Induction chemotherapy followed by chemoradiation versus upfront chemoradiation in locally advanced head and neck cancers A prospective randomized study

Abd ElLateef AA[1], Mohamed AE[1]

[1] Department of Clinical and Radiation oncology, Sohag University, Faculty of Medicine; Egypt

Correspondence should be addressed to Ahmed El Sayed Mohamed, Department of Clinical and Radiation Oncology, Sohag University, Faculty of Medicine; Egypt, dr_ahmed_sayed76@yahoo.com

Abstract

Background: Upfront concurrent chemoradiotherapy remains the standard of care for treating locally advanced squamous cell carcinoma of the head and neck (LA SCCHN), however, defining the role of induction chemotherapy in these patients yet to be determined.

Methods: The current prospective randomized study divided 144 patients with LA SCCHN to receive concurrent chemoradiation (CRT) or induction chemotherapy followed by concomitant chemoradiotherapy (IC+CRT) to investigate its effect on RR, DFS, PFS and OS. This work conducted between January 2015 and December 2016 at Sohag University hospital and Sohag Cancer Center.

Results: With a median follow up of 23 months, the initial response rate was 92.9% for the CRT arm and 80% for the IC+CRT arm with a significant difference in the median time to reach initial response (3 months and 2 months for CRT and IC+CRT respectively; p= 0.0008). However, no significant difference between the study groups in ORR (66.67% and 52.78% for CRT and IC+CRT, respectively; p= 0.23). There was no statistically significant difference as regards acute toxicity profile; however, late toxicity was significantly higher in CRT; p-value =0.04. No significant differences found in the cumulative DFS, PFS for different subgroups, (p= 0.8; p= 0.26, respectively), however, larger tumors in stage III/IV were associated with worse OS (p= 0.03).

Conclusion: Induction chemotherapy followed by chemoradiation may be not inferior to standard treatment of LA SCCHN tumors with significant early-onset response and less frequent late toxicity. This might hold promise for these patients especially with larger tumor size; however, confirmation mandates larger prospective studies.

Key words: Head and Neck cancers, Induction chemotherapy, Concurrent cheoradiation.

Introduction:

Advanced head and neck cancers have a worse survival despite recent progress achieved recently in understanding the epidemiology, pathogenesis, and management of head and neck cancers. [1] This may be due to complexity of head and neck cancers as survival and locoregional tumor control influenced by many factors.

Many randomized trials and meta-analyses of clinical trials showed significantly improved OS, DFS, and local control when a concomitant or alternating systemic therapy and radiation regimen compared with radiotherapy (RT) alone for advanced disease. However, no OS improvement were demonstrated by most of 1980s and 1990s randomized trials that explored induction chemotherapy followed by radiotherapy and /or surgery in comparison to locoregional treatment alone. [2]

However, some of these studied showed beneficial less distant metastases rates. [3] Also, a subsequent radiotherapy durable response was linked to the use of induction chemotherapy.[3, 4] Thus, induction chemotherapy was favored to avoid morbid surgery, and improve overall quality of life of the patient even without OS improvement due to facilitation of organ preservation.

Randomized trials and related meta-analyses indicated that concurrent chemotherapy/RT offered shorter duration of therapy compared to induction therapy followed by radiation. [5-13] Moreover, meta-analyses reported that it was more efficacious than an induction chemotherapy strategy. [2, 14]

Despite that, interest in induction chemotherapy increased as advances in surgery, RT, and concurrent modalities have yielded improved locoregional control rates; thus, distant metastases role as a source of treatment failure has increased and induction chemotherapy offers greater drug delivery to reduce their frequency. [15, 16] So, defining the role of induction chemotherapy in these patients yet to be determined.

This study conducted to explore the benefit of induction chemotherapy followed by chemoradiotherapy to be as equally effective as upfront chemoradiotherapy for locally advanced squamous cell head and neck cancer.

Patients and Methods:

A phase III prospective randomized two-study conducted on patients with newly diagnosed head and neck squamous-cell carcinoma, with T3/T4 and any N, or T1/T2 with N2/3 and no distant metastasis (M0) were eligible and age allowed to be18-70 years, PS 0- 2. This study carried out at Sohag University hospital and Sohag cancer center between January 2015 and December 2016.

