Optimizing a Convenient Protocol in Induction Treatment Of Locally Advanced Head And Neck Cancers: Taxotere-Cisplatin- 5 Fluorouracil versus Cisplatin-5 Fluorouracil

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Abstract:

Background: Induction docetaxel cisplatin and 5-fluorourcil (TPF) followed by concomitant chemoradiotherapy (CT/RT) in locally advanced squamous cell carcinoma of the head and neck (LASCCHN) is the most efficacious strategy but on the other hand it lowers the compliance of the patients due to its high toxicity. We preferred to use the cisplatin 5-fluorouracil (PF) as induction due to better compliance and lower toxicity.

Materials and methods: A total of 52 patients received either TPF of PF as induction before chemoradiation were studied retrospectively. Treatment compliance, febrile neutropenia and response rates (RR) were analyzed as well as progression free survival (PFS)

Results: Treatment delays during chemotherapy were much lower in the PF arm compared to TPF 1/25 (4%) versus7/27 (25.9%) respectively with significant P value (P=0.051). Neutropenia G3-4 with PF was significantly lower than the TPF regimen 8% (2/25) versus 40.7% (11/27) (P=0.06). RR (CR+PR) after concomitant CT/RT was almost the same in both arms 88% in the PF versus 85.2% in the TPF with non-significant P value. Comparison of progression-free survival (PFS) between PF group and TPF group showed no significant difference (p=0.305).at 18 months follow up, the PFS at PF arm was 75.4 % vs 92.1% in the TPF arm.

Conclusion: Induction PF protocol suits better our population as it yielded better compliance, lesser toxicity with maintaining the same efficacy.

Keywords: locally advanced squamous cell carcinoma head and neck, TPF, PF, chemoradiotherapy

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Background:

Many studies addressed the issue of induction chemotherapy in LASCCHN with unfortunately lack of overall survival advantage over concurrent chemoradiotherapy but other benefits appeared to be appealing to use this induction such as tumor downsizing to better fit to radiation fields, organ preservation benefit and eradication of micrometastasis decreasing metastatic disease [1].

Before TPF, induction chemotherapy with PF has demonstrated a benefit in locally advanced disease by reducing tumor size to better fit to radiation fields and eradication of micrometastasis [2-3].

the TAX-324 study proved that TPF protocol provided long term survival benefit compared with PF in LASCCHN [4].

TPF protocol is till today the famous induction regimen because of possible better RR and survival over other protocols used before however the advantage of survival from any induction treatment is still debatable [5-6-7-8].

When we started to use TPF at our center we noticed severe toxicity requiring intensive supportive treatment. patients already having bad nutritional status as a normal effect from their disease are required to start chemoradiotherapy after this induction regimen.

as a result, the majority of these patients didn't complete the scheduled radiation schedule due to the interruptions occurred from toxicity and hence alteration of the whole protocol. And radiobiologically, treatment gaps in radiation alters tumor outcomes specially in head and neck cancers

we thought to compare between the previous PF regimen to the TPF protocol in our center in terms of toxicity and efficacy and to study the difference in compliance, toxicity, RR and PFS.

Patients and Methods:

A total of 52 patients who attended to Kasr El Eini Oncology center with LASCCHN from January 2022 till December 2022 were studied. After Ethical committee approval data were collected from our electronic medical records. We identified 25 patients received PF induction protocol and 27 patients received TPF protocol. All patients had squamous cell carcinoma histology. Other pathology was excluded. All patients with ECOG PS of zero and one were included and any higher PS patients were excluded. Any patient with early disease (stage I-II) was excluded from the trial Table 1.

Induction chemotherapy

PF protocol consisted of cisplatin 100 mg/m2 divided on 2 days, 5-fluorouracil 1 gm/m2 continuous IV infusion day1-5, every 3 weeks for 3 cycles. all patients received the whole 3 cycles and two out of twenty five received one extra cycle due to radiotherapy waiting list.

TPF protocol consisted of 5-fluorouracil 750mg/m2 day 1-5, docetaxel 75 mg/m2 day 1, cisplatin 75 mg/m2devided on 2 days, every 3 weeks for 3 cycles. Four patients (15 %) had delays in chemotherapy cycles due to grade 4 neutropenia.

Toxicity due to chemotherapy was assessed after each cycle and tumor response was assessed after completing the whole 3 cycles.

Concomitant chemoradiotherapy

All patients started chemoradiotherapy after 4-6 weeks from last cycle, four patients from the TPF arm started the concomitant protocol two weeks later (8 weeks) because of mucositis G4 and febrile neutropenia G4 however all patients from the PF arm started radiotherapy before 6 weeks.

