 1,000 cells/μlL after CTx, subcutaneous G-CSF 100 μg/body/day was injected

Re-treatment on day 29 required ANC of ≥2,000 cells/μl, a platelet count of ≥100,000/μl, a hemoglobin level of ≥9.5 g/dl, AST, ALT and alkaline phosphatase levels below 2.5 times the upper limit of normal (ULN), a 24-h creatinine clearance rate of more than 50 ml/min and resolution of all other non-hematological toxicities (except alopecia, musculoskeletal pain and fatigue) to be baseline or less than grade 1. If there were some toxicities as above, cycle 2 CTx was delayed, and if the delay exceeded 14 days, the patient was removed from the study.

Patients were monitored for toxicity (medical interview, physical examination and complete blood cell counts) during treatment. Blood and urine chemistries were performed three times a week.

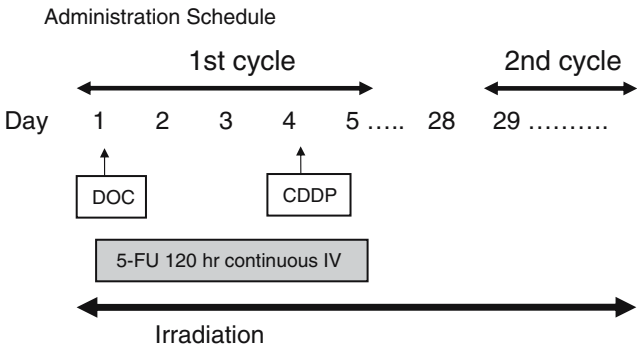

Fig. 1 Administration schedule of docetaxel (DOC), cisplatin (CDDP), and 5-fluorouracil (5-FU) in phase I study of patients with advanced squamous cell carcinoma of the head and neck. *IV* intravenous infusion

Toxicity assessment

Toxicity was assessed once per cycle according to the 2003 Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Resolution of effects such as myelosuppression, mucositis, fever (>38.0°C) and other disorders was required prior to initiating the second treatment cycle.

Clinical response and further treatment

The clinical response was assessed for each patient according to the combined findings of CT, MRI and ultrasonic examinations at 3 weeks after the end of the CRTx. The definitions of a complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were based on the standard definitions established by the WHO [20]. Pathological responses of the primary site were confirmed by biopsies in all cases. In the case of N1-3 lymph node disease, fine needle aspiration cytology of the neck lymph nodes was performed. Responses at the primary site and the regional nodes were scored separately, and the overall response was based on the worst of the two responses.

Surgery of the primary tumor site and/or metastatic lymph nodes was recommended for operable patients who failed to achieve CR after the end of the CRTx. Surgery was carried out routinely 4–6 weeks after the end of the CRTx.

We considered the criteria of unresectable patients with SCCHN as follows: (1) with invasion to the prevertebral fascia and muscle and (2) with common or internal carotid artery invasion that was concluded to be unable to remove as a result of the artery occlusion test.

Follow-up

Once treatment ended, patients were evaluated at 2 weeks, then every month from the first 1 year, every 2 months from 1 to 3 years, every 3 months from 3 to 5 years and annually thereafter.

When recurrence in the primary site and/or neck lymph nodes occurred, the patients with respectable disease were carried out operation.

Statistical analysis

Exact tests for contingency tables, Kaplan–Meier estimates of local–regional control, disease-free survival and overall survival and stratified log-rank tests were used to test for differences in response rates, estimated times to events and differences in the distributions of these events [21]. All *P* values are two sided.

Results

Characteristics of the patients

From January 2001 to April 2004, 50 eligible patients were identified. Table 1 outlines the characteristics of the patients. Twenty-five patients were selected from arm 1 and 25 from arm 2. About 80% of the patients in arm 1 and 2 had stage T3 or T4 primary tumors. Nodal metastases were present in 80% of the patients in arm 1 and 84% of those in arm 2. There was no significant difference in these factors of characteristics between the two arms.

In arm 1, there were four patients with unresectable disease; all four patients were with invasion to the prevertebral fascia and muscle. In arm 2, there were also four patients with unresectable, three patients were with invasion to the prevertebral fascia and muscle and one patient was with common or internal carotid artery invasion that was concluded to be unable to remove as a result of the artery occlusion test.

After CRTx, there were five PR patients. In arm 1, there were four PR patients. Two patients underwent surgery and two patients were unresectable, and received oral 5-FU (TS-1; 100 mg/day) [22]. In arm 2, there were five PR patients. Three patients underwent surgery, but two patients were unresectable, and received oral 5-FU (TS-1; 100 mg/day) [22].

