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Abstract

Introduction: Globally, there is marked variation in overall incidence and presentation of head and neck cancers, these cancers account for 11.5 per 100,000 population in G.C.C states. Concomitant chemotherapy and external beam radiotherapy (EBRT) is indicated in such cancers with aim of organ preservation, control and possible cure. Hyper fractionated radiotherapy with concomitant chemotherapy or cetuximab is a lesser explored option. In this study we wish to assess the tolerability and efficacy of cetuximab with altered fractionation and compare this with the chemotherapy (cisplatin).

Materials & Methods: This is a randomized controlled study from a single institute in Kuwait. Locally advanced head and neck cancer cases excluding cancer nasopharynx are enrolled for the study. Stage III or stage IV-A cases were enrolled with histopathology squamous cell carcinoma. Patients were randomized into 2 arms. Arm A: to receive platinum–based CT i.e. cisplatin in a dose of 100 mg/m² 3–weekly or 40 mg/m² weekly during radiation; Arm B: received cetuximab with a loading dose 400 mg/m², one week before radiation followed by weekly dose of 250 mg/m² during radiation. Radiotherapy was delivered using intensity modulated radiotherapy (IMRT) or 3D–conformal radiotherapy (CRT). The primary objective was to evaluate whether the use of cetuximab with concurrent hyperfractionated radiation regimen will have loco regional control rates (LC) and Disease–free survival (DFS) that are comparable to concurrent cisplatin in patients with LAHNC. The secondary endpoints were to compare the impact of using concurrent cetuximab vs chemotherapy regimen on Overall Survival of patients (OS) and acute and late adverse events.

Results: From November 2012 to November 2017, 40 patients were randomized. The median age of was 51 years (range 27–72 years). Thirty–five patients are male and remaining was female. 14 patients have their primaries in larynx, 11 in oropharynx, 8 in oral cavity, and 5 has tumor in hypopharynx. Two patients had disease in nasal sinus or overlapping subsides. 50% has T4 lesions while 35% has T3 lesions, Nodal status was (N0-1) in 20 patients and (N2-3) in 20 patients. Overall staging showed a majority to have stage IV disease (63%). HPV was negative in 2 cases in Arm 1 and positive in 2 cases in Arm 2. 22 patients were randomly allocated in Arm A (platinum–based) while 18 were in Arm B (cetuximab). CR was achieved in 59% in arm A vs 50% in Arm B, while PR was 27.3% and 27.8% respectively. Disease progressed in 2 patients in Arm B only.

Out of these 40 patients, 14 patients failed (6 and 8 in arm A and B respectively). Locoregional failure was documented in 6 (27.3%) vs 7 (38.9%) of arm A and B respectively, which was statistically not significant possibly related with lower number of cases. 2 years DFS was 56.5% vs 77.3% in cisplatin vs cetuximab arm (denoting nonsignificant increase of relapse rate in cisplatin arm). However, 2 years OS was 80.7% vs 57.3% in cisplatin and cetuximab arm respectively (p value=0.04).

Conclusion: Though cetuximab has lesser side effects but it is not indicated in treatment of LAHNC. Concurrent
cisplatin is a trusted option for concomitant setting regardless of the HPV status and tumor location. However, in the context of cisplatin ineligible patients, cetuximab should be used only with hyper fractionation. This preliminary study could represent a good core of large international multicenter RCT.

**Keywords:** Hyper fractionated radiotherapy, Cetuximab, Locally advanced head neck cancers.

**Background**

Head and Neck cancer (HNC) has known geographic variation and disparity in incidence, etiology, natural behavior and outcome. For example, United Kingdom has the lowest incidence (3% of all malignancy) while in Bombay (India), HNC cancer constituted 27% of all cancers.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) Among the GCC (Gulf Cooperation Council) states, HNC account for 11.5 per 100,000 population. 25%–35% of Kuwait population are expats from South Asian origin.\(^4\)

Non-surgical organ preservation treatments have evolved as a valid option for the treatment of patients with locally advanced head & neck cancer (LAHNC). The current standard of care for those patients is concomitant chemoradiotherapy (CRT). This includes radiotherapy (RT) with fractions size of 1.8 – 2Gy, to a total dose of 66 – 70Gy’s over 6–7 weeks and platinum–based chemotherapy (CT).\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^8\) The reported absolute benefit of adding concomitant chemotherapy to locoregional radiotherapy is 4–8%.\(^7\)

