Definitive Radiotherapy Concurrent with Carboplatin in the Treatment of Locally Advanced Head and Neck Cancers in Patients Ineligible for Cisplatin

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Abstract: Purpose: The objective of this work is to analyze the clinical outcomes and practicability of concurrent carboplatin plus radiation therapy (RT) in patients diagnosed as locally progressive squamous cell carcinoma of the head and neck (LA-SCCHN) that are ineligible for cisplatin treatment. **Patients and methods:** Thirty-one patients with histologically confirmed LA-SCCHN were eligible. All patients received carboplatin concurrent with conventionally fractionated RT. **Results:** The median age of our patients was 65 (range: 40–75) years with malepredominance. Laryngeal cancer constitutes 51.6% with 61.3% had ECOG-PS 2 and 71% had stage IV disease. Carboplatin administered tri-weekly in 22 (71%) patients. The main causes for choosing carboplatin were advanced age and performance status (PS) of 2 (61.3%). Twenty-five (80.6%) patients received the pre-specified dose of carboplatin. Twenty-seven (87.1%) patients received RT to 70 Gya total dose. The median duration of RT was 54 days (range, 47–65). Complete response was observed in 32.3% of patients. The commonest grade 3/4 toxicities were oral mucositis and vomiting (22.6%), nausea (19.4%), dysphagia (12.9%), and anemia (19.4%). At the end of the study, 21 (67.7%) patients were alive with a median duration of follow-up to 25 (range, 9-44) months. The median overall survival (OS) and progression-free survival (PFS) were not reached with 2-year OS & PFS rates were 74.7% and 54.8% respectively. **Conclusion:** Concurrent radiation therapy plus carboplatin is feasible and is a treatment option for LA-SCCHN patients who are ineligible for cisplatin treatment.
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1. Introduction

Globally, cancers affecting head and neck account for more than 550,000 cases yearly worldwide [1]. The report of 2017 of the United States, statistics, concerning head and neck tumor, it measured 63,030 new cases and the number of deaths reached 13,360 cases [2]. Nearly 95% of these cancers are squamous cell carcinomas (SCC) originating principally from the oropharynx, hypopharynx, larynx and oral cavity [3].

The standard of care for organ preservation is definitive concurrent chemoradiotherapy (CRT) that is considered the merely possibly remedial treatment in surgically unresectable or unfit subjects with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) stage III to IVb. The customary fractionation program is 70 Gy (2 Gy/fraction) over seven weeks, with concurrent high-dose cisplatin100mg/m^2 on days 1, 22, and 43. This regimen was dependable mostly on the trials by the Intergroup [4] and the Radiation Treatment Oncology Group (RTOG) 91-11 [5], employing cisplatin-based concurrent chemoradio-therapy.

A total of 233 subjects included in a retrospective work, 50% of the participating patients who received high-dose cisplatin-based CRT for treatment from head and neck tumor affected with acute kidney injury in spite of cautious in selection of patients, addition of mannitol to keep urinary stream, and liberal hydration [6]. Thus, patients who are disqualified for cisplatin therapy, for instance elderly patients, cardiac, renal, respiratory or neurogenic disordered, are generally treated with radiation therapy alone as a definitive treatment.

Carboplatin is ananalog of cisplatin second-generation characterized by a lower incidence of neurotoxicity, gastrointestinal toxicity and nephrotoxicity in contrast to cisplatin [7]. Carboplatin has been conventionally used as an alternative to cisplatin for treatment of head and neck cancers concurrently with radiation therapy, especially in patients who may be ineligible for cisplatin due to its toxicity. However, the efficacy and toxicity of concurrent carboplatin and radiation therapy are not clear for LA-SCCHN patients who are ineligible for treatment with cisplatin [8].

In the present investigation, we prospectively explored the clinical conclusions, feasibility, and toxicity of concomitant carboplatin and radiation therapy in LA-SCCHN patients who are disqualified for treatment by cisplatin.

2. Patients and methods

This is a prospective study that was conducted at Clinical Oncology Department, Faculty of Medicine, Tanta University between August 2014 and August 2017. This study was approved by our faculty ethical committee with written informed consent was obtained from all included patients.

Patients with histologically confirmed locally or regionally advanced stage III or IV (Union for International Cancer Control Tumor, Node, Metastasis classification, 7th edition) [9] SCCHN without evidence of distant metastasis were eligible for this study.

