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Concomitant Chemoradiotherapy with Altered Cisplatin Regimen in Management of Locally Advanced Head and Neck Cancers

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Abstract

Purpose: Evaluation the tolerability, toxicity profile, and the outcome of treating locally advanced squamous cell carcinoma of the head and neck with altered cisplatin dose regimen concomitantly with radiotherapy.

Materials and methods: This study was based on a retrospective analysis of 48 patients treated with Concomitant Chemoradiotherapy (CCRT) using fractionated cisplatin doses of 20 mg/m^2 from days 1 to 5 in the first and fifth weeks of radiotherapy. The follow-up was performed during the treatment and four weeks after the end of radiation in cooperation with the Otorhinolaryngology department.

Results: 45 patients (93.8%) out all 48 completed the whole treatment protocol. The incidence of grade II or acute toxicities were: mucositis 64.6%, dysphagia 50% and grade II or III haematological events 14.6%. The late toxicities included: Xerostomia 33.3% dysphagia 29.2% trismus 14.6% deafness 14.6% dysgeusia 16.7%. The median follow-up time was 3.7 years after the treatment. 15 patients (31.3%) experienced recurrences and the 2-year disease free survival (DFS) was 70.8%. The 2-year overall survival (OS) was 85.4% among all patients.

Conclusion: The studied altered cisplatin protocol shows higher compliance and tolerability in comparison to the standard high cisplatin schedule and similar to the weekly one. Regarding the OS and DFS, the study shows comparable results with other cisplatin regimens. However, further phase III randomized multicentre studies are required to determine the most effective and least toxic cisplatin regimen in head and neck cancer patients treated with CCRT.

Keywords: Cisplatin; Head and neck cancer; Toxicity; Overall survival; Chemo radiation; Compliance

Introduction

The superiority of Concomitant Chemoradiotherapy (CCRT) over Radiotherapy (RT) alone in the management of locally advanced squamous cell carcinoma of the head and neck is has previously been demonstrated through several randomized trials [1]. It is now considered the standard treatment of locally advanced inoperable head and neck cancers; it is also employed as an adjuvant treatment in high risk patients, improving the local control rate (LCR) by 10% and the overall survival (OS) by 6% compared to RT alone [2,3,4,5,6]. Various chemotherapeutic agents have been tested in the last six decades with an obvious superiority of platinum based chemotherapy in head and neck cancers. However, whether cisplatin is more effective alone or combined with other agents has not yet been determined. Multiple cisplatin regimens with different dosages and schedules have been studied in order to identify the most effective and least toxic regimen with indefinitely results [2]. The standard high dose cisplatin regimen of 100 mg/m^2 every 3 weeks (on days 1, 22, and 42 of treatment) is usually accompanied by several acute toxicities which may interrupt the treatment plan, which could lead to reduce the previously prescribed total cisplatin dose. That's why arises the need of different cisplatin schedule having the same effect and better toxicity profile. One of the most widely used alternatives is a weekly low dose cisplatin schedule (30-50 mg/m^2), which was tested in several studies showing higher compliance with an acceptable toxicity profile in comparison to the high dose regimen [1,7]. Regarding the treatment outcome demonstrates the meta-analysis study by Jacinto et al. that there is no superiority of the weekly protocol over the triweekly standard regimen. Interestingly showed the study that there is no difference in acute toxicity between the two schedules [8]. Several other studies demonstrate the superiority of the high dose cisplatin regimen over the weekly low dose regimen in terms of OS and DFS [3,9,10].

Methodology

Patient's criteria

This retrospective study was conducted at SRH Wald-Klinikum Gera hospital aiming to evaluate the compliance, toxicity as well as the outcome and efficacy of treating 48 patients in the period from March 2010 to August 2015 and comparing the results with similar, previously conducted studies. The patients were selected with the following inclusion criteria: histopathologically diagnosed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx; stage III or IV according to AJCC 7th Edition; normal haematological, renal and liver functions; performance status Eastern Cooperative Oncology Group (ECOG) ≥ 2; no history of prior chemotherapy or radiotherapy.

Table 1: Patient`s characteristics.