Patients were randomly assigned into two treatment arms: Induction chemotherapy (IC) (platinum-based; Cisplatin/5FU or TPF) followed by radiotherapy 70 Gy with or without standard chemotherapy; second arm was concurrent chemoradiotherapy (CRT) of 70 Gy with standard chemotherapy (cisplatin 100 mg/m2 every 3 weeks) or modified (weekly cisplatin 35 mg/m2). Treatment arm stratified according to the site of disease and staging parameters. Equal numbers of patients (74) assigned to each group. Initial assessment of response carried out 8 weeks after treatment end of each arm. Thereafter, assessment done every 2 months. Response rate (RR), toxicity, DFS, PFS and OS were endpoints targeted for this study.

Consent: written informed.

Statistical analysis

Data was analyzed using STATA intercooled version 12.1. Quantitative data represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally distributed, Mann-Whitney test used. Qualitative data presented as number and percentage and compared using either Chi square test. Survival analysis done using Kaplan-Meier method and comparison between two survival curves done using log-rank test. Graphs produced by using Excel or STATA program. P value considered significant if it was less than 0.05.

Results:

Patient's characteristics

With a median follow up of 23 months for the whole group; seventy-four patients allocated in each arm with a median age was 58 years and 60 years for IC+CRT arm and CRT arm respectively; smokers were slightly more in CRT (67 % to 48%). As regards tumor site distribution, there was a statistically significant difference between both groups (p= 0.009). Laryngeal site was present in two thirds for CRT group while laryngeal, nasopharyngeal and hypopharyngeal tumors distributed evenly in IC arm (27, 24 and 27 % respectively). Majority in both were SCC (78% in both). High-grade tumors were 24.3% in CRT while 29.7 % in IC group. Stage IV (A/B) was significantly more frequent in IC+CRT group (64%) than CRT group (40%) with P value= 0.04. As regards chemotherapy protocol, 70% were 5FU/platinum while 30 % received Docetaxel/platinum/5FU. [Table 1]

Response rate

Overall, two patients in the CRT and four patients in the IC+CRT group missed follow up. The initial response rate was 92.9% (CR, 75.68%; PR, 16.22%) for the CRT arm and 80% (CR, 59.46%; PR, 16.22%; SD, 5.41%) for the IC+CRT arm at the first assessment post-treatment with a significant difference in the median time to initial response (3 months and 2 months for CRT and IC+CRT respectively; p= 0.0008). However, with a median follow-up of 23 months; the overall response (ORR) was 66.67% for CRT and 52.78% for IC+CRT with no significant difference between the study groups (p= 0.23). There was no significant difference between the two groups as regards local or distant progression frequency (p= 0.24). [Table 1]

Toxicity

As regards toxicity, there were statistically significant difference between the two arms as regards neutropenia (nearly 30% in IC group and 16% in CRT, p= 0.03). There was no statistically significant difference as regards non-hematological acute toxicity profile. However, CRT arm was more likely to experience higher chronic toxicity, late skin toxicity (21 % CRT vs 3% IC) and xerostomia (21 % CRT vs 3% IC) with p-value =0.04. [Table 2]

DFS, PFS, OS

No statistically significant differences found in the cumulative DFS, PFS and OS in both treatment arms when analyzed for different subgroups: age, smoking status, grade, stage, nodal status and the use of IC (p= 0.8; p= 0.26). [Table 3; Fig. 1; Fig. 2]. However, smaller tumors in stage III/IV were likely to have OS with p-value= 0.03. [Table 4; Fig. 3]

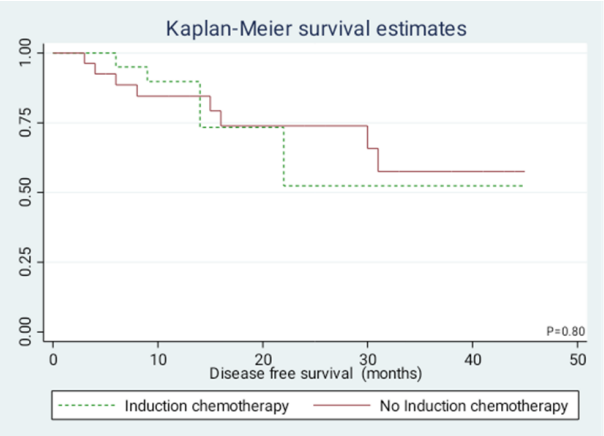

Figure 1: Relative disease free survival of patients according to treatment arm

Table 1: Demographic data of upfront induction chemotherapy group and standard CRT