Radiotherapy was given using IMRT technique to almost all the patients except two patients from the PF arm and three patients from the TPF arm received 3DCRT and this was because overload on the IMRT machines.

All patients planned to receive 70 Gy/35 fractions over 7 weeks to the high risk planned target volume and from 60 Gy to 54Gy /30-27 fractions to the normal neck node levels according to high or low risk of recurrence.

All patients planned to receive cisplatin 30 mg/m2 weekly with radiation for 7 weeks and blood count creatinine were done before each cycle.

Only 2/25 patients in the PF arm had interruption in the RT course however 7/27 patients from the TPF arm had interuptions.3/25 patients from the PF arm discontinued the course of RT and 8/27 patients from the TPF arm had the same discontinuation.

Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Age was expressed as mean and standard deviation and range. Qualitative data was expressed as frequency and percentage. Comparison of qualitative variables between the two groups was done using either Pearson's Chi-square test or Fisher's exact test.

Comparison of age between two groups was done using Mann-Whitney test (non-parametric t-test) as it was not normally distributed.

Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. All tests were two-tailed. A p-value < 0.05 was considered significant.

Results:

Patient characteristics

Median age of patients in the PF arm was 50 and 51years in the TPF arm.19 patients out of 25 from the PF arm were males and 23 patients out of 27 in the TPF arm were males. Most of the patients in both arms had ECOG PS of 1 and few had zero. Any higher PS was excluded from the study.

Also the majority of patients in both arms had moderately differentiated squamous cell carcinoma histology. Cancer larynx constituted about 48 % in both arms followed by oral cavity tumors which was about 21 % also in both the PF and the TPF arms table 1

Induction chemotherapy

In the PF arm, all the patients received the 3 cycles of chemotherapy, moreover 2 out of 25 patients received one extra cycle due to radiotherapy waiting list. only one patient had delay in his 3rd cycle 14 days due to G3 mucositis. 2 patients had febrile neutropenia. 3 patients had G3-4 mucositis.

In the TPF arm, all patients received the 3 cycles of chemotherapy. seven patients had delay more than 10 days during the 2nd and 3rd cycles and this was because febrile neutropenia and G3-4 mucositis. also, the incidence of nausea and vomiting was much higher in the TPF arm 20 patients versus 12 patients in the PF arm (P=0.053).

96% (24/25) of the patients treated with PF didn't have any delay during chemotherapy vs 74% (20/27) with TPF protocol (P=0.05)

Neutropenia G3-4 with PF was significantly lower than the TPF regimen 8% (2/25) versus 40.7% (11/27) (P=0.006) table 2.

Response rate was assessed one month after completion of the induction protocol, in the PF arm 40% of the patients had response (CR+PR) vs 66.7 % in the TPF arm. With a significant P value of 0.013 favoring the TPF arm.13 patients in the PF arm had stable disease and 2 patients progressed. In the TPF arm 6 patients had stable disease and only one patient progressed after completion of the induction protocol table 3.

Sequential chemoradiotherapy

All patients started chemoradiotherapy after 4-6 weeks after last cycle, four patients from the TPF arm started the concomitant protocol two weeks later (8 weeks) because of mucositis G3-4 and febrile neutropenia however all patients from the PF arm started radiotherapy before 6 weeks.

During chemoradiation,3 out of 25 patients in the PF arm needed hospitalization due to febrile neutropenia and mucositis, however 8 out of 27 patients in the TPF arm were admitted to the hospital mainly because febrile neutropenia, mucositis necessitating parenteral nutrition and antibiotics. toxicity related breaks in radiotherapy also were much higher in the TPF arm, 7 patients had almost one week interruption in their radiation course mainly due to mucositis compared to only 2 patients in the PF protocol had the same interruption.

overall, 3 patients in the PF arm discontinued the concomitant protocol, all of them dropped the last week of radiotherapy and the last 2 doses of weekly cisplatin due to mucositis G3-4 and 8 patients from the TPF arm discontinued the concurrent protocol, 6 of them only received 4 cycles of weekly cisplatin then stopped and 2 of them dropped the last week of chemotherapy and radiotherapy and this also was because of severe mucositis and febrile neutropenia. table 2.

After 6 weeks from completion of protocol, the RR (CR+PR) was 88% in the PF versus 85.2% in the TPF with non-significant P value of 1. In the PF arm 1/25 had SD and 2/25 had PD however in the TPF arm 2/27 had SD and 2/27 had PD figure 1.