Interestingly, several trials of altered fractionation schemes showed similar magnitude of benefit, especially with hyperfractionation schedules. Clinical trials of hyperfractionation in which two doses are delivered per day for 6–7 weeks appear to result in greatly reduced late effects if the total dose is titrated to produce equal or possibly slightly more acute effects. Tumor control is the same or slightly improved.\(^9\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^12\)

Few phase III trials utilized altered fractions schedules with concomitant chemotherapy. They showed to be superior to dose escalated hyperfractionated radiotherapy with less acute reactions & equivalent late reactions and improvement of therapeutic ratio.\(^13\)\(^,\)\(^14\)\(^,\)\(^15\)\(^,\)\(^16\) However, the acute toxicity of treatment remained an issue which makes treatment in many occasions intolerable.

Bonner et al in 2006 showed that Epidermal growth factor inhibitors (EGFRI), cetuximab, used concomitantly with various fractionation schemes improves locoregional control and reduce mortality without increasing the common toxic effects.\(^17\) Till recently, the only available reports comparing concomitant cetuximab with platinum chemotherapy were all retrospective and imbalanced, including retrospective reports from MSKCC and UT Health Science Center with the University of Alabama, and reported no significant differences in survival.\(^18\)\(^,\)\(^19\) In addition, cetuximab use with altered fractionation radiotherapy was not properly assessed, although almost 50% of Bonner’s trial patients received hyperfractionation in part of their treatment, yet the study was not powered to detect differences between different fractionation schemes. To be noted as well, Bonner and colleagues excluded oral cavity tumors from their study.\(^17\) It is an attractive option for patients assuming that efficacy can be maintained. We previously published our data about the feasibility of hyperfractionation with chemotherapy and it was encouraging.\(^20\)

Recently, 2 randomized trials comparing cisplatin with cetuximab in HNC radical treatment were published. Both trials confirmed the inferiority of cetuximab, as regards local control and overall survival. However, both trials were designed for only oropharyngeal human papilloma virus positive patients.\(^21\)\(^,\)\(^22\)

In this report we aimed to assess the tolerability & efficacy of cetuximab and altered fractionation, and compares it to the rather standard arm of platinum

**Patients and Methods**

This is a randomized controlled study from a single institute in Kuwait.

The primary endpoints were Evaluate whether the use of cetuximab with concurrent Hyperfractionated radiation regimen will have locoregional control rates (LC) & Disease–free survival (DFS) that are comparable to concurrent cisplatin in patients with LAHNG (excluding nasopharynx).

The secondary endpoints were to compare the impact of using concurrent cetuximab vs chemotherapy regimen on Overall survival of patients (OS) and Acute and late adverse events.

**Corresponding author:** Khaled AL Saleh, MD., Radiation Oncology Dept., Kuwait Cancer Control Center, Kuwait. Email: kalsalehdr@hotmail.com
Patients were randomized into 2 arms. **Arm A:** to receive platinum-based CT i.e. cisplatin in a dose of 100 mg/m² 3–weekly or 40 mg/ m² weekly during radiation. **Arm B:** received cetuximab with a loading dose 400 mg/m², one week before radiation followed by weekly dose of 250 mg/m² during radiation.

**Radiotherapy was delivered using intensity modulated radiotherapy (IMRT) or 3D–conformal radiotherapy (CRT).** A total dose of 69.6 Gy/ 58 Fr/ 5.8 Ws was delivered to the primary site and high–risk draining lymphatics using 1.2 Gy fractions twice daily, 6 hours apart. A further boost of 6 Gy/ 5 Fr was given as a boost to gross residual disease. Target volume definitions was carried out according to institutional policy.

A total number of 300 eligible patients were planned for statistical analysis. However, we faced poor accrual and failed to make it a regional multi–institutional study. This is the final analysis after recruiting only 40 patients. This analysis was done before reaching the target number due to the negative results from the DeEscalate and RTOG 1016 published for safety of the patients. In spite of small cohort number, it is comparable to many other trials conducted to define value of different treatment strategies, mainly altered fractionation in HNC e.g. EORTC22843, Cairo1990, EORTC22962 and DAHANCA 9,23,24,25,26

All patients were planned for regular follow–up for 5 years (from the date of accrual) or until death. Patients with recurrent/progressive disease will be considered for salvage surgery or palliative chemotherapy.