Eligibility criteria

All patients aged between 16 and 75 years with pathologically proven SCC of the oral cavity, oropharynx, larynx or hypopharynx confirmed radiologically by computed tomography (CT) or magnetic resonance imaging (MRI) with no systemic metastasis. Ineligibility for cisplatin treatment due to of any of the following reasons: old age, renal impairment (creatinine clearance [CCr] less than 60 ml/min), neurologic impairment (peripheral neuropathy or hearing impairment), cardiac dysfunction (a history of myocardial infarction, unstable angina or chronic heart failure), or performance status (PS) of ≥2 according to the Eastern Cooperative Oncology Group (ECOG). Adequate hematologic picture, hepatic and renal function.

Exclusion criteria

Patients were excluded if they received prior chemotherapy and/or radiotherapy, had prior surgery, active infection, or had a second malignancy.

Treatment

Administration of induction chemotherapy (ICT) regimen as an IV infusion of carboplatin (area under the curve AUC, 5; day 1) and 5-fluorouracil (1000 mg/m^2, continuous infusion days 1–4) repeated every 21 days for three cycles.

All patients received carboplatin concurrent with conventionally fractionated RT. Carboplatin was administered either tri-weekly [AUC, 5 on days 1, 22 and 43] or weekly (AUC, 2 on days 1, 8, 15, 22, 29, 36 and 43) according to the physicians' discretion.

The regimen was discontinued if there was unacceptable toxicity, which renders further treatment detrimental to patients, delay of more than two weeks for blood counts to recover or for renal toxicity to improve to grade 2 or less, or at patient request.

Radiotherapy

For tumor localization, the extent of the primary tumor and the neck nodes were assessed by using a CT scan. The field arrangement was individualized. All cases were treated with three-dimensional conformal radiation therapy (3DCRT) with 6 MV linear accelerator. The gross tumor volume (GTV) was treated with 2 Gy per fraction, five days per week to a total dose of 70 Gy, 60 Gy to the high-risk clinical target volume (CTV) and 54 Gy to low-risk CTV. Selected patients with the resectable residual disease after definitive CRT had salvage surgery.

Evaluation

Pretreatment evaluations included; medical history and physical examination, laboratory tests, endoscopy, CT, MRI and [18F]-fluorodeoxyglucose positron-emission tomography/CT fusion imaging if indicated. Assessment of tumor response by CT or MRI 4–6 weeks after the completion of CRT or when clinical signs suggested progressive disease, according to the guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 [10].

The World Health Organization (WHO) grading system [11] and the Radiation Therapy Oncology (RTOG) acute morbidity scoring criteria [12] are used to record the toxicities during the course of treatment.

Follow-up

The first follow-up visit was one month after finishing CRT. Evaluation for locoregional control, treatment toxicity and survival outcomes was done every two months for the first year, every 3–4 months for the second and third year and at 6 month intervals later.

Statistical analysis

The estimation of locoregional control (LRC) rate is the primary objective. The estimation of overall survival (OS), progression-free survival (PFS), and evaluation of adverse events in all included patients are the secondary objectives. Progression-free survival was defined as the time between treatment start and development of disease progression, relapse, or death from any cause. Overall survival was defined as the time interval between the date of diagnosis and the date of death or last follow-up.

Kaplan-Meier method was used for estimating the survival rates. All analyses were performed using SPSS software, version 21.0 and p-value <0.05 was considered statistically significant.

3. Results

Patient characteristics

Between August 2014 and August 2017, 31patients with LA-SCCHN underwent definitive CRT with carboplatin. Table 1 shows the baseline characteristics of included patients. The median age of included patients was 65 (range: 40–75) years with 19 (61.3%) patients were older than 65 years of age with male predominance (67.7%). Laryngeal cancer constitutes 51.6% of all cases with 61.3% of all cases had ECOG-PS 2 and 71% of patients had stage IV disease. Carboplatin was administered every three weeks in 22 (71%) patients.

Table 2 shows the main causes of choosing carboplatin. If any of the five causes are present, the

patient is considered to be disallowed for the treatment with cisplatin. The most mutual reasons for selecting carboplatin were progressed in ages age and PS of 2 followed by renal impairment [10 patients were considered to have a renal impairment with median CCr of 53 ml/min], cardiac dysfunction and hearing impairment.

