

A Review of Chemotherapy for Locally Advanced Head and Neck Cancers

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Received: November 28, 2013; Revised: December 16, 2015; Accepted: December 28, 2015

Abstract

Context: Chemoradiation provides a survival advantage as well as increased rate of organ preservation compared with radiation alone in locally advanced head and neck squamous cell carcinoma (LAHNSCC).

Evidence Acquisition: Combined modality protocols can be used in 3 forms: a) induction chemotherapy or neoadjuvant therapy before definitive surgery or radiotherapy, b) Concurrent chemo- radiotherapy, and c) sequential therapy consisting of induction chemotherapy followed by concurrent chemo radiation.

Results: Despite an improvement in organ preservation, induction treatment has no impact on survival. Ongoing phase III trials comparing sequential therapy with concurrent chemoradiation may establish which of these two approaches is superior.

Conclusions: Until those trials have been completed, Taxane- based sequential therapy can be a reasonable alternative to concurrent chemo radiotherapy in the patients with locally advanced disease.

Keywords: Radiotherapy; Head and Neck Neoplasms; Chemotherapy

1. Context

Head and neck squamous cell carcinoma (HNSCC) comprise 3 - 5% of total cancers and more than 60% of patients refer at the advanced stage (1). Conventional treatment plan for Loco-regional advanced cancers is surgery followed by adjuvant radiotherapy. In cases who refuse surgery or not fit for the procedure radiotherapy is used as definitive treatment.

Despite the current advances in local treatment of HNSCC, prognosis of these patients is very poor. About 50 - 60% of patients with locally advanced head and neck squamous cell carcinoma experience a local recurrence and up to 30% of them will have metastasis within two years of initial treatment (2-4). In the current decade, a trend has been made for adding chemotherapy to the conventional treatment to improve survival, reduce metastasis (5-7) and to increase organ preservation (8, 9). Extensive studies have been performed to evaluate the impact of chemotherapy in treatment of HNSCC. Most of these studies have focused on the cancers of larynx, hypopharynx, oropharynx, and oral cavity (10-12). Chemotherapy is used in three different settings: induction or neoadjuvant therapy, concomitant chemo-radiotherapy, and sequential treatment which consists induction Che-

motherapy followed by concomitant chemo-radiotherapy (13). In this review, we will present the major findings of the articles evaluating efficacy of these three forms of chemotherapy for the treatment of LAHNSCC

2. Evidence Acquisition

2.1. Induction (Neoadjuvant) Chemotherapy Randomized Clinical Trials (RCT's)

The earlier studies regarding efficacy of chemotherapy in head and neck cancer goes back to 1970's. The first lunched chemotherapy regimen for HNSCC was consisted of 100 mg/m² cisplatin at the first day followed by continuous infusion of 5-FU (1000 mg/m²) for 5 consecutive days (PF) (14-16). Induction chemotherapy has been prescribed for preserving organs and also increasing survival rate (17-21).

2.1.1. Impact of Induction Chemotherapy on Survival Rate in LAHNSCC

Table 1 shows the results of 8 RCT's which studied the effect of induction chemotherapy on survival rate (6, 7,

22-27). Only 2 out of 8 studies have showed the efficacy of induction chemotherapy on improvement of overall survival and the other 6 studies showed no significant improvement. In a phase III RCT by Paccagnella et al. LA-HNSCC patients were assigned to loco regional treatment (including radical radiotherapy and/or surgery followed by adjuvant radiotherapy for non-operable and operable disease, respectively) with or without induction chemotherapy. In patients with operable tumor, chemotherapy reduced metastasis but had no effect on survival rate while in non-operable patients, chemotherapy improved survival rate besides reducing metastasis (5-year surveillance: 21% vs. 8%) (7).

In another study (GETTEC Trial), 318 oropharyngeal squamous cell carcinoma were assigned to chemotherapy with cisplatin (10 mg/m² day 1) and 5-FU 1000 mg/m² day 1-5 via continuous 24 hours infusion) followed by locoregional treatment (surgery and radiotherapy or radiotherapy alone) or locoregional treatment without chemotherapy. Patients receiving chemotherapy showed improved median survival rate (5.1 years vs. 3.3 years P = 0.03) (6).