Patients were considered eligible if he/she had measurable LAHNC, pathologically proven squamous cell carcinoma (SCC) arising in the oropharynx, hypopharynx, oral cavity or larynx. He/She must have stage III or IVA disease with an expected survival of 12 months. Only medically fit patients with Karnofsky performance status is > 60% were included. An informed detailed consent was obtained from the patient/legal representative. Laboratory values performed within 14 days prior to CRT should be satisfactory.

Patient was excluded if he/she had received prior systemic chemotherapy within the last three years, had undergone previous surgery for the tumor, other than biopsy, had received prior radiation therapy to the head and neck area. HPV test was not mandatory in this study population.

Post–treatment evaluations started 4 weeks after completion of radiation therapy. Radiological assessment of response was done at 8–10 weeks post treatment. Responses will be reported according to RECIST criteria.27

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**Figure 1.**

- Potentially Eligible (n=66)
  - Occult metastatic disease (n=6)
  - Kuwaiti Travelled Abroad (n=15)
  - Comorbidities (n=4)
  - Lost follow up (n=1)
  - Randomized Patients (n=40)

- Arm A (n=22)
  - Cross Over to Arm B (n=2)
  - Disease Free (n=1)
  - Locoregional Failure (n=1)

- Arm B (n=18)
  - Continued Arm A (n=20)

---

27. RECIST criteria.

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Kuwaiti Travelled Abroad (n=15)
Subsequent follow-up evaluations will commence after the 8-week post-treatment, every four weeks (±1 week) for years one and every 8 weeks for year two, and then, every 4 months (± 2 weeks) for year three to five. MRI was performed every 3 months for first 1 year then every 6 months for next 3–4 years. PET scan was performed at 3 months then annually or as clinically indicated.

**Statistical methods and consideration**

Overall survival was calculated from the date of histological diagnosis. Progression free survival (PFS) was calculated from the date of starting of treatment till disease progression or death whichever comes first. Survival analysis was done using Kaplan–Meier, comparisons was done using Log–rank test. Differences were considered significant when p was ≤ 0.05 and highly significant when p ≤ 0.01. Patients lost for follow up with disease were considered as censored. At the time of data analysis stratification of the patients according to sub sites, prognostic and risk factors including HPV status (if available) was done.

**Results**

Out of 66 initially potentially eligible patients, 6 were excluded for having metastatic disease, 4 with comorbidities that contraindicated cisplatin treatment. One patient that was planned to be enrolled was excluded as he lost follow up for 2 months before even starting treatment. Also, 15 Kuwaiti patients were not randomized as they choose to be treated outside the country (Figure 1).

From November 2012 till November 2017, 40 patients were randomized. The patient characteristics are shown in table 1. The median age of was 51 years (range 27–72 years). Thirty–five patients are male and almost 43%of them are of Asian origin. Most of these patients gave a history of cigarette smoking (68%).

Regarding the primary site of their disease; 14 patients have their primaries in larynx, 11 in oropharynx, 8 in oral cavity, and 5 has tumor in hypopharynx. Two patients had disease in nasal sinus or overlapping subsides. Regarding stage of disease at diagnosis; 50% has T4 lesions while 35% has T3 lesions. Nodal status was (N0–1) in 20 patients and (N2–3) in 20 patients. Overall staging showed a majority to have stage IV disease (63%). HPV was negative in 2 cases in Arm 1 and positive in 2 cases in Arm 2. (Table 1)

Regarding study arms, 22 patients were randomly allocated in Arm A (platinum–based) while 18 were in Arm B (cetuximab). 20 Patients in Arm 1 received cumulative dose ≤ 200 mg/m² (90% compliance) while 16 received at least 6 weeks of cetuximab in Arm 2 (89% compliance).

<table>
<thead>
<tr>
<th>Age:</th>
<th>Arm A (n,%)</th>
<th>Arm B (n,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Median (Range)</td>
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<td></td>
</tr>
<tr>
<td>Gender</td>
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<tr>
<td>– Male</td>
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<tr>
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<td>– Asian</td>
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<td>– Non–Smoker</td>
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<tr>
<td>– T2</td>
<td>2</td>
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<tr>
<td>– T3</td>
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<td>– T4</td>
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<td>– Tx</td>
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<tr>
<td>– N0</td>
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<td>– N1</td>
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<td>– N3</td>
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<tr>
<td>– II A</td>
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<td>– III</td>
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<td>– stage x (Tx)</td>
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</table>