Characteristic	Number	%
Total number of patients	48	-
Male/Female	41/7	85.4/14.6
Median age (range)	57.7 (32-74)	-
Disease location		
Oropharynx	6	12.5
Larynx	4	8.3
hypopharynx	12	25
Oral cavity	26	54.2
Type of treatment		
Adjuvant	32	66.7
Definitive	16	33.3
Insertion of peg	41	58.4
T stage		
T1	4	8.3
T2	11	22.9
T3	18	37.5
T4	15	31.3
N stage		
N0	9	18.8
N1	6	12.5
N2	33	68.7
N3	0	0

Exclusion criteria were: nasopharyngeal carcinoma; Para nasal sinus tumors; adenocarcinoma of head and neck; evidence of distant metastases; recurrent situations; prior radiotherapy or chemotherapy treatment; synchronous double primary malignancies or history of another malignancy; Patients who performed follow up after the treatment in other facilities, death caused by comorbidities before the end of 5-years follow-up.

The median age of patients was 57.7 years at the time of diagnosis. The female patients represent 14.6% of the studied cases. Additional patient's characteristics are summarized in **Table 1.**

All patients provided written informed consent, including agreement to be registered in the German clinical cancer registration program. The internal institutional approval was also acquired

Pre-treatment investigations

Before starting the treatment, all patients were evaluated with obtaining the medical history, general clinical and local examination in collaboration with the Otorhinolaryngology department including pre-treatment endoscopic examination, complete haematological and biochemical profiles, renal scintigraphy and audiogram. Human Papillomavirus (HPV) status was not routinely investigated at the time of diagnosis.

Chemotherapy and Radiotherapy protocols

The patients were treated in the first and fifth radiation weeks with cisplatin 20 mg/m^2 daily from day 1 to day 5 and from day 21 to day 25 with the pre-treatment supporting medications and followed by intravenous hydration for 7 days after the last chemotherapy day. The total Cisplatin dose was 200 mg/m^2 for all patients. No dose modifications were performed. The two chemotherapy cycles and the subsequent supportive measures were conducted exclusively in the inpatient **(Figure 1).**

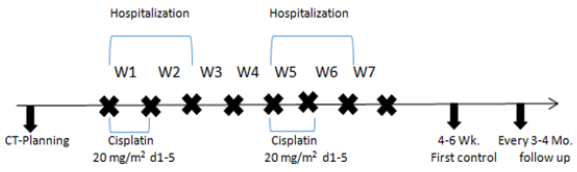

Figure 1: Treatment protocol.

The radiotherapy dose in the primary tumour area was ranging between 70-72 Gy in the definitive CCRT and 66 Gy in the adjuvant postoperative situations. The non-involved cervical Lymph nodes received 50 Gy. The plans were based on IMRT for all patients.

Follow up and treatment evaluation

The patients were assessed at third as well as the fifth treatment weeks and at the end of the treatment in the Otorhinolaryngology department. Follow up was planned at 4 weeks and then regularly every 3-4 months after the treatment for three years in both Radiotherapy and Otorhinolaryngology departments. After that continue the patients their follow-up for further two years in the Otorhinolaryngology department. The treatment toxicities

were assessed according to the common toxicity criteria (CTCAE). The Overall survival (OS) was defined as the time between the date of diagnosis and the date of death from the disease. The disease free survival (DFS) was defined as the time between the diagnoses until the incidence of local or systemic recurrence.

Results

Tolerability and toxicity

Of all 48 patients completed 45 (93.8%) the whole treatment protocol without the need of interruption or farther modification of the schedule. One patient died during the treatment from cerebrovascular event and subsequent cardiovascular decompensation. One patient didn't receive the second cycle of cisplatin because of grade II nephrotoxicity. The third one developed persistent grad III neutropenia and required postpone of the second cisplatin cycle for one weak.6 patients were 70 years or older at the time of diagnosis. All these patients have completed the treatment schedule without interruptions 85.1% of the patients acquired percutaneous endoscopic gastrostomy tube (PEG tube) as a part of the treatment protocol. The rest of patients either refused the prophylactic PEG or have had previous gastric operations and were unsuitable for this procedure [3]. Patients received combined chemotherapy with 5-fluorouracil (5-FU) without obvious increase of treatment induced toxicities and without the need of treatment interruption or treatment protocol modification. Three of them suffered later from recurrences.