2.1.2. Impact of Induction Chemotherapy on Organ Preservation in LAHNSCC

Two major studies assessing the role of chemotherapy in organ preservation has been published; which evaluated the role of induction chemotherapy for organ preservation in advanced laryngeal and hypopharyngeal primaries.

The leading study for organ preservation in head and neck scc was published at 1995 by Ann Arbor Veterans Affairs Medical Center in New England Journal of Medicine (4). They evaluated the effect of induction chemotherapy on larynx preservation in stage III and IV laryngeal cancers who were candidate for total laryngectomy. In this Phase III randomized trial 332 patients with squamous cell carcinoma of larynx were assigned to chemotherapy followed by definitive radiotherapy or surgery followed by adjuvant radiotherapy. Patients with less than partial response after two cycles of induction chemotherapy (cisplatin day 1 and 5FU day 1-5) underwent salvage surgery. Larynx was preserved in 64% of patients in chemotherapy group after a median follow up of 33 months. Two-year survival rate was not different between two groups (68%) (4).

The second study was conducted by European Organization for Research and Treatment of Cancer (EORTC) (8). In this study, 450 resectable advanced laryngeal (tumor stage T3 and T4) or hypo pharyngeal SCC who were candidate for total laryngectomy were assigned to sequential or alternating arm. In sequential arm, patients with 50% or more reduction of tumor size after 2 cycles of cisplatin plus 5FU received two another cycles followed by definitive conventional radiotherapy and all non-responders u. Patients in alternating arm received four cycles of cisplatin plus 5FU (5FU dose lower than

sequential arm) at weeks 1, 4, 7, 10, and 60 Gray radiation was administered between cycle in three divided 20 Gy doses. All non-responder after two cycles of chemotherapy and after 50 Gy of radiation in sequential and alternating arms respectively underwent total laryngectomy. There was no significant difference in overall survival between groups and larynx was preserved in 42% of patients.

2.2. Concurrent Radiotherapy/Chemotherapy (Chemoradiation)

Despite the positive results obtained from induction chemotherapy studies regarding organ preservation, the need for a better modality to improve the regional control of the tumor and achieving better results still remained. The risk of local recurrence was still high in operable patients undergoing induction chemotherapy (1). This resulted to consideration of induction chemotherapy with PF as an alternative and not a standard regimen in advanced cancers (especially in cases which organ preservation is of critical importance) (28).

Second generation of studies used concurrent chemoradiation and sequential treatments (29-41). Table 2 shows studies that comparing the results of radiotherapy vs. concurrent chemoradiation (5, 29, 42-46). Improved local control and survival rate is observed in concurrent chemoradiation compared to radiotherapy alone. Results of a phase III clinical trial was published by Calais et al. in 1999, which showed improved 3 year overall survival benefit for patients with advanced oropharyngeal cancers. 226 patients were randomly allocated into two groups: one receiving radiotherapy alone and the other receiving concurrent chemo radiation. Chemotherapy comprised of carboplatin (70 mg/m² per day) and 5-FU (600 mg/m² per day) using continuous intravenous infusion for three 4 days cycles during radiotherapy. In the concurrent chemo radiation arm, three-year overall survival rate (51% vs. 31%), disease free survival rate (42% vs. 20%) and local control (66% vs. 42%) were significantly better than radiotherapy alone arm. Hematologic toxicity and oral mucositis (71% vs. 39%) were also raised in concurrent chemo radiation group compared to radiotherapy alone (44).

In another phase III clinical trial known as RTOG 91-11, preservation of larynx was evaluated (46). Patients with stage III and IV laryngeal squamous cell carcinoma were randomly assigned in three groups. Group 1 received induction chemotherapy with PF (Cisplatin 100 mg/m² day 1 plus 5FU 1000 mg/m² per day for 5 days continuous intravenous infusion) followed by radiotherapy (70 Gy). Patients in this group who respond completely or partially after two cycles of induction chemotherapy received another more cycle of chemotherapy before starting of radiotherapy. Group 2 received concurrent chemotherapy (Cisplatin 100 mg/m² on day 1, 22, and 43 of radiotherapy course) with radiotherapy (70 Gy), and

the third group received radiotherapy alone. Five-year laryngectomy free survival (the primary end point of the study) was 44.6, 46.6, and 33.9% for induction, concurrent and radiotherapy alone respectively. Difference in laryngectomy free survival was significant between concurrent chemoradiation and radiotherapy alone ($P = 0.011$) and induction chemotherapy and radiotherapy alone ($P = 0.011$). Preservation of larynx was higher in concurrent chemoradiation compared to induction chemotherapy ($P = 0.0029$) and radiotherapy alone ($P = 0.0017$). Although the overall survival rate was higher in induction chemotherapy patients, but this finding was not statistically significant (46).