Table (1): Patients and tumor characteristics

Characteristics	No (%)
Age (years)	
Median	65
Range	38-75
Mean±SD	56.97±10.93
>65	19 (61.3)
≤65	12 (38.7)
Gender	
Male	21 (67.7)
Female	10 (32.3)
Smoking	
Yes	17 (54.8)
No	14 (45.2)
Site	
Larynx	16 (51.6)
Oral cavity	5 (16.1)
Oropharynx	7 (22.6)
Hypopharynx	3 (9.7)
Performance status	
0	2 (6.4)
1	10 (32.3)
2	19 (61.3)
Tumor grade	
1	6 (19.4)
2	15 (48.4)
3	10 (32.2)
T stage	
1	2 (6.4)
2	8 (25.8)
3	6 (19.4)
4	15 (48.4)
N stage	
0	4 (12.9)
1	5 (16.1)
2	16 (51.6)
3	6 (19.4)
Stage	
III	9 (29)
IVa	16 (51.6)
IVb	6 (19.4)
Creatinine clearance (ml/min)	
median (range)	62 (37-117)
Carboplatin administration	
Triweekly	22 (71)
weekly	9 (29)
Induction chemotherapy	
Yes	25 (80.6)
No	6 (19.4)
Resectability	
Yes	19 (61.3)
No	12 (38.7)

Table 2: Indication for carboplatin

	No. (%)
Age over 65 years old	19 (61.3)
PS of 2	19 (61.3)
Renal impairment	10 (32.2)
Cardiac dysfunction	4 (12.9)
Hearing impairment	1 (3.2)

Treatment compliance

Twenty-five (80.6%) patients received the pre-specified dose of carboplatin. All patients received an optimal dose of radiation therapy, defined as 60 Gy or more. Twenty-seven (87.1%) patients received a total dose of 70 Gy. The median duration of RT was 54 days (range, 47–65). Treatment interruption was reported in 26 (83.9%) patients with 8 (range, 0-18) days median time of interruption and 4 (12.9%) patients discontinued their planned treatment after 60 Gy due to side effects.

Seventy-one percent of patients received tri-weekly carboplatin plus RT. However, tri-weekly carboplatin was less tolerable than the weekly regimen.

Clinical response

Ten patients (32.3%) had complete response (CR) and a partial response (PR) was in 12 (38.7%) patients. 22/31of patients (71.0%) was the total response rate (CR and PR). Disease stability was reported in 8 (25.8%) patients and only one patient (3.2%) developed progressive disease.

Two subjects undertook rescue surgery for remaining neck disease three and four months after end of RT with postoperative neck edema was the major complication.

Toxicity

Table 3 shows the main toxicities observed during CRT. The main non-hematological toxicities reported was mainly related to the radiation effect on surface mucosa with the resultant grade III/IV mucositis & vomiting seen in 7 (22.6%) patients, nausea in 6 (19.4%) patients, and dysphagia in 4 (12.9%) patients. The other non-hematological toxicities were grade I and II and were managed properly.

Myelotoxicity was common, with grade I-II anemia, leukopenia, and thrombocytopenia seen in 61.2%, 80.6%, and 74.2%, of patients, respectively. Tri-weekly regimen showed higher rates of toxicities versus weekly regimen; however, it was non-significant. Three patients developed an infection, including two with pneumonia, and one with febrile neutropenia. However, the regimen was well tolerated with no treatment-related death was reported.

Survival

At the end of the study, 21 (67.7%) cases were still alive after a follow-up period ranged from 9-44 (median 25) months. As regards the survival outcome, the median OS was not reached. The mean OS was

34.6 (95%CI, 30-39.3) months with 74.7% 2-year OS rate. The median PFS was not reached. The mean PFS was 27.8 (95% CI, 22.1-33.4) months with 54.8% 2-year PFS rate. (Figs. 1 & 2).

Table (3): Toxicity of treatment

Toxicity	Grade I/II No (%)			Grade III/IV No (%)			*p*
	Total	Triweekly	Weekly	Total	Triweekly	Weekly	
Hematological							
Anemia	19 (61.2)	15 (78.9)	4 (21.1)	6 (19.4)	4 (66.7)	2 (33.3)	0.383
Leukopenia	25 (80.6)	19 (76.0)	6 (24.0)	3 (9.7)	2 (22.7)	1 (33.3)	0.302
Thrombocytopenia	23 (74.2)	18 (78.3)	5 (21.7)	5 (16.1)	3 (60.0)	2 (40.0)	0.229
Non-hematological							
Mucositis	24 (77.4)	18 (75.0)	6 (25.0)	7 (22.6)	4 (57.1)	3 (42.9)	0.360
Anorexia	29 (93.5)	20 (69.0)	9 (31.0)	0 (0)	0 (0)	0 (0)	0.350
Nausea	23 (74.2)	18 (78.3)	5 (21.7)	6 (19.4)	3 (50.0)	3 (50.0)	0.317
Vomiting	20 (64.5)	14 (70.0)	6 (30.0)	7 (22.6)	5 (71.4)	2 (28.6)	0.980
Dysphagia	20 (64.5)	15 (75.0)	5 (25.0)	4 (12.9)	2 (50.0)	2 (50.0)	0.603
Diarrhea	8 (25.8)	5 (62.5)	3 (37.5)	0 (0)	0 (0)	0 (0)	0.540
Neuropathy	9 (29.0)	7 (77.8)	2 (22.2)	0 (0)	0 (0)	0 (0)	0.593
Renal impairment	4 (12.9)	3 (75.0)	1 (25.0)	0 (0)	0 (0)	0 (0)	0.849