Treatment

RTx in arm 1 was designed to be more intensive than in arm 2, in terms of both total dose and the time of delivery. The mean dose delivered to the primary tumor was 75.4 Gy (range 72–76.8 Gy) in arm 1 and 68.2 Gy (range 66–70Gy) in arm 2. The average number of days of administration were 48 days (range 45–52 days) in arm1 and 51 days (range 49–53 days) in arm 2 ($P = 0.019$). All patients received two cycles of planned CTx concurrently with RTx.

Table 1 Baseline patient characteristics

Patient characteristic	No. of patients	
	Arm 1 ($n = 25$)	Arm 2 ($n = 25$)
Sex		
Male	22	21
Female	3	4
Age (years)		
Average	56.2	60.0
Range	49–71	48–74
Performance status		
0	20	21
1	5	4
Primary site		
Nasopharynx	2	3
Oropharynx	7	6
Hypopharynx	6	6
Larynx	8	7
Oral Cavity	2	3
Paranasal sinus	0	1
T-satge		
T1	0	0
T2	5	5
T3	13	14
T4	7	6
N-stage		
N0	5	4
N1	6	6
N2	7	8
N3	7	7
Stage		
III	7	8
IV	18	17

Toxicity

Acute and late high-grade (grade 3–4) toxicities are listed in Table 2. Mucositis was the most common adverse effect observed in arm 1 (68%, 17/25) and arm 2(40%, 10/40). Leukocytopenia and neutropenia were also observed frequently in arm 1 (48 and 44%) and arm 2 (36 and 32%).

Mucositis was significantly more frequent in arm 1 ($P = 0.048$). Leukocytopenia and neutropenia were also more frequent in arm 1, but there was no statistically significant difference between two regimens ($P = 0.190$ and 0.130).

Late toxicities were rarely observed. There was no difference between the two arms.

Outcome

Three weeks following completion of the CRTx, all patients underwent biopsies of the primary tumor and/or fine needle aspiration cytology with ultrasound technique

Table 2 Acute and late toxicities (grades 3–4)

Toxicities	Arm 1 ($n = 25$)		Arm 2 ($n = 25$)		P
	No. of patients	Percent	No. of patients	Percent	
Acute toxicities					
Leukocytopenia	12	48	9	36	0.190
Febrile neutropenia	4	16	2	8	0.142
Neutropenia	11	44	8	32	0.130
Anemia	4	16	3	12	0.632
Thrombocytopenia	2	8	1	4	0.265
Elevated AST, ALT level	1	4	2	8	0.265
Elevated creatinine level	1	4	2	8	0.265
Mucositis	17	68	10	40	0.048
Late toxicities					
Xerostomia	2	8	1	4	0.265
Subcutaneous	2	8	3	12	0.468
Bone	0	0	1	4	0.349
Skin	2	8	1	4	0.265

of neck lesions to determine the pathological response [11, 16, 17]. As can be seen in Table 3, the overall clinical response rate and the pathological CR were 100% (25/25) and 84% (21/25) in arm 1, and 100% (25/25) and 80% (20/25) in arm 2. The primary site CR and metastatic lymph node CR were 88% (22/25) and 80% (16/20) in arm 1, and 84% (21/25) and 76% (16/21) in arm 2. There was no significant difference in these rates between the two arms.

After the CRTx, there were five PR patients. In arm 1, there were four PR patients. Two patients underwent surgery. Two patients were unresectable; all two patients were with invasion to the prevertebral fascia and muscle. They received oral 5-FU (TS-1; 100 mg/day) [22]. In arm 2, there were five PR patients. Three patients underwent surgery. Two patients were unresectable; one was with invasion to the prevertebral fascia and muscle, and one was with invasion to the prevertebral fascia and muscle. They also received oral 5-FU (TS-1; 100 mg/day) [22].

Table 3 Clinical response at primary site and metastatic lymph nodes

Site	Arm 1 ($n = 25$)		Arm 2 ($n = 25$)	
	Primary site	Metastatic lymph node	Primary site	Metastatic lymph node
CR	22	16	21	16
PR	3	4	4	5
NC	0	0	0	0
PD	0	0	0	0
NE	–	5	–	4

Overall response in arm 1 is CR21, PR4 and in arm 2 is CR20, PR5

NE not evaluable because N0 at baseline

The median follow-up of surviving patients was 42 months (range 24–62).

