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Toxicity analysis in concomitant chemoradiotherapy versus accelerated radiation therapy following induction chemotherapy in locally advanced head-and-neck carcinoma in Indian scenario

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ABSTRACT

Objective: Toxicity analysis in patients of locally advanced head and neck carcinoma (LAHNC) when induction chemotherapy (InCT) with TPF (docetaxel, carboplatin, 5-fluorouracil) is followed by concomitant chemoradiotherapy (CCRT) in one arm, and accelerated radiation therapy (RT) in other arm. Toxicity analysis in patients of locally advanced head-and-neck carcinoma (LAHNC) when induction chemotherapy (InCT) with TPF (docetaxel, carboplatin, and 5-fluorouracil) is followed by concomitant chemoradiotherapy (CCRT) in one arm and accelerated RT in other arm.

Materials and Methods: Fifty patients with LAHNC were taken and divided into two arms of 25 each. All patients received three courses of 3-weekly InCT with docetaxel 80 mg/m², carboplatin 300 mg/m², and 5-fluorouracil 600 mg/m². This was followed by arm A patients receiving CCRT, wherein total radiation dose of 64 Gy/32 fractions/6.2 weeks (i.e., 2 Gy/fraction) with five fractions per week was given along with three weekly carboplatin 300 mg/m² for three cycles. Arm B patients received accelerated RT given six fractions per week, total dose 64 Gy/32 fractions/5.2 weeks (i.e., 2 Gy/fraction).

Results: Fifteen percentage of the total patients developed Grade 3 or 4 neutropenia during InCT. Grade 3 or 4 thrombocytopenia was seen 23% of all patients during InCT. Grade 3 or 4 neutropenia and thrombocytopenia was also reported in 31% and 23% patients of arm A during CCRT. Acute Grade 3 or 4 radiation dermatitis, mucositis, and pharyngitis was seen in 21%, 33%, and 12% patients of arm B as compared to 17%, 22%, and 9% patients of arm A, respectively, showing more of acute radiation reactions in the accelerated RT arm of the study. Late Grade 3 or 4 radiation-induced skin, mucosal, subcutaneous tissue, and salivary gland toxicity was not observed in any of the arms of the study. Disease status at last follow up, in arm A– 52% remained alive with no evidence of disease (NED), 39% remained alive with residual disease (RES) and 9% had locoregional recurrence (REC) while in arm B – 46% remained alive with NED, 46% remained alive with disease and 8% had locoregional recurrence. In arm B – 46% remained alive with NED, 46% remained alive with disease, and 8% had locoregional recurrence.

Conclusion: InCT followed by either CCRT or accelerated RT are associated with slightly increased but manageable toxicity profile and good complete response rates. Therefore, both can be used as alternative treatment modality to CCRT alone in institutions where there is a lot of burden of patients and a long waiting list for RT.

Key words: Accelerated radiation therapy, concomitant chemoradiotherapy, induction chemotherapy, locally advanced head-and-neck carcinoma

INTRODUCTION

Head-and-neck cancer (HNC) is a malignancy arising mostly from the surface epithelium of upper aerodigestive tract consisting of wide spectrum of malignancies including cancers of oral cavity (lips, buccal mucosa, alveolar ridges, floor of mouth, oral tongue, retromolar trigone), nasopharynx, oropharynx (soft palate, tonsil structures, base of tongue, oropharyngeal wall), hypopharynx (pyriform sinuses, post-cricoid, posterior pharyngeal wall), larynx, paranasal sinuses, and major and minor salivary glands. Majorly HNC are squamous cell carcinoma (SCC) on histopathology.[1] Worldwide incidence of HNC cases is 686,328 annually which amounts for 4.8% of all cancers while the incidence in India is 145,087 annually which is 14.3% of all cancers.[2] Tobacco smoking and alcohol consumption acting individually as well as synergistically are the dominant etiological factors, while others include immunosuppression and viral infection (human papillomaviruses and Epstein–Barr virus).[3] Stage at the time of diagnosis is the most important determinant of prognosis. Majority of HNCs are locoregionally advanced (Stage

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III or IV) at the time of presentation and have cure rates between 30% and 40% despite the availability of multimodality therapy.[4]