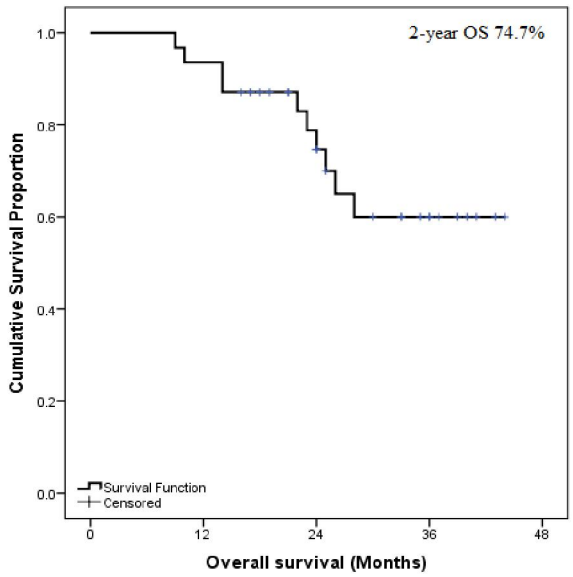

Figure 1: Overall survival

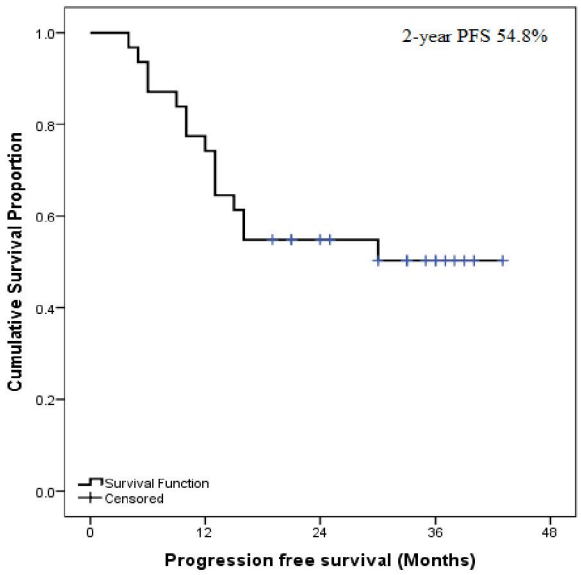

Figure 2: Progression free survival

4. Discussion

Concurrent radiation therapy with high dose cisplatin represents the definitive treatment for unresectable, surgically unfit LA-SCCHN [4, 13] with 40% CR and median OS of 19.1 months. Two phase III adjuvant trials confirmed that the therapy with cisplatin enhances loco-regional control and disease-free survival (DFS) in comparison to radiation alone with mixed results on OS [13, 14]. Bernier et al. [14] established that both 5-year PFS (47% vs 36%) and OS (53% vs 40%; HR=0.70; 95% CI 0.52–0.95) favored contemporary CRT above RT alone.

In addition to cisplatin, cetuximab (Cmab, anepidermal growth factor receptor monoclonal antibody), was used in combination with RT with significant improvement of the loco-regional control, PFS, and OS compared with radiation therapy alone. Regarding toxicity, concurrent Cmab and RT led to a higher grade III/IV skin toxicity versus RT alone (35.1 vs. 21.2%, $p<0.05$) [16]. Other trial reported grade III/IV radiation dermatitis in more than 30% of patients [17, 18]. Severe skin reactions could lead to treatment interruption and dose reduction with a quality of life reduction. Currently, no recommendation supports the use of concurrent RT with Cmab as an alternative to RT alone in patients with cisplatin intolerance.

The mechanism of action of both carboplatin and cisplatin is similar. They both induce the same platinum-DNA adducts. Hongo et al. [19] demonstrated that carboplatin required 7.5 times longer incubation time and concentration of drug 10 times higher than cisplatin to make an equal degree of conformational change on plasmid DNA. Myelosuppression is recognized to be higher with carboplatin than cisplatin however induces low neurotoxicity, nausea with hyperemesis and nephrotoxicity [20].