In another study performed on 46 patients with piriform sinus cancer, concurrent chemoradiation had a profound improving effect on regional control and larynx preservation; and larynx was preserved in more than 50% of patients undergoing this modality program (35).

2.3. Sequential Therapy RCT's

Sequential therapy comprises of induction chemotherapy followed by concurrent chemoradiation, which may need surgery as a complementary treatment. Theoretically, this modality has the advantages of both methods; so that induction chemotherapy part of this program increases the response to local treatment, organ preservation, decrease distant metastases rate and enables the clinician to evaluate the response to treatment. The concurrent chemoradiation part improves the regional control, survival rate (1). Several phase II trials have been performed focusing on the sequential modality program (42-57).

One study performed in Michigan University applied the following protocol to the larynx cancer patients: induction chemotherapy with PF followed by response assessment and then based on response concurrent chemoradiation or surgery was performed for responder and non-responder respectively. Results were too much favorable; 62% of patients were disease-free with the affected organ preserved in a 2-year follow-up (49).

Consistent with previous study, another study was performed in Yale University. Advanced head and neck cancer patients received cisplatin as the induction Chemotherapy agent followed by concurrent chemoradiation. Complete response was observed in 67% of patients and survival rate without disease progression was estimated to be 60% in a 5-year period (55). Another study in advanced larynx cancer patients showed that sequential therapy resulted in a 47% survival rate, disease-free survival rate of 78% and loco-regional control of 78% after a 5-year follow-up (50).

2.4. RCT's Focusing on Taxan-Based Protocols

Third generation of chemotherapy studies focus on addition of a taxan to induction chemotherapy for improv-

ing its efficacy. The primary objective of these studies was to apply a stronger induction regimen comparable to concurrent chemoradiation which also has fewer complications compared to the latter modality. Table 3 shows the result of these studies (54-66). To evaluate the efficacy of induction chemotherapy regimen including paclitaxel, cisplatin and 5-FU, four studies were conducted by Dana Farber Institute (54-57).

Hitt et al. in 2002 compared sequential concurrent chemoradiation with two induction Chemotherapy protocols: paclitaxel + cisplatin vs. cisplatin + 5-FU. At the end of treatments, overall response rate was 98% and 88% respectively. Survival rate was higher on non-surgical patients receiving taxan (58).

In Phase III trial TAX323, induction regimen of TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5) was compared with PF regimen every 3 weeks for four cycles. Patients without progression of disease received radiotherapy alone within 4 to 7 weeks after completing chemotherapy. Progression free and overall survival rates were significantly higher in TPF group (59). Next study which followed TAX323 entitled TAX324 evaluated the same regimens for induction chemotherapy, but unlike TAX323, concurrent chemoradiation with weekly carboplatin was prescribed after induction chemotherapy. TPF receiving patients had better overall survival (the median overall survival 71 months vs. 30 months in PF group ($P = 0.006$)); better loco-regional control ($P = 0.04$). Neutropenia grade 3 or 4 was observed more in TPF group and thrombocytopenia combined with anemia was observed to a bigger extent in the second group of study (60).

Induction chemotherapy with paclitaxel and carboplatin followed by concurrent chemoradiation with paclitaxel was administered in head and neck cancer patients in a phase II trial. Larynx preservation after two years was favorable in oropharynx cancer patients (84%), while being unfavorable in larynx cancer patients (74%) (12).

