Faridpur Med. Coll. J. 2016;11(2):54-57

Original Article

Induction Chemotherapy for Advanced Head and Neck Cancer Patients: Outcomes of A Quasi-Experimental Study.

MN Haque[1], ASMJ Chowdhury[2], MY Ali[3], NN Biswas[4], MS Rahman[5], SK Biswas[6], MM Uddin[7]

Abstract:

A quasi experimental study was conducted on outcomes of Induction Chemotherapy for advanced head and neck cancer patients from October 2015 to September 2016 at Faridpur Medical College Hospital, Faridpur. A total of 40 patients with Stages T3/T4, N0-N3, M0 and histological proved Squamous cell carcinoma of the head & neck (SCCHN) were selected to receive three cycles of chemotherapy prior to loco-regional primary concurrent chemoradiotherapy (CCRT). The induction chemotherapy regimen was a combination of Inj. paclitaxel and Inj cisplatin. The primary end point of study was clinical outcome of the patients. The response rate to induction chemotherapy was 55% for the primary tumor (CR: 12% and PR: 43%). Complete disappearance of the primary tumor occurred more often than that of the lymph node metastases. The response rate to induction chemotherapy for lymph node metastases was 24% (CR: 10% and PR: 14 %).

Key words: Head and Neck Cancer, Squamous Cell Carcinoma, Concurrent Chemoradiotherapy, Induction Chemotherapy, Paclitaxel, Cisplatin, Primary Response.

Introduction:

Head and neck squamous cell carcinoma is one of commonest malignant tumors, frequently diagnosed in an unresectable advanced stage[1]. For those patients with locally advanced SCCHN (stage III/IV, LA-SCCHN), the prognosis is quite poor, and 40%-60% of patients relapse and 30%-50% of patients live for 3 years after treatment with surgery and radiotherapy (RT)[2,3]. Given that, the comprehensive, sequential, multi modality treatment regimens play an important role in the whole treatment[4]. Several large, randomized controlled trials have demonstrated the superiority of a combined modality treatment regimen[5-7]. These results were confirmed by a recent meta-analysis on a randomized trials and demonstrating an absolute survival benefit for the addition of chemotherapy of 4.5% at 5 years, regardless of the sequence used (adjuvant, induction or concomitant)[8]. Concurrent chemoradiotherapy (CCRT) seemed to be considered the standard management for LA-SCCHN in many centers[5,9,10]. However, this regimen was challenged by the introduction of induction chemotherapy (IC), which produced response rates of 80-90%, with complete response rates of 20-40% in LA-SCCHN[11]. In this case, several studies aimed to intensify the treatment regimen by adding IC before CCRT. IC followed by CCRT is also known as sequential chemoradiotherapy. One small randomized phase II study demonstrated that patients with LA-SCCHN had a benefit for sequential chemoradiotherapy in terms of radiologic complete response rates (CR)[12]. However, the others failed to demonstrate a survival benefit following addition of IC to primary CCRT[13-16]. IC followed by CCRT is often used in patients with LA-SCCHN despite no clear evidence exists in prolonging survival for those patients with LA-SCCHN. Against this background, we present a quasi experimental study to evaluate the primary response and toxicity of IC prior to primary CCRT.

1. Dr. Md. Nizamul Haque, MBBS, FCPS (Radiation Oncology), Associate Professor & Head, Department of Radiotherapy, Faridpur Medical College, Faridpur.

2. Professor ASM Jahangir Chowdhury, MBBS, MS (Orthopaedics), Professor of Orthopaedics and Principal, Faridpur Medical College, Faridpur.

3. Professor Md. Yusuf Ali, MBBS, FCPS (Medicine), Professor & Head of Department of Medicine, Faridpur Medical College, Faridpur.

4. Dr. Nripendra Nath Biswas, MBBS, DLO, FCPS (ENT), Asstt. Professor & Head, Department of ENT, Faridpur Medical College, Faridpur.

5. Dr. Md. Shafiqur Rahman, MBBS, DLO, Senior Consultant, Department of ENT, Faridpur Medical College Hospital, Faridpur.

6. Dr. Swapan Kumar Biswas, MBBS, FCPS (Surgery), MRCS (Edin), Asstt. Professor, Department of Surgery, Faridpur Medical College, Faridpur.