In Fig. 2, 3 and 4, Kaplan–Meier estimate of local–regional control, disease-free survival and overall survival are shown. Local–regional control was better significant in arm 1 than arm 2 ($P = 0.048$). There were also trend toward improved disease-free survival ($P = 0.059$) and overall survival ($P = 0.078$) in arm 1. Mucositis was significantly more frequent in arm 1 ($P = 0.048$).

Patterns of recurrence

Recurrence sites were shown in Table 4. Recurrence site included primary tumor, regional neck lymph node and distant metastasis. Recurrence of primary tumor and regional neck lymph node was more frequent in arm 2 (20%, 5/25) than arm 1 (8%, 2/25) ($P = 0.036$).

Three patients with resectable tumor (one patient in arm 1 and two in arm 2) were carried out operation. But there were seven patients with unresectable disease: two with distant metastasis in arm 1, one with

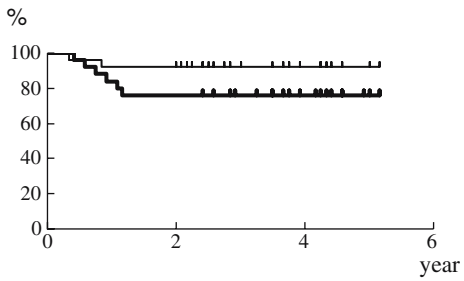

Fig. 2 Kaplan–Meier estimate of local–regional control. Local–regional control was better significant in arm 1 than arm 2 ($P = 0.048$). *Thin line* arm 1, *thick line* arm 2

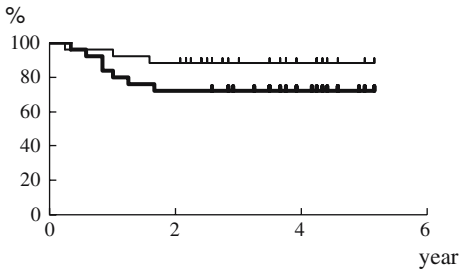

Fig. 3 Kaplan–Meier estimate of disease-free survival. There was trend toward improved disease-free survival ($P = 0.059$) in arm 1, compared to arm 2. *Thin line* arm 1, *thick line* arm 2

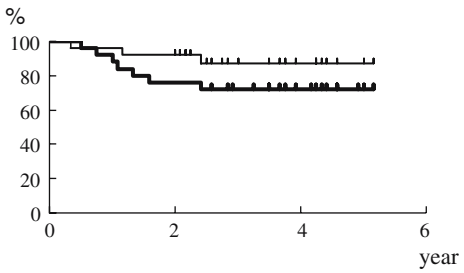

Fig. 4 Kaplan–Meier estimate of overall survival. There was trend toward improved overall survival ($P = 0.078$) in arm 1, compared to arm 2. *Thin line* arm 1, *thick line* arm 2

invasion to the prevertebral fascia and muscle in arm 2 and four with distant metastasis in arm 2.

Discussion

In the early 1980s a review of the time fractionation schedules in the normal tissues of rodents led to the hypothesis that a low dose per fraction could give reduced morbidity in the late-reacting normal tissues [23]. The European Organization for Research on the Treatment of Cancer (EORTC) carried out a randomized controlled trial in oropharyngeal cancer in which 1.15 Gy was given twice per day to a total dose of 80.5 Gy and compared with 2 Gy per fraction to 70 Gy in the same overall time. Acute reactions were slightly more troublesome, but in the Hfx group there was an increase in local tumor control (56 vs. 38% at 5 years) and overall survival ($P = 0.05$) [2, 3].

In a phase III trial by the Radiation Therapy Oncology Group (RTOG), fractions of 1.2 Gy were given twice a day for 5 days/week, and patients were assigned to receive total doses of 81.6 Gy, and Hfx has also been shown to improve the outcome of RTx for SCCHN [24].

Combination RTx and CTx is another promising approach to SCCHN. Multiple studies have demonstrated combination RTx and CTx to be highly effective in increasing survival of patients with SCCHN [4–6]. Concurrent CRTx and induction CTx followed by RTx have been established as an appropriate standard of care for many patients with SCCHN.

Using PF, Taylor et al. [12] compared Cfx RTx plus concurrent CTx and CTx followed by Cfx RTx for toxicity and efficacy in patients with SCCHN. After all treatments, CR did not differ between the two groups (52 vs. 50%). However, in terms of the overall response rates, the Cfx RTx plus concurrent CTx was better than the CTx followed by RTx (93 vs. 78%, $P = 0.003$). Severe and worse toxic events were similar between the treatment programs. The Cfx RTx plus concurrent CTx with PF achieved improved disease control, predominantly of regional disease, compared with CTx followed by RTx.