The late toxicity profile was as follows: Xerostomia 33.3%, Dysphagia 29.2%, trismus 14.6%, hearing loss 14.6%, impaired taste sensation in 16.7% of the patients.

Table 2: Compliance and treatment related toxicities in comparison to relevant studies.

	Present study	Rades et al. [3]		Iqbal et al. [9]	Sautois et al. [12]	Noronha et al. [8]		Fayette et al. [9]		Rades et al. [7]	
Cisplatin regimen/ Acute Toxicity (%)	Fx 3q	q1w	q3w	1q	q1w	q1w	q3w	q1w	q3w	q3w	Fx 3q +5-FU
Mucositis	64.6	93	95	98	35.7	82.6	89.9	61.2	87.6	40	45
Grade ≥ II											
Dysphagia	50	NE	NE	99	NE	76	71.1	48.2	63.4	NE	NE
Hematological events	14.6	9	33	23	46.5	26	82	NE	NE	39	22
Leukopenia	8.3	NE	NE	24	25	10	55	NE	NE	NE	NE
Infection	4.2	1	12	NE	8.9	46.6	76.2	NE	NE	NE	NE
Nausea and Vomiting	4.2	NE	NE	NE	7.1	15.3	29.5	20.6	51.5	28	5
Nephrotoxicity	2.1	3	21	3	5.4	0	0.7	36.2	50	18	1
Thrombosis	2.1	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Toxic deaths	2.1	4	2	NE	NE	0	0	NE	NE	4	1
Xerostomia	33.3	47	59	NE	NE	55.2	54	NE	NE	65	62
Dysphagia	29.2	NE	NE	NE	NE	14.7	10.4	NE	NE	NE	NE
Ototoxicity	14.6	NE	NE	NE	NE	7.8	28.6	NE	NE	10	1
Trismus	14.6	NE	NE	NE	NE	8.6	7.1	NE	NE	NE	NE
Dysgeusia	16.7	NE	NE	NE	NE	23	28	NE	NE	NE	NE
Stenosis	4.2	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Osteonecrosis	4.2	NE	NE	NE	10.7	NE	NE	NE	NE	NE	NE
Hospitalization	100	NE	NE	53	64	13.3	31.1	7.9	30.9	NE	NE
Compliance*	95.8	63	50	68	30.3	88.7	94	66.7	42.2	52	90

Abbreviations: Fx: fractionated cisplatin day1-5 in Week 1 and 5; q1w: once weekly cisplatin; q3w: every 3 weeks cisplatin; 5-FU: 5 Fluorouracil; NE: not evaluated

Compliance*: patients completed the treatment plan without interruption or modification.

2 patients developed stenosis and 2 patients suffered from osteoradionecrosis. The summery of the toxicities are outlined in **Table 2**.

Survival analysis

The follow up period was from June 2010 until September 2018. At the time of analysis were 38 patients (79.2%) alive. The median follow up was 3.7 years and 14 patients (29.2%) have completed 5-year follow-up at the time of analysis. 15 patients (31.3%) had recurrences, 9 developed local-regional relapses and 6 had systemic failure with distant metastases. In the definitive CCRT subgroup, suffered 8 patients (50.0%) from recurrences while in the adjuvant subgroup only 7 patients (21.9%) had recurrences. One patient required salvage surgery after the definitive CCRT because of incomplete response. The estimated 2 and 3 year OS for all patients were 85.4% and 79.2% and the DFS were 70.8% and 68.8% subsequently. In the subgroups analysis showed the definitively treated patients 2 and 3 year OS of 62.5% and DFS of 50% while in the adjuvant subgroup was the 2 and 3 year OS 90.6% and 87.5% and the DFS was 81.1% and 78.1% subsequently. **(Table 3)**

Table 3: 2 and 3 years overall survival and diseases free survival.

Patients Outcome	All patients	Adjuvant treatment	Definitive treatment
2 years OS	85.4%	90.6%	62.5%
3 years OS	79.2%	87.5%	62.5%
2 years DFS	70.8%	81.1%	50%
3 years DFS	68.8%	78.1%	50%

Discussion

The CCRT is the standard treatment of locally advanced head and neck carcinoma in both definitive inoperable sitting and in case of high rick postoperative situations. Cisplatin is one of the most widely accepted chemotherapeutic agents in the CCRT, either alone or in combination with other agents aiming to reduce the toxicity and overcoming the resistance [6,11].