7. Dr. Md. Maiyeen Uddin, MBBS. MS(Ortho), D-Ortho, Senior Consultant (Orthopaedic surgery), General Hospital, Faridpur.

Address of correspondence :
Dr. Md. Nizamul Haque, MBBS, FCPS (Radiation Oncology), Associate Professor & Head, Department of Radiotherapy, FMC, Bangladesh. Cell Phone: +88-01730302100,
Email: drmnhaque@hotmail.com

Materials and Methods:

Between October 2015 and September 2016, 40 previously untreated patients with head and neck squamous cell carcinoma were randomly selected to receive 03 cycles of chemotherapy before local treatment (CCRT). Patients with stage T3/T4, N0-N3, M0 carcinomas of the oral cavity, oropharynx, hypopharynx and supraglottic larynx were eligible for this study. Minimum laboratory criteria required to include Hemoglobin more than 10 gm/dl($\geq$ 60%), Absolute WBC count $\geq$ 4000 cell/ml, Platelets count $\geq$100,000 cells/ml, S. Bilirubin level $\leq$ 1 mg/dl, AST level not more than four times the normal upper limit and S. Creatinine level $\leq$ 1.5 mg/dl. Patients with bone or cartilage involvement, distant metastasis, previous or concomitant other malignancy, significant complicating disease, age $\geq$ 70 years or inadequate performance (Karnofsky <70) were excluded from the study. Induction chemotherapy with Inj. Paclitaxel, 175 mg/m^2 was given in 3 hours continuous infusion on day 1 and Inj. Cisplatin, 75 mg/m^2 was given in 2 hours continuous infusions on days 1 of 1st cycle with appropriate hydration, pre and post medications. The patients started next 02 cycles on day 21 and day 42. All patients were hospitalized for the 03 cycles of chemotherapy. The response to chemotherapy was evaluated within 2 weeks after completion of the 3rd cycle. CCRT was advised for each patient after 2 or 3 weeks of completion of the third cycle chemotherapy and referred to a related specialized Hospital/ Institute.

Results:

The peak age incidence was found in the age group of 61- 70 years (50%) (Figure-1) Median weight of the patients was 47.8 kg. Among 40 patients, most of them were male (82.5%), married (95%), muslim (87.5%), businessman (47.5%), middle class (55%) and smoker (85%). Male to female ratio is 4.7:1. In the study group, maximum patients were living in rural area (77.5%) and their education level is above primary up to SSC (60%). According to primary sites of the disease, most of the patients have oropharyngeal (30%) and hypopharyngeal (17.5%) cancers. In consideration of stage, maximum patients involved with T3 (65%), N0 (47.5%) disease (Table II).

Treatment related haematological and non-haematological acute toxicities of the patients were studied. Nausea (87.5%), anorexia (82.5%) and alopecia (100%) were the most common toxicities (Table III).

The primary response to chemotherapy was evaluated within 2 weeks after completion of the 3rd cycle. Five patients (12%) had complete clinical response and 17 patients (43 %) achieved partial response (PR) with more than 50% regression (Figure 2). Information of nodal response to treatment could be evaluated in only 21/40 patients with nodal involvement. Only 2/21 patients (10%) achieved a complete response and 3/21 (14%) a partial response (Figure 3).

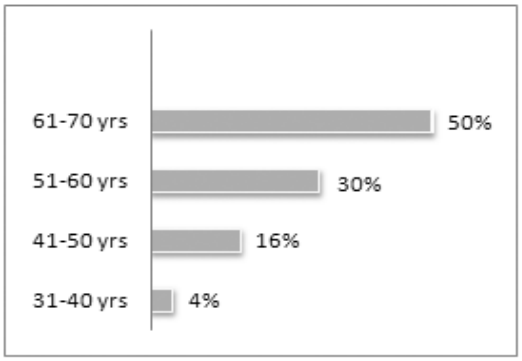

Fig.1: Age of the patients

Table-I: Characteristics of the patients.