Jeremic et al. [25] compared the group with Hfx RTx alone to a tumor dose of 77 Gy in 70 fractions and the group with the same Hfx RTx plus concurrent low-dose (6 mg/m^2) daily cisplatin. As compared with Hfx RTx alone, Hfx RTx plus concurrent cisplatin offered a survival advantage, as well as improved locoregional progression, free survival and distant metastasis-free survival.

Brizel et al. [26] compared Hfx RTx plus concurrent CTx with PF, and Hfx RTx alone in patients with SCCHN. The randomized trial between the combined-treatment group received 1.25 Gy twice daily, for a total of 70 Gy, and 5 days of treatment with 12 mg/m^2/day of cisplatin and 600 mg/m^2/day of 5-FU during weeks 1 and 6 of RTx versus the group treated only

Table 4 Recurrence site in recurrence and dead patients

Site	Arm 1 ($n = 25$)		Arm 2 ($n = 25$)	
	No. of recurrence patients (%)	No. of dead patients (%)	No. of recurrence patients (%)	No. of dead patients (%)
P only	0 (0)	0 (0)	1 (4)	0 (0)
N only	0 (0)	0 (0)	1 (4)	1 (4)
P and N	1 (4)	0 (0)	1 (4)	1 (4)
M only	1 (4)	1(4)	2 (8)	2 (8)
M+ (P and/or N)	1 (4)	1 (4)	2 (8)	2 (8)
Total	3 (12)	2 (8)	7 (28)	6 (24)

P primary site, *N* metastatic lymph node, *M* distant metastasis

with Hfx RTx received 1.25 Gy twice daily, for a total of 75 Gy. Hfx RTx plus concurrent CTx with PF was more efficacious and not more toxic than Hfx RTx alone.

Docetaxel was shown to be an effective agent in SCCHN in multiple phase II studies [27–29]. Its mechanism of action and side-effects are different from both cisplatin and 5-FU. Myelotoxicity is the dose-limiting toxicity (DLT) for the taxanes, whereas myelotoxicity of PF is mild.

Different investigators also examined the combination of docetaxel and RTx. Mauer et al. [30] showed that it was possible to combine doses of docetaxel up to 20 mg/m^2/week with Cfx RTx to a total dose of 60 Gy in patients irradiated at the thorax. Toxicity was mild, with esophagitis and neutropenia as dose-limiting toxicities.

We had reported Cfx RTx with concurrent TPF CTx. It achieved an overall response rate of 100%, and the pathological CR rate was 84% [17, 18]. The response rates and pathological CR rates of the Cfx RTx with concurrent TPF CTx were better than those of TPF CTx followed by Cfx RTx [19].

In the present study, we compared Hfx and Cfx RTx with concurrent TPF CTx in patients with locally advanced SCCHN. Both regimens were generally well tolerated and resulted in a high overall response rate of 100% and CR rate of 84 and 80%. Local–regional control was better significant in Hfx RTx, compared to Cfx RTx, with concurrent TPF CTx ($P = 0.048$). There were also trend toward improved disease-free survival ($P = 0.059$) and overall survival ($P = 0.078$) in Hfx RTx, compared to Cfx RTx, with concurrent TPF CTx.

Table 2 shows grades 3–4 toxicities of two regimens. Mucositis was the most common adverse effect observed in Cfx RTx with concurrent TPF CTx (40%) and Hfx RTx with concurrent TPF CTx (68%). Leukocytopenia and neutropenia were also observed frequently in the Cfx RTx with concurrent TPF CTx (36 and 32%) and the Hfx RTx with concurrent TPF CTx (48 and 44%). Toxicity of treatment is a major concern, especially in Hfx RTx with concurrent TPF CTx. Severe mucositis, as the major toxicity, was more frequent in the group of Hfx RTx with concurrent TPF CTx ($P = 0.048$). Leukocytopenia and neutropenia were also more frequent in the group of Hfx RTx with concurrent TPF CTx, but there was no statistically significant difference between two regimens ($P = 0.190$ and 0.130).

In conclusion, Hfx RTx with concurrent TPF CTx required more supportive care and experience to deliver, with more frequent mucositis and hematological toxicity. Given these reservations, local–regional control was better significant in Hfx RTx than Cfx RTx, with concurrent TPF CTx ($P = 0.048$), and there were trend toward improved disease-free survival ($P = 0.059$) and overall survival ($P = 0.078$) in Hfx RTx, compared to Cfx RTx, with concurrent TPF CTx.

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