Academic Journal of Cancer Research 5 (2): 40-45, 2012
ISSN 1995-8943

DOI: 10.5829/idosi.ajcr.2012.5.2.7181

Concomitant Boost with Concurrent Chemoradiation Versus Standard Fractionated Chemoradiation in Head and Neck Cancer

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Abstract: Cancers of the head and neck represent one of the commonest malignancies in males in the developing countries and presents with locally advanced disease. Altered fractionation and chemoradiation alone have shown a benefit in outcome for patients with locally advanced head and neck cancer. In an attempt to further improve the outcome in these patients, the present study was planned. A total of sixty patients (30 in each group) were included in this prospective study. In group A patients received standard fractionation with chemoradiation which was compared to group B where patients received concomitant boost in the last week of radiation with concurrent chemotherapy. Results have showed an increased toxicity in the Arm B where patients received concomitant boost with chemoradiation. The treatment outcome in terms of disease free interval did not differ significantly between the two arms. In conclusion, altered fractionation with concurrent chemoradiation should only be used in a protocol setting and routine use of this protocol is not recommended. The patients should be treated with either chemo radiation or altered fractionation depending on the site and stage of the disease.

Key words: Concomitant Boost · Chemoradiation · Cancer Head And Neck

INTRODUCTION

Cancers of head and neck are one of the most common malignancies occurring world over and is five times more common in the developing countries as compared to the developed countries [1]. These comprise of the cancers of the upper aerodigestive tract anatomically extending from the base of skull to the clavicles.The predominat histopathology within these anatomically defined regions is the squamous cell carcinoma which comprises of more than 95% of Head and Neck cancers. They are commonly associated with a prolonged history of tobacco and alcohol abuse [2]. More than 60% patients present for treatment in stage III and IV disease which is generally associated with a poor treatment outcome. Management of Head and Neck squamous cell carcinoma (HNSCC) has been extensively investigated over the last few decades. Radical surgery for advanced head and neck is unsatisfactory as it results in poor cosmesis with limited speech and the end result is often limited regional local control and survival. Radiation therapy has served as an archetype for treatment of malignant epithelial squamous cell carcinoma. Standard fractionation schedules have arrived at delivering multiple fractions of 2 Gy each for five days in a week over seven weeks [3]. However, accelerated tumour clonogen repopulation during fourth to fifth week of conventional fractionation is one of the obstacles to cure of squamous cell carcinoma of the upper respiratory and the digestive tracts [4]. Various modifications in the fractionation schedules have been explored in attempt to improve local control and survival outcome in these patients. Accelerated fractionation aims at shortening the overall treatment time using conventional or near

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conventional dose fractionation. Concomitant boost is one of the ways of accelerated fractionation where a second fraction is added during the fourth and the fifth week of treatment, thus limiting the opportunity for accelerated proliferation. A landmark study by RTOG 90-03 compared three fractionation schedules with a standard fractionation schedule and demonstrated an advantage of 8% in the local control with hyperfractionation and concomitant boost technique. There was also a trend toward better disease free survival though it did not translate into a benefit in the overall survival. Though there was an increase in acute toxicity, the late toxicity was comparable [5]. Concurrent chemotherapy with radiation has now been recommended as the standard treatment for locally advanced head and neck cancer. Pignon *et al*. in a meta analysis of 93 randomized trials showed that addition of chemotherapy was associated with 5% increased in overall survival. The use of concurrent chemotherapy with radiotherapy was the most effective modality with an absolute benefit in survival of 8% at five years [6].

In an attempt to assess the potential integration of these two modalities and to minimize accelerated tumour repopulation, the present study was designed to investigate the feasibility and efficacy of the treatment regimen using concurrent chemotherapy with cisplatin and 5 Fluorouracil with conventional fractionation for four weeks followed by concomitant boost versus standard fractionated boost.