Characteristics	Number (%)
Sex	
Male	33 (82.5)
Female	7 (17.5)
Marital status	
Married	38 (95)
Unmarried	2 (5)
Religion	
Muslims	35 (87.5)
Hindus	5 (12.5)
Education	
Illiterate	5 (12.5)
Below primary	8 (25)
Above primary up to SSC	24 (60)
HSC and above	3 (7.5)
Occupation	
Farmer	11 (27.5)
Businessman	19 (47.5)
Officials	3 (7.5)
Daily laborer	7 (17.5)
Socio-economic status	
Poor class	12 (30)
Middle class	22 (55)
Upper class	6 (15)
Residence	
Rural	31 (77.5)
Urban	9 (22.5)
Smoking status	
Smoker	34 (85)
Non smoker	6 (15)

Table II: Primary sites and stages of the disease

Characteristics	Percentage (%)
Primary site	
Oral tongue	5 (12.5)
Floor of the mouth	3 (7.5)
Retro-molar trigone	4 (10)
Gingivas	3 (7.5)
Oropharynx	12 (30)
Hypopharynx	7 (17.5)
Supraglottic larynx	6 (15)
TNM stage (AJCC)	
T3	26 (65)
T4	14 (35)
N0	19 (47.5)
N1	9 (22.5)
N2	7 (17.5)
N3	5 (12.5)

Table III: Toxicities to treatment

Toxicities	Percentage (%)
Nausea (G-II & III)	35 (87.5)
Vomiting	12 (30)
Mucositis (G-II&III)	8 (20)
Anorexia	33 (82.5)
Diarrhoea	10 (25)
Constipation	6 (15)
Weight loss	9 (22.5)
Alopecia	40 (100)
Neuropathy	4 (10)
Anaemia	7 (17.5)
Leucopenia	5 (12.5)
Thrombocytopenia	3 (7.5)

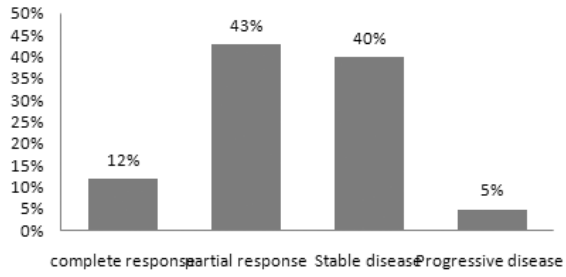

Fig. 2: Tumour responses to treatment

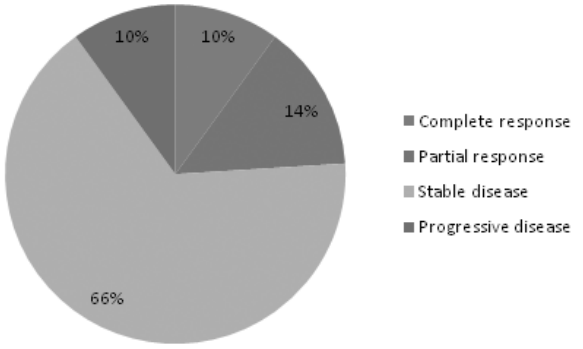

Fig. 3: Nodal responses to treatment

Discussion:

The current study was conducted at the Faridpur Medical College Hospital, Faridpur from October 2015 to September 2016, on outcomes of Induction Chemotherapy for patients with Stages T3/ T4, N0-N3, M0 Squamous cell carcinoma of the head & neck. A total of 40 histological proved squamous cell carcinomas of the head & neck were treated with chemotherapy of Inj Paclitaxel, 175mg/m^2 given on day 1 and Inj Cisplatin, 75mg/m^2 given on day 1, 03 weekly for 03 cycles. The main outcome variables of the study were toxicities and clinical outcome of the patients. In the study population, the peak age incidence was found in the age group of 61-70 years (50%). The SCCHN was steady increasing with increase age of the patients (Figure 1). Median weight of the patients was 47.8 kg. Among 40 patients, most of them were male (82.5%), married (95%), muslim (87.5%), businessman (47.5%), middle class (55%) and smoker (85%). Male to female ratio is 4.7:1. In the study group, maximum patients were liveing in rural area (77.5%) and their education level is above primary up to SSC (60%) (Table:I). According to primary sites of the disease, most of the patients have oropharyngeal (30%) and hypopharyngeal (17.5%) cancers. In consideration of stage, maximum patients were involved with T3 (65%), N0 (47.5%) disease (Table II). Treatment related haematological and non-haematological acute toxicities of the patients were studied. Nausea (87.5%), anorexia (82.5%) and alopecia (100%) were the most common toxicities (Table III). All the toxicities were manageable.