Variables	chemo radiotherapy (N=74)	Induction chemotherapy (N=74)	P value
Age			
Median (years)	60	58	0.60
Smoking			
Non-smoker	24 (32.43%)	38 (51.35%)	0.10
Smoker	50 (67.57%)	36 (48.65%)	
Site			
Larynx	48 (64.86%)	20 (27.03%)	
Nasopharynx	12 (16.22%)	18 (24.32%)	
Hypopharynx	4 (5.41%)	20 (27.03%)	0.009
Oral cavity	0	8 (10.81%)	
Tongue	6 (8.11%)	6 (8.11%)	
Oropharynx	2 (2.70%)	0	
Cheek	0	2 (2.70%)	
Mouth floor salivary	2 (2.70%)	0	
Pathology			
SCC	58 (78.38%)	58 (78.38%)	
Undifferentiated	6 (8.11%)	12 (16.22%)	
Carcinoma			0.38
Anaplastic	2 (2.70%)	4 (5.41%)	
NK SCC	4 (5.41%)	0	
Adenocarcinoma	2 (2.70%)	0	
Clear cell carcinoma	2 (2.70%)	0	
Grade			
G1/G2	4(5.41%) /48(64.86%)	10(13.51%) /38(51.35%)	0.23
G2-3	4 (5.41%)	4 (5.41%)	
G3/G4	16(21.62%) /2(2.70%)	14(18.92%) /8 (10.81%)	
Stage			
III	44 (59.46%)	26 (35.14%)	0.04
IVA	30 (40.54%)	42 (56.76%)	
IVB	0	6 (8.11%)	
Initial response			
Progressive	6 (8.1%)	14 (20%)	0.09
Responsive	68 (92.9%)	56 (80%)	
Time to initial response (ms) Median	3 (1.5-6)	2 (1.5-6)	0.0008
Duration of response (ms)			
Median (range)	12.5 (1-44)	11.5 (2-45)	0.85
Over all response			
Progressive	24 (33.33%)	34 (47.22%)	0.23
Responsive	48 (66.67%)	38 (52.78%)	
Recurrence site			
Local	18 (24.30%)	22 (29.73%)	0.24
Distant	6 (8.10%)	12 (16.22%)	

Table 2: Toxicity profile among upfront induction chemotherapy group and standard CRT

Variables	chemo radiotherapy (N=74)	Induction chemotherapy (N=74)	P value
Hematological			
Neutropenia	12 (16.21%)	22 (29.73%)	0.03
Acute toxicity			
Mucositis grade			
0	2 (2.70%)	0	
1/ 2	44(59.46%)	36(48.65%)	0.09
3/ 4	28(37.84%)	38(51.35%)	
Acute skin toxicity grade			
0	4 (5.41%)	0	
1/ 2	58(78.38%)	52(70.27%)	0.16
3/ 4	12 (16.21%)	22(29.76%)	
Dysphagia			
No	22 (29.73%)	12 (16.22%)	0.17
Yes	52 (70.27%)	62 (83.78%)	
Chronic toxicity			
No	40 (54.05%)	58 (78.38%)	0.04
Pigmentation	2 (2.70%)	0	
Skin	16 (21.62%)	2 (2.70%)	
Xerostomia	16 (21.62%)	14 (18.92%)	

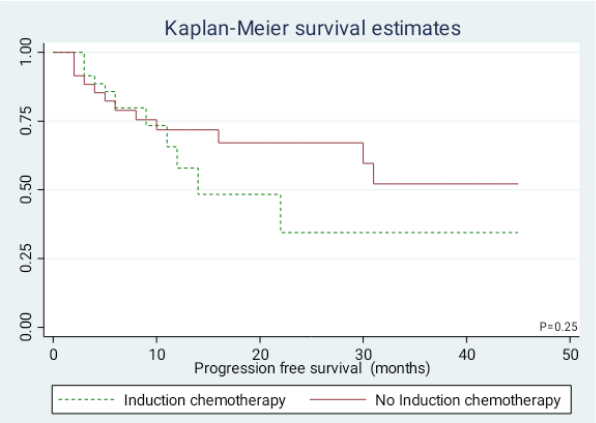

Figure 2: Relative progression free survival of patients according to treatment arm