MATERIALS AND METHODS

This prospective study was carried out over a period of one year. Previously untreated biopsy proven patients squamous cell carcinoma of the oropharynx and hypopharynx, with KPS of 80 and above without evidence of distant metastasis were included in this study. A total of sixty patients were included. Group A was the control group and group B was the study group. In group A (control group) the patients reconceived external radiotherapy to dose of 40 Gy in 20 fractions over 4 weeks. This was followed by boost of 20Gy in 10 fractions over two weeks to reduced volume after sparing the spinal cord. In group B, All the patients received external radiotherapy to a dose of 40 Gy in 20 fractions over 4 weeks, followed by 18 Gy in 10 fractions over 5 days i.e the patients were given two fractions of 1.8 Gy each in the last week of treatment. The second faction was delivered at a minimum interval of 6 hours. Both the groups received concurrent chemotherapy with cisplatin and 5-fluorouracil.Concurrent cisplatin was administered to a dose of 75mg /m^2 on day 1, 17 and 34 of treatment. Injection 5-Fluorouracil was 500 mg as an infusion twice weekly over a period of 6 hours such that the infusion continued during and one hour after the completion of radiation.

Radiation Planning and Treatment: A written consent was taken from all patients prior to treatment explaining in detail the treatment and its side effects. Individualized planning was done for each patient. Patients were positioned in supine position and a thermoplastic cast was used for each patient to immobilize the patient. Rubber traction was used to pull down the shoulders to prevent them from coming in between the radiation field. Two parallel opposed fields were marked to include the primary tumor and the draining lymph nodes. All planned fields were verified by a check x-ray using lead wires to outline the fields. Dose homogenization was achieved by using individualized wedges and compensators. The patients were treated on cobalt 60, Theratron 80R at 80cm source to surface distance.

Monitoring of Patients During Treatment: During the entire course of treatment, the patients were under close monitoring and supportive care. Maintenance of adequate intake and nutrition, oral dental hygiene and hydration was taken care of. Radiation reactions were monitored. Radiation reactions were graded according to the WHO grading system. Acute mucosal reactions were managed with daily cleaning with plain water, acetyl salicylate gargles and xylocaine viscous for local relief. Nasogastic feeding was done in patients with severe odynophagia. Fluoride paste was advised to prevent dental caries. Oral analgesics and antibiotics were prescribed wherever indicated. Multivitamins and antioxidants were frequently prescribed and local anti fungals were used in those with oral candidiasis. The patients were assessed every week for mucosal reactions and the weight loss was documented. During the treatment frequent conversation were carried out and constant moral support was given.

After completion of treatment, the patients were called for regular monthly check ups. A subjective and objective assessment was done at each visit and local reactions, response to treatment Karnofsky performance status and weight were noted. Wherever indicated a fibro optic endoscopy and CT scan was done.

For end result reporting the objective response was assessed as Complete response (CR): The disappearance of all known disease determined by two observations not less than four weeks apart; Partial Response (PR): A partial 50% or more decrease in total tumor size measured to determine the effect of two observations not less than four weeks apart; No Change (NC): A 50% decrease in total tumor size cannot be established nor has a 25%in the size of one or more measurable lesions been demonstrated; Progressive Disease(PD): A 25 % or more increase in the size of one or more measurable lesion or appearance of a new lesion.

The overall response was assessed from the first day of treatment to the date of first observation of progressive disease. The complete response was assessed from the date of observation of complete response to the date when disease progression was documented. In patients who achieved a partial response, only a period of overall response was recorded.

Statistical Analysis: The two groups were compared using the chi square test to check whether they were statistically comparable in terms of stage, sex, tumor site, performance and histology. The survival analysis was done using the Kaplan Meier method and the log rank test to check for any significant difference between the two arms.

RESULTS

The age of the patients was ranged from 25-70 years and mean age was 50.85 years. A total of 87% patients in group A and 89% in group B had history of smoking. Cancer of the hypopharynx constituted 38.9% of the cancers and orophaynx was the primary site in 61% of the patients. Majority of the patients i.e. 85.35% in group A and 92.3% in group B had locally advanced disease. Stage III disease was present in 38.24% and 46.15% patients and stage IV disease was present in 47.06% and 46.5% patients in group A and B respectively. Both the groups were statistically comparable.

A total of 66 patients were initially included in the study. There were 34 patients in group A and 32 patients in group B. Of the 34 patients included in group A, three patients left treatment within the first two weeks of treatment and the one did not did not come for boost treatment. In group B, two patients left treatment in the first ten days of treatment. Thus total number of patients evaluated 30 each in both the groups.