2.5. Meta-Analysis Studies

A meta-analysis of chemotherapy on head and neck cancer by MACH-NC collaborative group revealed that induction chemotherapy before surgery or Radiotherapy has no positive impact on loco-regional treatment results, but subgroup analysis showed that induction Chemotherapy regimen including cisplatin and 5-FU (PF) has a 5% increment of survival rate in a 5-year follow-up, while such an increase was not observed in carboplatin group. Addition of chemotherapy to radiotherapy in all stages of disease results in 8% improvement in 5-year survival rate. Eighty four RCT studies were analyzed in this study and it was demonstrated that this improvement in survival is observed in all regions of head and neck (oropharynx, larynx, hypopharynx, and oral cavity) and the main rationale for this

increased survival is the reduction of local recurrence due to the effect of chemotherapy (67).

Another meta-analysis performed on 42 RCT's revealed that adding chemotherapy to the local definitive treatment increases complications, response rate and local control of the tumor.

A slight improvement about 4% in survival rate was observed (50% against 54%), but in studies using concomitant chemoradiation this improvement was noticeable (50% vs. 58%). Concomitant treatment reduced mortality

up to 22% (8 - 33%, 95% C.I.) (68). In another meta-analysis study, eight RCT's addressing efficacy of induction therapy with PF and local treatment alone were evaluated. Induction Therapy had no effect on loco-regional control, but it significantly reduced metastasis and increased survival rate, though this increase was very slight (69). Results of the other three meta-analysis showed that survival rate is increased very scarce in chemotherapy modality (2.8, 4, and 6.5%). Improved survival was just observed in studies applying concomitant chemoradiation (68).

Table 1. Randomized Clinical Trials on the Efficacy of Induction Chemotherapy on Survival Rate of Advanced Head and Neck Cancer Patients ^a

Study	Chemotherapy Regimen	No. of Patients	Survival
Stell et al. (1983) (22)	MTX + F or Urea + MP + CTX	86	No effect
Toohill et al. (1987) (23)	PF	60	No effect
Martin et al. (1990) (24)	PF	75	No effect
Richard et al. (1991) (25)	VB	222	Improved
Jaulerry et al. (1992) (26)	PVB	100	No effect
Paccagnella et al. (1994) (7)	PF	237	Improved
Athanasiadis et al. (1997) (27)	PF	71	No effect
Domenge et al. (2000) (6)	PF	240	No effect

^a Abbreviations: CTX, cytoxan; F, 5-fu; M, mercaptopurin; MTX, methotroxat; VB, vincristin + bleomycin.

Table 2. Randomized Clinical Trials Comparing the Concomitant Radio Chemotherapy vs. Radiotherapy in Head and Neck Cancers ^a

Study	Survival (P value)	Regional Control (P value)	Chemotherapy Regimen	No. of Patients
Merlano et al. (1992) (42)	24% vs. 1% (0.001)	64% vs. 32% (0.03)	PF	157
Wendt et al. (1998) (43)	48% vs. 24% (0.003)	36% vs. 17% (0.004)	PF	270
Brizel et al. (1998) (29)	55% vs. 37% (0.07)	70% vs. 44% (0.01)	PF	116
Calais et al. (1999) (44)	51% vs. 31% (0.02)	66% vs. 42% (0.03)	CF	226
Adelstein et al. (2000) (45)	37% vs. 20% (0.01)		PF	295
Denis et al. (2004) (5)	48% vs. 25% (0.002)	22% vs. 16% (0.05)	CF	226
Forastiere et al. (2006) (46)			PF	547

^a Abbreviations: CF, carboplatin + 5-Fu; PF, cisplatin + 5-Fu.

Table 3. Studies on the Efficacy of Taxan-Based Induction Regimens in Head and Neck Cancer Patients^a

Study	2-Year Survival ^b	Response Rate ^b	Regimen	No. of Patients
Posner et al. (2001) (57)	79	93	TPF → RT	43
Colevas et al. (2002) (55)	68	94	TPF → RT	34
Watanabe et al. (2003) (66)	41	88	TPF → RT	48
Tsukuda et al. (2004) (65)		94	TPF → RT	18
Schrijvers et al. (2004) (64)	93	71	TPF → RT	34
Cmelak et al. (2007) (12)	76		PC → PC + RT	111
Vermorken et al. (2007); Tax323 (59)				358
	43	72	TPF → RT	
	32	59	Or : PF → RT	
Posner et al. (2007); TAX324 (60)				501
	67	72	TPF → RT + C	
	55	64	Or: PF → RT + P	
Pointreau et al. (2009) (61)				213
	73	80	TPF → RT	
	72	59.2	Or: PF → RT	
Larizadeh et al. (2010) (62)	83	85.5	TPF → RT	76

^a Abbreviations: C, carboplatin; PC, paclitaxol + carboplatin; RT, radiotherapy; TPF, docetaxel + cisplatin + 5-Fu.