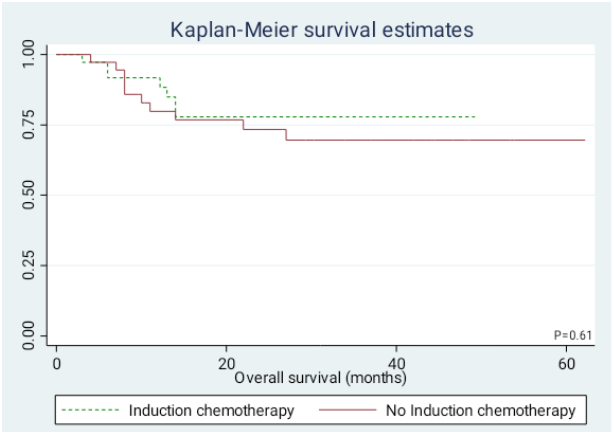

Figure 3: Relative survival of patients according to treatment arm

Table 3: Cumulative disease free/progression free survival and relation to different factors

Factors	No.	Cum survival at 24 ms %	Cum survival at 36 ms %	Cum survival at end of study (max 45 ms) %	P-value
Whole group	98	65.49	54.57	54.57	
Age					
≤60	58	81.34	69.72	69.72	0.24
>60	40	45.81	36.65	36.65	
Smoking					
Non-smoker	34	69.92	52.44	52.44	0.62
Smoker	64	60.66	53.08	53.08	
Grade					
G1/G2	68	53.24	39.93	39.93	0.10
More than G2	30	86.15	86.15	86.15	
Stage					
III	50	70.01	60.01	60.01	0.31
IVA/IVB	48	59.25	47.40	47.40	
N classification					
N0/ N1	50	65.66	39.39	39.39	0.94
N2/N3	48	62.03	62.03	62.03	
Induction chemotherapy					
Yes	42	52.44	52.44	52.44	0.80
No	56	73.97	57.53	57.53	
PFS					
Whole group	146	51.43	42.86	42.86	
Age					
≤60	88	58.50	50.15	50.15	0.95
>60	58	40.78	32.62	32.62	
Grade					
G1/G2	98	43.23	32.42	32.42	0.19
More than G2	48	64.34	64.34	64.34	
Stage					
III	70	48.37	41.46	41.46	0.91
IVA/IVB	76	56.46	45.16	45.16	
N classification					
N0/ N1	70	46.35	27.81	27.81	0.73
N2/N3	76	57.06	57.06	57.06	
Induction chemotherapy					
Yes	74	34.50	34.50	34.50	0.26
No	72	67.05	52.15	52.15	

Table 4: Overall survival and relation to different factors

Factors	No.	Cum survival at 24 ms %	Cum survival at 36 ms %	Cum survival at end of study (max 62 ms) %	P-value
Whole group	148	75.18	72.40	72.40	
Age					
≤60	88	77.06	77.06	77.06	0.61
>60	60	72.85	66.78	66.78	
Gender					
Females	46	61.38	61.38	61.38	0.06
Males	102	81.06	77.01	77.01	
Grade					
G1/G2	100	77.10	72.82	72.82	0.78
More than G2	48	71.01	71.01	71.01	
Stage					
III	70	77.72	77.72	77.72	0.37
IVA/IVB	78	73.58	67.45	67.45	
T classification					
T1/T2	40	94.12	94.12	94.12	0.03
T3/T4	108	68.33	64.91	64.91	
N classification					
N0/ N1	70	71.33	71.33	71.33	0.82
N2/N3	76	79.31	74.02	74.02	
Induction chemotherapy					
Yes	74	77.86	77.86	77.86	0.61
No	74	73.41	69.55	69.55	

Discussion:

The use of IC followed by a radiotherapy or CRT as a routine treatment in patients with inoperable disease is controversial.

The current study conducted to compare the benefit of IC+CRT with upfront definitive CRT in LAHSCC. No superiority found in DFS, PFS and OS between both treatment arms. [Table 3; Fig. 1; Fig. 2; Table 4, Fig.3].

These results are in agreement with Paccagnella et al. where they found no effect on survival rate in operable LAHSCC patients, however, in non-operable patients; chemotherapy improved survival rate (5-years OS: 21% vs. 8%) [17]. In contrary to the present work, the GETTEC Trial found a significant median OS benefit in favor of receiving induction chemotherapy in patients with oropharyngeal cancers (P = 0.03). [18]

These results matched the outcome of MACH-NC collaborative group meta-analysis that showed no positive impact on loco-regional treatment results if IC used prior to surgery or radiotherapy. However, the use of IC+CRT led to improvement in survival in all stages of oro-pharynx which contradicts our results. (19).