The antitumor effect of cisplatin is more powerful than carboplatin. It is not clear whether carboplatin has the same radio-sensitizing effect as cisplatin or not. In model, carboplatin could exchange cisplatin in some individuals who have not allowed to given cisplatin, particularly in individuals with baseline hearing impairment, inadequate renal function, and marginalrecital status, or those who may have trouble accepting hydration with high fluid volume accompanied with higher doses of cisplatin such as patients with congestive heart failure or severe emphysema [21].

Although 71% of our patients had stage IV and 38.7% had unresectable tumors, about 32% achieved CR. These results suggest that concurrent carboplatin and radiation therapy achieved very good treatment outcomes. As regards the survival outcome in our study, the median follow-up was 25 (range, 9-44) months with the median OS and PFS were not reached. The mean OS was 34.6 months with 74.7% 2-year OS rate. The mean PFS was27.8 months with 54.8% 2-year PFS rate.

In a prospective randomized clinical trial in individuals complained from locally advanced nasopharyngeal carcinoma (NPC), concurrent carboplatin (100 mg/m^2) administered weekly during RT demonstrated better tolerability with comparable efficacy when compared with concurrent tri-weekly cisplatin (100 mg/m^2) and RT [22]. The 3-year OS and DFS was 79% vs 78% and 61% vs 63% for the carboplatin and cisplatin regimens, respectively (p>0.05).

For LA-SCCHN other than NPC, a prospective randomized three-arm phase III trial [23] compared the 3-year survival rate with 70 Gy radiation therapy given alone, concurrent cisplatin (100 mg/m^2 tri-weekly) plus RT, and concurrent carboplatin (AUC, 7 tri-weekly) plus RT. This trial reported that platinum-based containing therapy prolonged the 3-year survival significantly when matched with radiation therapy (RT) alone. Survival rate was 42% for carboplatin, 52% for cisplatin, and 17.5% for RT alone.

There is no precise agreement of debarment for the cisplatin use. Therefore, in our study, we considered the patient ineligible for high dose cisplatin based on the known toxicity of cisplatin and on the exclusion or inclusion conditions used in the clinical trials using cisplatin for head and neck cancer. So, we enumerating five factors in the materials and methods section. Carboplatin has less nephrotoxicity, neurotoxicity, nausea and vomiting, no requirement for much hydration, compared with cisplatin. So, we would think carboplatin is safer than cisplatin for those who encounter our criteria.

Although all of our patients were considered ineligible for cisplatin therapy, mainly due to old age or poor performance status, they received an optimal dose of radiation therapy, defined as more than 60 Gy.

Regarding the toxicity of carboplatin; in a study by Jodrell et al. [24], there was a significant correlation among administered AUC dose of carboplatin and the probability of development of leukopenia and thrombocytopenia. Hence, we can avoid themyelotoxicity induced by high doses of carboplatin that can cause infection. Low dose weekly carboplatin plus RT may be less myelotoxic.

There was no grade III/IV neurotoxicities, nephrotoxicity. However, discontinuation or dose reduction of carboplatin was necessary owing to myelotoxicity in the patients of the current work. Three patients taken an infection and febrile neutropenia.

Tri-weekly carboplatin plus RT was not compared in clinical trials with weekly carboplatin plus RT. In the above-mentioned randomized study for locally advanced NPC, weekly carboplatin plus RT was as efficient as RT plus tri-weekly cisplatin that caused grade III or IV leukopenia and thrombocytopenia in 10% and 8% of patients respectively [22]. For non-nasopharyngeal LA-HNSCC, Tri-weekly carboplatin plus RT caused Grade III or IV leukopenia and thrombocytopenia in 18% and 27% of patients respectively [23]. These results suggest that the myelotoxicity of weekly carboplatin plus RT is lesser than that produced by tri-weekly carboplatin plus RT and may be considered as an alternative therapy in LA-SCCHN.

In the present work, high percentage of cases (71%) received tri-weekly carboplatin plus RT. However, tri-weekly carboplatin caused moremyelotoxicity which subsequently leads to infection and neutropenic fever that can be explained by the older age of our patients. Therefore, weekly carboplatin plus radiation therapy is more favored in our hospital due to its mild myelotoxicity.

In conclusion, concurrent radiation therapy plus carboplatin is feasible and is a treatment option for LA-SCCHN patients who are ineligible for cisplatin treatment. This study has restrictions, with a small number of patients and performance at a single

oncology center. So, our results should be confirmed with more prospective multi-institutional studies with a large number of patients.

Conflict of Interest

No conflict of interest as declared by the authors.

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