^b Data are presented as %.

3. Results

More than 3 decades is past from the commencement of studies on chemotherapy treatment effect on head and neck cancers. Studies have shown that chemotherapy can increase primary response to treatment and can be beneficial in organ preservation to some extent, but its role in improvement of survival rate and the best treatment protocol is not clearly defined yet (1). Review of the literature shows that inadequate number of patients, different protocols and regimens complicate the procedure of making an ultimate decision. Another reason for different and sometimes controversial results might be the heterogenic nature of head and neck cancers and the effect of other factors such as e-Cadherin gene expression in these cancers (70).

The following results can be obtained from induction studies:

-Induction chemotherapy has a response rate of up to 80 - 90%. This finding can be of clinical importance, so that by limiting local treatment (surgery or radiotherapy), patients experience lesser disabilities induced from local treatments (14).

-According to Warden's study, response to induction Chemotherapy can predict future response to Radiotherapy. This default can be considered for selection of ultimate modality. Patients responding to induction treatment can be treated with organ-preservation based modalities such as radiotherapy. Those who do not respond well to chemotherapy are not a good candidate for radiotherapy and should undergo radical dissection. Although radiotherapy is not recommended for these

patients, but some researchers believe that concomitant Radiochemotherapy can be of benefits in patients not responding to induction therapy (16-18).

- Induction chemotherapy will ultimately increase organ preservation and quality of life (19).

- Though the effect of induction Chemotherapy on increasing survival rate is not proved yet, but it is noticeable that this modality has no negative impact on survival rate; so in cases which organ preservation is one of the primary objectives, this protocol can be used before local treatments in advanced local tumors (20-22).

Due to the inefficacy of induction chemotherapy on inducing a profound impact of survival rate, second generation of studies was designed so that concomitant therapy was used as the sensitizing procedure for radiotherapy to improve local control of tumor. Recent RCT's and meta-analysis have demonstrated that concomitant Radiochemotherapy is more effective in improvement of survival rate and local control compared to induction Chemotherapy. Due to the more extended complications, these modalities are the modality of choice in patients whom are generally healthy (32, 40-44), (45-51), (52-58), (59-65), (66-72).

Meta-analysis studies have shown the following results:

- Induction Chemotherapy does not increase survival rate,

- Induction chemotherapy with cisplatin results in a 5% increase in survival rate,

- Radiochemotherapy concomitant regimens have an 8% increased surveillance (67-69).

Sequential therapies comprising induction chemotherapy and concomitant radiochemotherapy were introduced to aggregate the possible benefits of both modalities and seem to be an appropriate method in treating head and neck cancers. Early commencement of systemic treatments which results in removal of hidden metastatic sites and simultaneous application of radiotherapy with chemotherapy improves the chance of local treatment in this modality program (62).

Third generation of studies consisting taxan-based regimens were formed to improve the efficacy of induction chemotherapy. Results of these studies revealed that adding taxan to PF regimen leads to improved outcomes, but the question that whether TPF regimen as induction chemotherapy can be equal to concomitant chemotherapy or not still remains (54-60). There are some other ongoing phase III trials in which the efficacy of taxan-based regimens is compared to concomitant radiochemotherapy.

4. Conclusions

Phase III clinical trials will reveal that which of concomitant radiochemotherapy or sequential therapy is of clinical benefit to the patients. Till that time, sequential therapies based on TPF can be an acceptable alternative for concomitant radiochemotherapy in advanced head and neck cancers.

Authors' Contributions

Mohammad Hassan Larizadeh is the archival author and attests to the integrity of the original data and the analysis reported in this manuscript. Dr. Larizadeh also attests to approving the final manuscript.

Funding/Support

This research was approved and supported by a grant (K/13-91) from Kerman Neuroscience Research Center.

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