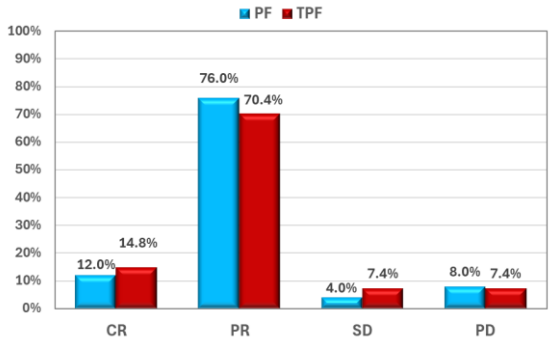

Figure 1: Response Rate after CT/RT

Follow up

During the period of the study, in the PF group; there were 8 patients progressed and 3 patients died (one of them had severe pneumonia probably related to tracheostomy and the other 2 had upper airway obstruction from aggressive local disease) while in the TPF group 6 patients progressed and 3 patients died (2 of them had upper airway obstruction due to aggressive local disease and one had pulmonary embolism). The median follow-up period was 14.8 months (ranged 3.1 to 25.8 months). Comparison of PFS between PF group and TPF group showed no significant difference (p=0.305). the PFS at 12 months in the PF arm was 75.4 % and 92.1%. and at 18 months follow up it was 32.3 % in the PF arm and 53.4% in the TPF arm. The median progression free survival was 15.9 months in the PF arm and was not reached in the TPF arm. table 4, figure 2.

Among those who had progressed in the PF arm, one had distant metastasis, 3 had nodal recurrences and referred for neck dissection. And the remaining 5 patients had progressive disease and received 2nd line chemotherapy.

Among those who had progressive disease from the TPF protocol, one had distant metastasis,4 had progressive disease and both received 2nd line chemotherapy and 2 had neck dissection for nodal progression.

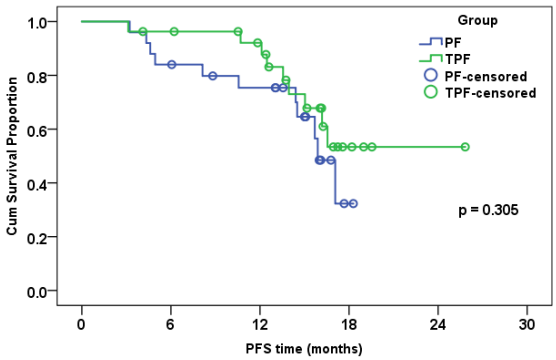

Figure 2: PFS analysis

Discussion:

In our center, we use induction chemotherapy in most of our patients because the majority of them present with locally advanced disease meaning that we need to downsize tumors as much as possible to better fit in the radiation fields. In table 1, more than 90 % of the patients in both arms present with either N2 or N3 disease. the idea of giving neoadjuvant chemotherapy is mainly for cytoreduction facilitating organ preservation and avoiding morbid surgery rather than better survival as the idea of OAS advantage from induction chemotherapy continues to be unclear [9-10-11].

the main focus of our study is to show a similar response from a less toxic CT combination. after induction protocol we had 40 % RR (CR+PR) in the PF arm and 66.7 % in the TPF arm P=0.013 in the TPF. the data from the TAX324 trial showed that the RR after induction chemotherapy was 64 % for the PF arm and 72 % for the TPF arm with P=0.07 [13].

In the TAX324 trial ,Neutropenia G3-4 occurred in 56 % of the PF arm and 83 % in the TPF arm ,in our cohort neutropenia G3-4 in the PF arm was 8% compared to 40.7% in the TPF arm P=0.006.the lower rates in our patients may be due to lower doses of cisplatin and fluorouracil used in our TPF arm as we used 75 mg/m2 instead of 100 mg/m2 in the cisplatin dose and 750 mg/m2 d1-5 instead of 1gm/m2 d1-5 in the fluorouracil dose of the original trial. This could be the explanation of lower toxicity in our cohort than the patients in the TAX324 trial. Another example supporting the lower doses of our cohort resulting in lower toxicity is the rate of G3-4 anemia and thrombocytopenia in our study which was much less than those of the original trial, anemia G3-4 in both PF and TPF arms were 11% compared to 34% in the TAX324 study also G3-4 thrombocytopenia in both protocols was only 7.4 % vs 24% in the TAX324 study [4].