Table 1: Acute toxicity in patients ;Arm A vs Arm B

Toxicity	Grade	Group A	Group B	P value
Mucositis	Grade 3 or 4	43.3%	51.3%	0.03*
Dermatitis	Grade 2 and above	78.3%	81.7%	0.34
Pain	Grade 2 and above	69%	75.4%	0.16
Dysguesia	Grade2 and above	85.3%	94.4%	0.012*
Dysphagia	Grade 2 and above	87.2%	96.4%	0.016*
Weight loss	Grade2 and above	57%	75.2%	0.001*

Treatment Toxicity: Weekly monitoring of radiation reactions was done and the maximum grade of reactions during the treatment was recorded. At completion of treatment 46.7% and 38.46% patients had grade 2 mucositis in group A and B respectively (Table-1). Grade 3 mucosistis was present in 43.2% and 48.52% patients in group A and B respectively. One patient in group B had grade 4 mucositis. Grade 2 or more dermatitis was present in 78.3% and 81.7% in group A and B respectively. Grade 2 and above pain was present in 69% and 75.4 % patients respectively. Grade 2 or more dysguesia occurred in 85.3% and 94.4% patients respectively.Grade2 or more dysphagia occurred in 87.2% and 96.4% in group A and B respectively. Four patients in group A and 7 patients in group B required ryle's tube feeding. Grade 2 or more weight loss was observed in 57% and 75.2% patients in group A and B respectively. Statistically significant increase in mucositis, dysguesia, dysphagia and weight loss was observed in patients receiving concomitant boost radiotherapy with concurrent chemotherapy (p value: 0.03; 0.012;0.016 and 0.001) respectively.

Three patients in group A and five patients in group B had a treatment gap of 10-23 days due to severe mucositis. The mean gap in group A was 3.03 +/- 6.15 days whereas the mean gap in group B was 10.53 +/- 11.2 days. All the patients completed the planned treatment. Gap correction was done wherever the treatment gap increased to more than ten days. Thus the patients in group B had a larger gap in duration of treatment gap due to increased radiation reactions as compared to group A.

Response to treatment: Both local and tumor lymph nodal response was assessed at four weeks of completion of treatment. In group A 76.47% patients and in group B, 65.38% patients had a complete clinical local response to treatment. Partial response at local site was observed in 23.53% in group A patients and 34.62% in Group B. On assessing the nodal response it was observed that 65.38% patients in group A and 68.5% patients in group B had a complete clinical regression of involved lymph nodes. A partial response was observed in 26.92%

Table 2: Local and Nodal tumor response

	Local response			Nodal response		
Response	Group A	Group B	P value	Group A	Group B	P value
Complete response	76.4%	72.1%.	0.95	65.38%	68.75%	0.59
Partial response	23.53%	27.8%	0.96	29.92%	12.5%	0.139
No response	0	0		11.53%	6.25%	0.75
Progressive disease	0	0		0	12.5%	0.173

patients in group A and 12.5% patients in group B. In 3 patients in group A and 2 patients in group B, there was no change in the size of involved lymph nodes. In group B, 1 patient had clinical progression of disease. A complete local and nodal response was observed in 49.06% patients in group A as compared to 53.85% in group B. No statistical difference in response to treatment was observed between the two groups.

Disease Free Survival and Patterns of Failure: Patients who demonstrated a complete clinical response were considered for the disease free survival analysis. At last follow up at 15 months, 32% patients in group A and 33% patients in group B were disease free. One patient in each group underwent radical neck dissection. The patient in group A presented with distant metastasis after 15 months and the patient in group B was disease free at follow up of 15 months. Two patients in group A and none of the patients in group B had a local recurrence. One patient in group B had a nodal recurrence. None of the patients in either groups had both local and nodal recurrence. Four patients in group A and 2 patients in group B had distant metastasis. All the patients who developed distant metastasis were locally free of disease. Death occurred in 3 patients in group A and in 1 patient in group B. Two patients died of cardiac events. One patient had treatment related death.