Table 1. Characteristics between Arm A and Arm B
The overall tolerance and toxicities of the treatment were recorded in these patients according to the arm assigned (Table 2). Oral mucositis was moderate–severe, and that is managed conservatively with no treatment interruptions. To be noted, 2 patients in Arm (A) suffered from severe neutropenia that required prolonged hospital admission and platinum–based chemotherapy was discontinued. Also, two patients were shifted from cisplatin to carboplatin due to drop of renal parameters. These former two patients were shifted to cetuximab arm (a cross–over that is not allowed in our study design). These two cases are excluded from the treatment outcome analysis; however, they are included in the toxicity profile comparison (intend–to–treat patients). Six patients had acute renal toxicity in Arm 1 (all grade I–II) and, so far, no late renal impairment. 8 patients in each arm had feeding gastrostomy electively.

<table>
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<th></th>
<th>Arm A</th>
<th>Arm B</th>
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<td><strong>Hematological Toxicity</strong></td>
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<td><strong>Xerostomia</strong></td>
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<tr>
<td><strong>Feeding Tube Insertions (elective)</strong></td>
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</table>

Table 2. Comparing toxicity between Arm A and Arm B

Out of these 40 patients, 14 patients failed (6 and 8 in arm A and B respectively). Actually, 2 of them could not achieve complete remission rather than having recurrent disease. Two patients have not completed the planned chemotherapy course due to toxicity (One developed grade IV pancytopenia with radiation interruption).

Locoregional failure was documented in 6 (27.3%) vs 7 (38.9%) of arm A and B respectively, still statistically not significant? low number. Distant failure was in 2 patients in each arm (9% vs 11%). 2 years DFS was 56.5% vs 77.3% in cisplatin vs cetuximab arm (denoting non–significant increase of relapse rate in cisplatin arm). However, 2 years OS was 80.7% vs 57.3% in cisplatin and cetuximab arm respectively (p value=0.04). The outcome was not significantly correlated with any known prognostic factor apart from stage.

Figure 2. Disease free survival duration/month

Figure 3. Overall survival duration/month

The response rate, defined as complete (CR) or partial response (PR) on first assessment after finishing treatment) was similar in both arms. CR was achieved in 59% in arm A vs 50% in Arm B, while PR was 27.3% and 27.8% respectively. Disease progressed in 2 patients in Arm B only.
Discussion

To our knowledge, this is the first and only study to compare an anti EGFR with cisplatin in the context of altered fractionation radiotherapy in HNC. In spite of low accrual and small number of patients in both arms, the findings were significant. Together with the recently published RTOG1016 and DeEscalate trials, it was unethical to continue our study. Nevertheless, our trial is different from these 2 trials in 3 major points: (1) the study cohort included all HNC subsites (except nasopharynx) and not only the oropharynx (2) HPV was not specified, taking into account low prevalence of HPV positivity in our population (3) it involved Asian and Middle Eastern population.

In cases where platinum based predicted toxicity is high, hyperfractionation should be the only radiation schedule to be used with cetuximab. The survival benefit in Bonner’s trial was only obvious with hyperfractionation. Normal fractionation with cetuximab is not superior to radiation alone and its comparison with cisplatin is unfair. The profile of toxicity was similar to that of previous trials. Cisplatin showed higher incidence of acute renal toxicity, hematologic toxicity, nausea and vomiting. Cetuximab arm skin toxicity was not significantly high as initially presumed.

One finding that needs more elaboration and further analysis in our study is the reversed correlation between the rate of relapse and overall survival. In our trial, 43.5% of patients receiving cisplatin had relapse within first 2 years. However, they did better than the 22.7% relapsed in cetuximab arm. They received salvage treatment, whether surgery or systemic treatment, and survived more. This resulted in having 19.3% (out of the relapsed 43.5%) deaths in cisplatin arm vs 42.7% in cetuximab arm.

Conclusion

In spite of being with less toxicity, cetuximab should not be used in treatment of LAHNC if patient eligible for platinum—based treatment, regardless of the HPV status and tumor location. Hyperfractionation schedule could not compensate for the detrimental effect of cetuximab. However, in the context of cisplatin ineligible patients, cetuximab should be used only with hyperfractionation. More studies are needed in our region to define patient characteristics and tailor effective radical treatment. This preliminary study could represent a good core of large international multicentric RCT.

Funding and Conflict of Interest

This work was supported by a grant from the Kuwait Foundation for the Advancement of Sciences (KFAS) [Grant No. 2012–1302–06]. The authors declare that there are no conflicts of interest regarding the conduct and publication of this study.

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