Table 1: Patient characteristics

		Group				
		PF (n=25)		TPF (n=27)		
		Count	%	Count	%	p-value
Gender	Male	19	76.0%	23	85.2%	
	Female	6	24.0%	4	14.8%	0.401
PS	PS 0	11	44.0%	9	33.3%	
	PS I	14	56.0%	18	66.7%	0.430
Site primary	Larynx	12	48.0%	13	48.1%	
	Oropharynx	5	20.0%	4	14.8%	
	Hypopharynx	3	12.0%	4	14.8%	
	Oral cavity	5	20.0%	6	22.2%	1.000
Histology	Moderately diff SCC	17	68.0%	20	74.1%	
	poorly diff SCC	8	32.0%	7	25.9%	0.629
Stage at presentation	Stage III	4	16.0%	4	14.8%	
	Stage IVA	13	52.0%	15	55.6%	
	Stage IVB	8	32.0%	8	29.6%	1.000

Table 2: Toxicity profile

		Group				
		PF (n=25)		TPF (n=27)		
G3-4 Toxicity		Count	%	Count	%	p-value
Mucositis	No	22	88.0%	23	85.2%	1.000
	Yes	3	12.0%	4	14.8%	
Neutropenia	No	23	92.0%	16	59.3%	0.006
	Yes	2	8.0%	11	40.7%	
Anemia	No	21	84.0%	24	88.9%	0.698
	Yes	4	16.0%	3	11.1%	
Thrombocytopenia	No	24	96.0%	25	92.6%	NA
	Yes	1	4.0%	2	7.4%	
Hypersensitivity	No	24	96.0%	21	77.8%	0.101
	Yes	1	4.0%	6	22.2%	
Nausea, vomiting	No	13	52.0%	7	25.9%	0.053
	Yes	12	48.0%	20	74.1%	
Creatinine > 2.5	No	24	96.0%	27	100.0%	NA
	Yes	1	4.0%	0	0.0%	
Treatment delays during CT cycles	No	24	96.0%	20	74.1%	0.051
	Yes	1	4.0%	7	25.9%	
Radiotherapy start delay	No	25	100.0%	23	85.2%	0.112
	Yes	0	0.0%	4	14.8%	
Hospitalization	No	22	88.0%	19	70.4%	0.120
	Yes	3	12.0%	8	29.6%	
RT interruption	No	23	92.0%	20	74.1%	0.143
	Yes	2	8.0%	7	25.9%	
Course discontinuation	No	22	88.0%	19	70.4%	0.120
	Yes	3	12.0%	8	29.6%	

Table 3: Response Rate after induction CT and concomitant CT/RT

		Group				
		PF		TPF		
		Count	%	Count	%	p-value
RR after concomitant CT/RT	CR	3	12.0%	4	14.8%	
	PR	19	76.0%	19	70.4%	
	SD	1	4.0%	2	7.4%	
	PD	2	8.0%	2	7.4%	
RR after concomitant CT/RT	CR+PR	22	88.0%	23	85.2%	
	SD+PD	3	12.0%	4	14.8%	1.000
RR after induction chemotherapy	CR	0	0.0%	2	7.4%	
	PR	10	40.0%	18	66.7%	
	SD	13	52.0%	6	22.2%	
	PD	2	8.0%	1	3.7%	
RR after induction CT	CR+PR	10	40.0%	20	74.1%	
	SD+PD	15	60.0%	7	25.9%	0.013

Table 4: Overall PFS analysis

	No.	No of events	Cumulative survival at 12 months (%)	Cumulative survival at 18 months (%)	Median survival (months)	p-value
Group						
PF	25	11	75.4 %	32.3 %	15.9	
TPF	27	9	92.1 %	53.4 %	Not reached	0.305

We noticed in our cohort that febrile neutropenia occurred in 2/25 patients from the PF arm and 11/27 from the TPF arm. we related the higher incidence in the TPF arm because we didn't use Growth colony stimulating factor (G-CSF) as a prophylaxis after each cycle, we give only G-CSF either when absolute neutrophil count (ANC) drops to less than 500/microliter or any fever more than 380 Celsius with ANC less than 1500/microliter according to the guidelines of our center.

Sanders et al. found that the toxicity produced from the TPF regimen might interfere with the continuation of the sequential protocol [14]. this is similar to our results, 25.9% of patients from the TPF regimen had delays in CT cycles and accordingly 15 % had delays in the radiation start and only 4% in the PF arm ha delay during CT cycles and no one had this delay in the start of RT.

G3-4 mucositis was 12 % in the PF arm and 14.8 % in the TPF arm. In the TAX324 trial mucositis G3-4 was 21% in the PF arm and 27 % in the TPF arm. we noticed a much less mucositis incidence in our PF arm [5]. same difference in toxicities could be attributed to the lower doses in the cisplatin and 5-FU doses in our cohort.