DISCUSSION

Concurrent chemoradiation with standard fractionated radiotherapy is considered the treatment of choice in locally advanced head and neck cancer. The evidence of this was derived from a number of large randomized control trials and meta analysis which has not only shown a superiority in terms of improved local control along with organ preservation but has also shown a benefit in the overall survival in these patients. On the other hand, various fractionation schedules have been intensely explored in the treatment of head and neck cancers. In the landmark phase III trial by the Radiation Therapy Oncology Group (RTOG) 9003, a head to head comparison of accelerated fractionation with hyperfractionation in the four arm study clearly demonstrated a superiority of altered fractionation in terms of local control without affecting the late toxicity though the overall survival was comparable [5]. In a study by Ghoshal *et al* patients treated with concomitant boost had a better 2-year disease free survival (71.7% vs. 52.17%, p-0.0007) and loco regional control rates 973.6% vs. 54.5%,p-0.0006) than with conventional fractionation. Grade 3 mucositis was seen in 35% patients in the concomitant boost arm whereas in the conventional arm only 19% had grade 3 mucositis. (p-0.01) [7]. Thus both concurrent chemo radiation and altered fractionation regimens have individually shown an increase in the acute toxicity as compared to standard conventional fractionated radiotherapy alone [8, 9]. In a study by the Radiation therapy Oncology Group (RTOG) evaluated the intermittent high dose cisplatin regimen (100mg/m^2) every three weeks for three cycles) during radiotherapy in 124 patients reported an improved outcome with complete response of 71% but with increased acute toxicity[10]. Clinical synergy between infusional 5- fluorouracil and cisplatin is evident in tumour types that are sensitive to both drugs such as squamous cell carcinoma of head and neck and oesophagus. Thus keeping in mind the anticipated toxicity of concurrent chemotherapy with altered fractionation, we used Cisplatin to a dose of 50mg/m^2 on day 1, 17 and 34 instead of the recommended dose of 100 mg/m^2 every three weeks. But despite that a significant increase in toxicity was observed in patients receiving concomitant boost with concurrent radiotherapy as a result an increased treatment interruption was observed in this group. However, all patients completed the planned treatment. In a study by Shaleen *et al*. [11] 95 patients were treated with concomitant boost radiotherapy with concurrent cisplatin 35 mg/m^2 given weekly. A total dose of 70Gy in 38 fractions was delivered over 6 weeks with concomitant boost in the last fraction. Acute grade III/IV mucosal toxicity was seen in 79% which resulted in a total weight loss of 7.9 kg from a mean pretreatment weight of 51 kg. Nasogastric tube placements were required in 26% (25/95) for an average

duration of 19.3 days. Mortality during and within 30 days of treatment was seen in 14% [11]. In our study the total dose of radiation and chemotherapy were low as compared to Shaleen *et al*. The reported grade 3 and above mucositis was observed in nearly 50% patients in Group B, and grade 2 or more weight loss was observed in 75% patients in group B as compared to 57% patients in group A. Twenty three percent of our patients required ryles tube feeding in the concomitant boost arm as compared to 13% in the conventional radiation arm. However, there were no treatment related deaths.

A non significant increase in complete clinical response (defined as a complete local and nodal response) was observed in patients who received concomitant boost with concurrent radiotherapy (54% vs 49%). Similar control rates have been reported for concurrent chemo radiotherapy protocols in advanced head and neck malignancies [12-14]. However, an inferior survival was reported in our study. At 15 months the survival was only 32% for group A and 33% for group B which was comparable for both the groups. However, this can be attributed to an extent that nearly 22% of our patients were lost to follow up and majority of our patients, nearly 47 % in both arms had stage IV disease.

The cardinal feature of our study was the reduction of overall treatment time with concomitant boost. Concomitant boost with concurrent chemotherapy was found to be a feasible approach in locally advanced head and neck cancer though no difference in terms of disease free survival was observed in our patients. We do not recommend the use of this protocol in our routine practice. Because these patients were recruited in a trial setting where utmost care is taken about the nutrition and acute treatment related problems during the entire course of treatment. Since both chemoradiation [6] and altered fractionation [15] has shown a parallel survival advantage of 8%, in a resource constrained setting where the patient burden is high and patients nutritional status is compromised, it may be better to treat the patients with either chemoradiation alone or with altered fractionation depending on the status of the tumour and institutional preference rather than treating with the a combination of the two modalities.

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