During the early 1990s, conventional radiotherapy (RT) was the standard of care in patients with locally advanced head-and-neck carcinoma (LAHNC) but because of the poor outcomes of RT alone other options were being tested to enhance the efficacy and the therapeutic ratio of RT. One of them was evaluating the effect of adding chemotherapy (CT) to RT, either before RT (as induction/neoadjuvant CT) or simultaneously with RT (as concomitant chemoradiotherapy [CCRT]). Meanwhile, oncologists were also assessing the effect of modified fractionated RT.[5]

Addition of CT to RT was analyzed in a meta-analysis and showed a small but significant survival advantage in favor of chemotherapy (4% at 5 years), which was higher (8% at 5 years) in case of concomitant chemoradiation as compared to sequential or adjuvant chemotherapy.[6] Rationale behind the combination of radiation and chemotherapeutic agents is known as "spatial cooperation." Radiation is effective for targeting localized primary tumor, but it is ineffective against disseminated disease. On the other hand, chemotherapy may cope with micrometastases, whereas it cannot control the larger primary tumor.[7]

Induction CT targets both primary tumor as well as disseminated disease. It acts by reducing the population of clonogenic cells and causing reoxygenation of the surviving hypoxic cells, both rendering tumors more susceptible to radiation therapy. It is beneficial for reducing the rate of distant metastases, increasing organ preservation, and survival rates. Induction chemotherapy (InCT) may also help in predicting tumor response to chemoradiation.[8,9] Hitt, Vermorken, and Posner have reported improvements in overall response rate, complete response rate, organ preservation, and survival in three separate phase III studies of InCT with TPF (taxane, platin, and fluorouracil) compared to InCT with PF only, followed by definitive therapy.[10-12]

CCRT is the standard first-line treatment for LAHNC. Both carboplatin and cisplatin are known to produce survival benefit in LAHNC when added to radiation therapy as CCRT but carboplatin was used in this study design due to ease of giving the drug on outpatient basis, its reduced renal, digestive, and neurologic toxic effects compared with cisplatin and its high radiosensitizing effect.[13] Thus, due to benefits of both InCT and CCRT, combining induction and concomitant chemotherapy with radiation in a sequential approach, has the potential for improving disease outcomes.

The rationale behind accelerated fractionation is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during treatment and therefore increases the probability of tumor control for a given total dose. Strategies to accelerate radiation can be divided into two categories: (a) Pure accelerated fractionation regimens, which reduce overall treatment time without concurrent changes in the fraction size or total dose and (b) hybrid accelerated fractionation, which reduces overall treatment time with changes in fraction size, total dose, and time distribution.[14] Improved local tumor control has been observed with accelerated treatments employing continuous radiation schedules without compromise in total dose.[15]

In CT with TPF is seen to be associated with more incidences of Grade 3 or 4 leukopenia and neutropenia.[11] About 30% and 60% of HNC patients receiving RT develop oral mucositis and more than 90% of patients receiving CCRT are affected.[16] Studies have proved that CCRT is associated with considerable early and late toxicities in HNC cases.[17] Rates of Grade 3 and 4 mucositis are more in CCRT as compared to RT alone.[13] Accelerating the radiation treatment also result in an increase in normal tissue toxicity, especially mucositis. Higher rate of severe late toxicities in the accelerated RT have resulted in an increase in non-cancer-related death rate.[15] Certainly, the complication rates of combined regimens are also higher than those of RT alone.[18] Thus, the inclusion of strategies to reduce treatment-related toxicities is getting more attention in the overall management of LAHNC, especially when the quality-of-life of patients is being prioritized as part of the multidisciplinary treatment approach.

Over the past couple of years, multimodality approaches are being tried to improve survival in patients of LAHNC. This study was done with the intent to analyze the adversities that emerge due to these novel combinations of treatments so that their feasibility can be assessed before considering them as a standard treatment modality.

MATERIALS AND METHODS

Eligibility Criteria

Fifty previously untreated, histopathologically proven patients of SCC of head and neck, attending the Department of RT were enrolled in this prospective, randomized, open-label, parallel study, in which combination of chemotherapy and radical radiation therapy was decided as the definitive treatment protocol. Period of the study was extended from January 2013 to November 2014. Written informed consent was obtained from all patients before their inclusion in the study. Eligibility criteria for patients was: American Joint Committee of Cancer stage III/IV, positive biopsy for SCC of head and neck, Karnofsky Performance Status (KPS)> 70, Hb>8.0 g/dL, TLC>4000/cmm, platelet count>100,000/cmm, blood urea< 40 mg/dL, serum creatinine <1.5 mg/dL, Serum glutamate oxaloacetate transaminase <35 IU/L, and serum glutamate pyruvate transaminase <40 IU/L. Patients excluded from the study were those having distant metastases; prior radiation, surgery, or chemotherapy for the disease; KPS <60; pregnant or lactating patient; associated medical conditions; primary in thyroid/salivary glands; histopathology other than SCC.