The primary response to chemotherapy was evaluated within 2 weeks after completion of the 3rd cycle. Five patients (12%) had complete clinical response (CR) and 17 patients (43 %) achieved partial response (PR) with more than 50% regression (Figure 2). Information of nodal response to treatment could be evaluated in only 21/40 patients with nodal involvement. Only 2/21 patients (10%) achieved a complete response and 3/21 (14%) a partial response (Figure 3).

Many recent studies have shown the efficacy of chemotherapy in the treatment of advanced, previously untreated head and neck cancer. Depending on the choice of drugs used, the overall response rates vary from 40-90%. In our study, the response rate after 3 cycles of chemotherapy (paclitaxel and cisplatin) was 55% with a complete response rate of 12%. This study may, however, be criticized as not testing the best induction chemotherapy, since our overall response rate was lower than has been reported after more intensive regimens[17-19]. Another criticism of our study is the small number of chemotherapy have been published and the preliminary results have not been encouraging[20]. Never the less we think that induction chemotherapy includes a potential for improvement of the results in advanced head and neck cancer and should be tested by further randomized trials.

Conclusion:

IC followed by CCRT could decrease the incidence of distant metastasis rate and improve the rates of CR. The current studies do not support the use of IC followed by CCRT over CCRT alone, and the further positioning of IC followed by CCRT as standard treatment for LA-SCCHN will come from more RCTs directly comparing IC followed by CCRT with CCRT alone.

References :

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64:9-29.
2. Posner MR, Haddad RI, Wirth L, Norris CM, Goguen LA, Mahadevan A, et al. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: evolution of the sequential treatment approach. Semin Oncol. 2004; 31: 778-785.
3. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst. 1996; 88:890-899.
4. Forastiere AA. Head and neck cancer: Overview of recent developments and future directions. Semin Oncol. 2000; 27:1-4.
5. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003; 21:92-98.
6. Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med. 1998; 338:1798-1804.
7. Budach V, Stuschke M, Budach W, Baumann M, Geismar D, Grabenbauer G, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. J Clin Oncol. 2005; 23:1125-1135.
8. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trials and 17, 346 patients. Radiother Oncol. 2009; 92:4-14.
9. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003; 349:2091-2098.
10. Ang KK, Harris J, Garden AS, Trotti A, Jones CU, Carrascosa L, et al. Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: radiation therapy oncology group phase II trial 99-14. J Clin Oncol. 2005; 23:3008-3015.
11. Argiris A. Induction chemotherapy for head and neck cancer: will history repeat itself? J Natl Compr Canc Netw. 2005; 3:393-403.
12. Paccagnella A, Ghi MG, Loreggian L, Buffoli A, Koussis H, Mione CA, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol. 2010; 21:1515-1522.
13. Chen JW, Lin SJ, Chen YH, Leu Hb, Wu TC, Huang PH, et al. A randomized control trial of induction chemotherapy combined with concurrent chemoradiotherapy for patients with locally advanced head and neck squamous cell carcinoma. Journal of Chongqing Medical University 2011; 36:1103-1106.
14. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, 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.
15. Cohen EE, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH 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.
16. Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen 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.
17. Al Sarraf M, Marcial V, Mowry P, Green H, Laramor G, Pajak T. Superior local control with combination of high dose cis-platinum and radiotherapy. An RTOG study (meeting abstract). Proc Ann Meet Am Assoc Cancer Res. 1985; 26:169.
18. Rooney M, Kish J, Jacobs J, et al. Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with 120-h 5-FU infusion and cisplatin. Cancer 1985; 55:1123-8.
19. Spaulding M, Ziegler P, Sundquist N, et al. Induction chemotherapy in head and neck cancer. A comparison of two regimens. Cancer 1986; 57:I 1 10-4.
20. Kun LA, Toohill RJ, Holoye PY, et al. A randomized study of adjuvant chemotherapy for cancer of the upper aerodigestive tract. Int J Radiat Oncol Biol Phys. 1986; 12:173-8.