Similarly, another meta-analysis study of eight RCT's showed similar results to the present work where induction therapy had no positive effect on loco-regional control, while it significantly reduced metastasis and increased survival rate, though this increase was very slight (20).

In addition, results of the current study matched the conclusion of another three meta-analyses that showed very scarce increase in survival rate in chemotherapy arm with no statistical significance. (21)

The initial response rate in this study was 92.9% (CR, 75.68%; PR, 16.22%) for the CRT arm and 80% (CR, 59.46%; PR, 16.22%; SD, 5.41%) for the IC+CRT arm at the first assessment post-treatment with a significant difference in the median time to initial response (3 months and 2 months for CRT and IC+CRT respectively; p= 0.0008). However, with a median follow-up of 23 months; the overall response (ORR) was 66.67% for CRT and 52.78% for IC+CRT with no significant difference between the study groups (p= 0.23). There was no significant difference between the two groups as regards local or distant progression frequency (p= 0.24).

These findings were in line with results from long-term update of RTOG-911 study that compared non-surgical 3 arms where response and laryngeal preservation was significantly better with CRT (83.6%) compared to IC followed by radiotherapy. [22]

Over decades; concurrent radiochemotherapy found to be more effective in improving the survival rate and local control compared to induction chemotherapy according to recent RCT's and meta-analyses. [21, 23-29] The current work showed in some way similar results as CRT arm had a lower local and distant recurrence rates than IC arm, however this was not statistically significant with 24%/ 8% local/distant rate for CRT compared to 29%/ 16% for IC, respectively (p=0.24). [Table 1].

However, aiming to improve the response rate and the organ preservation frequency, induction chemotherapy found to achieve these goals in the RCTs using second and third generation drugs. [13,30-35]

Results of the present study were not in match to this finding as the initial response rate was 92.9% (CR, 75.68%; PR, 16.22%) for the CRT arm and 80% (CR, 59.46%; PR, 16.22%; SD, 5.41%) for the IC+CRT arm. This finding had a significant median time to initial response in favor of CRT (3 months versus 2 months, respectively; p= 0.0008). However, with a median follow-up of 23 months; the overall response (ORR) was 66.67% for CRT and 52.78% for IC+CRT with no significant difference between the study groups (p= 0.23). These differences may be due to different chemotherapy regimens among the former studies and the current work. [Table 1]

As regards toxicity, there were statistically significant difference between the two arms as regards neutropenia, IC were more likely to experience frequent neutropenia more than CRT (nearly 30% in IC group and 16% in CRT, p= 0.03). Overall, there was no statistically significant difference between the study groups as regards non-hematological acute toxicity profile, grade 3/4 mucositis, skin and dysphagia, which were more in IC. However, CRT arm was more likely to experience higher chronic toxicity, late skin toxicity (21 % CRT vs 3% IC) and xerostomia (21 % CRT vs 3% IC) with p-value =0.04. [Table 2] These findings were matched to results from some RCTs. [12,15,35,36]

Limitations

The present work had some limitations. First, small sample sizes within the comparison groups. Second, heterogeneity of induction regimens that was in some instances due to un-availability of all drugs in-hand at the same time. Also, heterogeneity of concurrent chemotherapy schedule employed in the CRT group. Third, unequal distribution of tumor site between both arms as laryngeal site was nearly two-thirds in CRT group while laryngeal, Nasopharyngeal and hypo-pharyngeal sites were nearly equally distributed in IC.

Conclusion

The current study suggests that induction chemotherapy followed by chemoradiation may be non-inferior to the standard of care treatment for LA SCCHN tumors with significant early-onset response and less frequent late toxicity. This might hold promise for these patients especially with larger tumor size; however, confirmation mandates larger prospective study, homogenous tumor site distribution and homogenous chemotherapy regimen.

List of abbreviations

LA SCCHN= locally advanced squamous cell cancer of head and neck
IC= induction chemotherapy
CRT= concurrent chemo-radiation
5FU= 5-Flourouracil
TPF= Docetaxel/Platinol/Flourouracil
ORR= overall response
DFS= disease free survival
OS= overall survival
PFS= progression free survival

Conflict of interest

None declared.

Author's contributions

All authors carried out study design, data collection, analysis, interpretation of data, manuscript editing, the sequence alignment, and in the decision to submit the manuscript for publication. All authors read and approved the final manuscript

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