Treatment

InCT

All 50 patients received 3-courses of 3-weekly InCT with TPF consisting of injection docetaxel 80 mg/m^2, injection carboplatin 300 mg/m^{2+} and injection 5-fluorouracil 600 mg/m^2. InCT was preceded by pre-medication with injection ranitidine 50 mg, injection pheniramine maleate 25 mg, injection dexamethasone 16 mg, and injection palonosetron 0.25 mg.

Arm A

A total of 25 randomly selected patients who already have received InCT, were given concomitant conventional radical radiation therapy, given 5 fractions/week, in total dose of 64 Gy/32 fractions/6.2 weeks (i.e., 2 Gy/fraction) along with 3-courses of three weekly injection carboplatin 300 mg/m^2.

Arm B

A total of 25 randomly selected patients who already have received InCT were given accelerated radical radiation therapy, given 6 fractions/week, in total dose of 64 Gy/32 fractions/5.2 weeks (i.e., 2 Gy/fraction).

RT Technique

RT was delivered by Cobalt-60, in the supine position by parallel opposing fields including the primary tumor, disease extension, and neck nodes. The shrinking field technique was used to spare the spinal cord after a dose of 44 Gy.

Assessment

Toxicity arising from chemotherapy was assessed using the World Health Organization (WHO) toxicity criteria. Acute and late radiation toxicity was analyzed using the Radiation Therapy Oncology Group (RTOG) criteria. Tumor response (both primary and nodal response) was assessed by the WHO response criteria.

Follow-up

Patients were followed up weekly for 4 weeks in 1st month after completion of treatment and then monthly. At every visit, patients were clinically evaluated for local control of disease and treatment-related complications. The patients were also assessed for any evidence of distant metastasis during each follow-up.

RESULTS

Patient Characteristics

Mean age at the time of presentation of patients in arms A and B was 53 and 54 years, respectively. The study comprised 94% males and 6% females. 92% patients were from rural and 8% patients were from urban background. 96% patients were smokers while 4% were non- smokers. Patients with KPS 80 were 14% and KPS 90 were 86%. The most common primary tumor site was oropharynx in 74% cases. Base of the tongue was the most common primary tumor site in arm A (48%) while tonsil was the most common primary tumor site in arm B (40%). In arm A, 52% patients were of Stage III while 48% patients had stage IV, whereas 64% patients had Stage III and 36% patients had Stage IV in arm B [Table 1].

Table 1: Distribution of patients

Patient characteristics	Arm A (*n*=25) Concomitant RT (%)	Arm B (*n*=25) Accelerated RT (%)
Age group (years)		
≤50	40	48
>50	60	52
Gender		
Male	96	92
Female	4	8
Background		
Rural	88	96
Urban	12	4
Smoking		
Smoker	96	96
Non-smoker	4	4
KPS		
80	8	20
90	92	80
Site of tumor		
Oral cavity	0	12
Oropharynx	68	80
Oral cavity	12	0
Larynx	20	8
Stage-wise distribution		
III	52	36
IV	48	64

KPS: Karnofsky performance status

Response Rates Post-NACT

Complete response after three InCT was seen in 12% and 20% patients in arm A and B, respectively, while 88% patients in arm A and 80% patients in arm B developed partial response to InCT.

Hematological Toxicity during InCT

Hematological toxicity was assessed each time before InCT as per the WHO criteria. None of the patients developed Grade 3 or 4 anemia during InCT in both arms of the study. About 15% of the total patients developed Grade 3 or 4 neutropenia during InCT which got divided as 7% patients in arm A and 23 % patients in arm B. Grade 3 or 4 thrombocytopenia was seen 23% of all patients during InCT which got divided as 25% and 21% patients in arm A and B, respectively. Overall compliance to InCT was good [Table 2].