In our cohort, treatment delays were much less than in the TAX324 trial, for example delays in the PF arm was 4 % compared to 29 % in the original trial and in the TPF arm it was 26 % compared to 65 % respectively. Also, this could be attributed to the lower chemotherapy doses used in our protocol [5].

Nevertheless, the RR after completion of chemoradiotherapy showed no statistical difference between the 2 arms with much less toxicity favoring the PF. The RR in the PF arm was 88% vs 85 % in the TPF arm. Remco et al. compared RR between PF and TPF regimens and showed similar results as in our cohort (85% in both arms) [12]. the non-statistical significance between both arms proves that the use of the less toxic PF protocol could a valid option with maintenance of same efficacy.

In our cohort, the PFS at 12 months was 75.4 % % in the PF and 92.1 % in the TPF arm and at 18 months it was 32 % and 53.4 % resepctively.in the TAX324 trial the PFS at 12 months was 51% in the PF arm and 62 % in the TPF arm and at 24 months it was 42% and 53 % respectively [12].in our cohort, we noticed that in both arms our patients had a better PFS than the TAX 324 trial at 12 months and almost the same PFS after 18 months follow up, our explanation is that we had fewer delays in the CT cycles and less RT course interruptions but after 18 months follow up the PFS of our cohorts became almost the same as that of the TAX 324 trial.

Conclusion and Recommendations:

Although, TPF protocol is still the first choice in most centers as induction protocol, we think PF protocol is equally effective to our population as it yielded better compliance, lesser toxicity with maintaining the same efficacy. We encourage using PF to the less adherent and less compliant patients especially elderly people who probably will not tolerate such extensive therapy.

Abbreviations

Locally advanced squamous cell carcinoma of the head and neck: LASCCHN
Docetaxel cisplatin 5-fluorouracil: TPF
Cisplatin 5-fluorouracil:PF
Response Rate: RR
Progression free survival: PFS
Progressive disease: PD
Stable disease: SD
Complete response: CR
Partial response: PR
Chemoradiotherapy: CT/RT
Growth Colony Stimulating Factor: G-CSF
Absolute Neutrophil Count: ANC

References:

1. Fabregas JC, Loaiza-Bonilla A, Talebi TN, et al. Concurrent chemoradiotherapy versus induction chemotherapy followed by chemoradiotherapy (sequential approach) in the management of head and neck cancer. Expert Rev Anticancer Ther. 2013;13(9):1065–72.
2.Domenge C, Hill C, Lefebvre JL, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC) Br J Cancer. 2000 Dec;83(12):1594–1598.
3.Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009 Jul;92(1):4–14.
4.Lorch JH, Goloubeva O, Haddad RI, et al. Long term results of TAX324, a randomized phase III trial of sequential therapy with TPF versus PF in locally advanced squamous cell cancer of the head and neck. Lancet Oncol. 2011 Jan 11;12(2):153–159.
5. Lorch JH, Goloubeva O, Haddad RI, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomized phase 3 trial. Lancet Oncol. 2011;12(2):153–9.
6. Posner M, Vermorken JB. Induction therapy in the modern era of combined-modality therapy for locally advanced head and neck cancer. Semin Oncol. 2008 Jun;35(3):221-8.
7. Argiris A. Current status and future directions in induction chemotherapy for head and neck cancer. Crit Rev Oncol Hematol. 2013;88(1):57–74.
8. Balermpas P, Bauer C, Fraunholz I, et al. Concomitant chemoradiotherapy versus induction chemotherapy followed by chemoradiotherapy as definitive, first line treatment of squamous cell carcinoma of the head and neck. A retrospective single center analysis. Strahlenther Onkol. 2014 Mar;190(3):256-62.
9. Hitt R, Grau JJ, Lopez-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol 2014;25:216-225.
10. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol 2013;14:257-264.
11. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol 2014;32:2735-2743.
12. de Bree R, Wolf GT, de Keizer B, et al. Response assessment after induction chemotherapy for head and neck squamous cell carcinoma: From physical examination to modern imaging techniques and beyond. Head Neck. 2017 Nov;39(11):2329-2349.
13. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007 Oct 25;357(17):1705-15.
14. Sanders IW, Haslett K, Correa P, et al. Sequential TPF chemotherapy followed by concurrent chemoradiotherapy in locally advanced head and neck cancer–a retrospective analysis of toxicity and outcomes Scott Med J. 2014 Feb;59(1):50-5.