Table 2: Toxicity during induction chemotherapy (WHO criteria)

Toxicity type	Arm A (*n*=25) Concomitant RT (%)	Arm B (*n*=25) Accelerated RT (%)
Grade 3 or 4 anemia	0	0
Grade 3 or 4 neutropenia	7	23
Grade 3 or 4 thrombocytopenia	25	21

WHO: World Health Organization, RT: Radiotherapy

Hematological Toxicity During Concomitant Chemotherapy

Concomitant chemotherapy was given in arm A of the study and hematological toxicity was assessed in patients each time before CT. No Grade 3 or 4 anemia seen in any patient at any time during concomitant CT. Grade 3 or 4 neutropenia was seen in 31% patients and Grade 3 or 4 thrombocytopenia was seen in 23% patients. Two patients received only one cycle of concomitant chemotherapy [Table 3].

Table 3: Toxicity during concomitant chemotherapy (WHO criteria)

Toxicity type	Arm A (*n* = 25)*Concomitant RT (%)
Grade 3 or 4 anemia	0
Grade 3 or 4 neutropenia	31
Grade 3 or 4 thrombocytopenia	23

*2 patients left the treatment after first course of CCRT in Arm A, WHO: World health organization

Acute Radiation Reactions During RT

Radiation reactions were assessed during and after radiation treatment completion and were graded as per the RTOG Grades. Grade 3 or 4 dermatitis was seen in 17% patients in arm A and 21% patients in arm B. 22% patients in arm A and 33% patients in arm B developed Grade 3 or 4 mucositis. RTOG Grade 3 or 4 pharyngitis was also observed and was seen in 9% and 12% patients in arm A and B, respectively [Table 4].

Table 4: Radiation toxicity (RTOG criteria)

Toxicity type	Arm A (n = 25)*Concomitant RT (%)	Arm B (n = 25)**Accelerated RT (%)
Acute radiation toxicity		
Grade 3 or 4 dermatitis	17	21
Grade 3 or 4 mucositis	22	33
Grade 3 or 4 pharyngitis	9	12
Grade 3 or 4 laryngitis	0	0
Grade 3 or 4 salivary gland toxicity	0	0
Grade 3 or 4 upper GI toxicity	0	0
Late radiation toxicity		
Grade 3 or 4 dermatitis	0	0
Grade 3 or 4 subcutaneous toxicity	0	0
Grade 3 or 4 mucosal toxicity	0	0
Grade 3 or 4 salivary gland toxicity	0	0

*2 patients left the treatment after the first course of CCRT in Arm A, **1 patient left the treatment in Arm B. RTOG: Radiation therapy oncology group

Late Radiation Reactions

None of the patients in either of the arms developed Grade 3 or 4 late radiation dermatitis, late subcutaneous toxicity, late mucosal, and late salivary gland toxicity [Table 4].

Disease status at last follow-up

No evidence of disease (NED) was observed in 52% patients in arm A and 46% patients in arm B. residual disease (RES) was seen in 39% patients belonging to arm A and 46% patients in arm B. Recurrence was seen in 9% patients in arm A and 8% patients in arm B [Table 5].

Table 5: Disease status at last follow-up

Arms	Number of patients	Disease status		
		NED (%)	RES (%)	REC (%)
Arm A	23*	52	39	9
Arm B	24**	46	46	8

*2 patients left the treatment after the first course of CCRT in Arm A, **1 patient left the treatment in Arm B, NED: No evidence of disease, RES: Residual disease, REC: Recurrence

DISCUSSION

Convincing results of TAX 323 and 324 trials have established TPF combination CT as the most effective InCT regimens for LAHNC.[11,12] Various studies where InCT was followed by RT alone has shown more of locoregional failures, and it is well known from the published literature that both concomitant chemoradiation and accelerated radiation are capable of decreasing locoregional failures compared to RT alone in HNC.[12,15] Hence, the present study was planned to see the adversities associated and thus the feasibility where InCT with TPF was followed by CCRT and accelerated RT. Both RT and CT bring their own side effects and when they are combined in one or the other form have the risk of enhancement of these toxicities a notch higher.

In our study, most of the patients in both arms were above 40 years, i.e., 84% in arm A and 88% in arm Rao *et al.* and other studies conducted from India also reported similar age group presentations as seen in our study.[19] Overall, 94% patients were male, remaining 6% were female. Rao *et al.* and other studies conducted from India have also shown similar trends in their work on HNCs.[19] This indicates that HNC occurs more frequently in males than in females probably because most of the males are smokers. 92% patients were from rural areas while 8% patients belonged to urban background and this is because Haryana's economy is predominantly agricultural based and majority of the population lives in rural areas, and this is reflected in our study. Authors from this part of India, who have published their work on head-and-neck carcinomas, also confirm this type of findings.[20] Smoking is recognized etiological factor in HNC. In this study, overall 96% patients were smokers while 4% patients were those who never smoked. This correlates with reported etiology of the head-and-neck carcinoma available in the literature. Oropharynx was most common primary site observed in 74% cases. Base of the tongue was the most common primary site in arm A (48%) while tonsil was the most common primary site in arm B (40%). This is also in tune with literature on HNCs. In arm A, 52% patients were of Stage III while 48% patients had Stage IV, whereas 64% patients had Stage III and 36% patients had Stage IV in arm B. The arms were not exactly matching in site-wise and stage-wise distribution but are comparable. This is because of random selection of the patients for each arm.

During InCT, there were no incidences of either Grade 3 or 4 anemia in any of the arms at any time. Paccagnella *et al.* reported similar findings.[21] 15% of the total patients developed Grade 3 or 4 neutropenia during InCT. Grade 3 or 4 thrombocytopenia was seen 23% of all patients during InCT. Similar toxicities were reported by Vermorken *et al.* in TAX 323 trial.[11] Assessment of hematological toxicity during three cycles of concomitant chemotherapy with carboplatin in arm A showed Grade 3 or 4 neutropenia and thrombocytopenia in 31% and 23% patients, respectively. There was no Grade 3 or 4 anemia seen. These are acceptably reported toxicities of carboplatin. Lasrado *et al.* reported similar findings.[22]

Skin irradiation with a defined time dose schedule produces reproducible pattern of gross changes that are dose dependent. The acute sequence occurs during the first 7 days following irradiation as erythema (1–2 week). As the radiation dose increases, pigmentation, epilation and dry desquamation start to appear on skin in about 2-3 weeks. This is followed by moist desquamation of skin in about 5-6 weeks, which either heals by 50 days following radiotherapy or progress to necrosis. This is followed by moist desquamation (5–6 weeks), which either

heals by 50 days following RT or progress to necrosis. In our study, Grade 3 or 4 acute radiation dermatitis was seen in 21% of patients in arm B and 17% of patients in arm A which is similar to study conducted by Overgaard *et al*.[23] Radiation-induced mucositis is defined as the reactive inflammatory process of the oropharyngeal mucosa. The severity of mucositis depends on the total dose, fractionation and duration of therapy, and associated infections. After 20–30 Gy in conventional fractionation, the mucositis becomes erythematous. After an additional dose of 10–12 Gy patches of mucositis begin to appear. As treatment continues, the patches become confluent. Complete healing may require 2–3 weeks after the end of therapy. Grade 3 or 4 acute mucosal reactions in arm B were seen in 33% of the patients while they were seen in 22% patients in arm A, which is higher as compared to a study by Overgaard *et al.*, which is explainable in the setup where this study was conducted, as most of the patients coming to our setup are from rural background and poor socioeconomic status leading to poor oral intake, poor oral hygiene, and non-affordability for the medicines.[23] Acute pharyngeal reactions to RT were experienced as different grades of dysphagia. Grade 3 or 4 pharyngitis was seen more in arm B compared to arm A and was seen in 12% and 9% patients respectively. Late radiation-induced side effects were more in arm A compared to arm B. This was similar to results of a study by Bourhis *et al*.[5] However, there were no Grade 3 or 4 late radiation toxicity reported in either of the arms.

Disease status at last follow-up showed NED in 52% patients in arm A and 46% patients in arm B. RES was seen in 39% patients belonging to arm A and 46% patients in arm B. Recurrence was seen in 9% patients in arm A and 8% patients in arm B. These results are also comparable to study by Bourhis *et al*.[5]

CONCLUSION

With emerging new treatment modalities for the management of HNC, it has become critical for the treating oncologists to take into consideration various patient, tumor, treatment, and disease-related factors. They should not just select the most efficacious treatment but also give due consideration to the risk and adversities associated with that treatment modality. However, this should not discourage treating physicians from adopting novel therapies, but instead, motivate them to have a better understanding of the mechanisms in action for every treatment approach. Thus, the toxicity analysis of this study will help various oncologists in Indian setup in selecting the treatment modality appropriate for their patients and situations. It is evident from the study that patients who received accelerated RT experienced more acute radiation toxicity than others. It can also be concluded from the study that InCT followed by CCRT may be recommended in the curative setting in LAHNC taking into account the good complete response rate and manageable toxicities.

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