Cisplatin is cleared majorly through the kidney and accumulated in the proximal renal tubules causing nephrotoxicity other known toxicities are ototoxicity and haematological toxicities. The half-life of cisplatin is 20-30 mints following bolus administration. Platinum and not cisplatin itself remain present in the tissues for as long as 180 days after the last administration. The concentration of cisplatin in tumour is more than in other tissues [12,13].

The total investigated dose of cisplatin is ranging from 180-300 mg/m^2 with widely accepted two regimens either high dose cisplatin 100 mg/m^2 every 3 weeks (D1, 22 and 42) with total dose of 300mg/m^{2}or weekly low dose ranging from 30-50 mg/m^2 with median total dose 240-280 mg/m^2 in both adjuvant and definitive treatment sittings [4,11,14,15,16]. Until now it's not yet clear wither the weekly cisplatin regimens is equal to the standard 3 weeks in the efficacy or not. One of the latest prospective phase 3 randomized trial by Noronha et al. proved the improvement in the 2-year Loco regional control (LRC) from 58.5% to 73.1% toward the high dose cisplatin arm, albeit with increase in the severe acute toxicities from 71.6% in the low dose arm to 84.6% in the standard every 3 weeks regimen [9].

It is also important to notice that in the most of studies did not complete all recruited patients the whole program with high dose cisplatin making the total not always 300mg/m^{2}as planned. However still the recommended cumulative dose of cisplatin that should be administered during radiotherapy seems to be at least 200 mg/m.16.22 altered cisplatin schedules have been investigated with different doses and time plans, as giving very low dose cisplatin (6 mg/m^2) daily the whole radiotherapy time showing high compliance and acceptable toxicity profile [23]. Another cisplatin schedule with 20 mg/m^2 in days 1-4 in the first and fifth treatment weeks was studied by Lau et al. proving that this regimen has an overall survival and loco regional control rates comparable to other cisplatin schedules Huguenin et al. [17]. Have also investigated fractionated cisplatin with 20 mg/m^2 in days 1-5 in the first and fifth treatment weeks with hyper fractionated radiotherapy comparing it with radiotherapy alone which shows improvement of the DFS and OS toward the CCRT arm [19]. A combination of fractionated cisplatin (20 mg/m^2) from d 1-5 and d 29-33 with 5 Fluorouracil (5-FU) 600 mg/m^2 in the first and fifth treatment weeks was studied by Rades et al. showing high compliance reaching 90% and better toxicity profile than the standard high dose Cisplatin 100 mg/m^2 every three weeks [20]. In the present study completed 95,8% of the patients the treatment protocol making it in the higher compliance level in comparison to other cisplatin protocols used in CCRT in head and neck cancers [9,20]. All patients in our study were hospitalized during the implementation of the chemotherapy. The need of hospitalization is highly variable between the different cisplatin regimens ranging between 7.9% and 64% which was required mostly for the treatment of chemotherapy induced toxicities. The toxic deaths in the present study was 2.1% which is comparable to other cisplatin regimens **(Table 2)** The incidence of grade II or more nephrotoxicity was 2.1% clearly lower than that in the standard high cisplatin protocol and quiet similar to that in the weekly cisplatin studies which ranges between 0 and 5.4% **(Table 2).** This lower incidence is likely because of excluding patients with impaired renal functions by doing renal scan for

all patients intended to receive cisplatin and because of the prolonged hydration time which continue to 7 days after the last cisplatin day **(Figure 1)** which prolonged the overall hospitalization time.

The grade II-III haematological toxicities were in our study 14.6% which is also lower than that in the standard cisplatin regimen which reach up to 82% as in Noronha et al. and comparable to the most of the incidences in the weekly cisplatin which range between 9% and 46%. Leukopenia was the most common haematological toxicity in our study affecting 8.3% of the patients, which is lower than that detected in the standard high dose cisplatin (100 mg/m^2 every 3 weeks) [9,21,22] . patients in our study suffered from pneumonia and septicaemia making the incidence of infections 4.2% compared to incidence ranging between 12% and 71.1% in the standard cisplatin regimen and within the range of incidences in the weekly cisplatin [7,9,22]. The late toxicity in the form of Xerostomia was in our study 33.3% lower than that in both weekly and every three weeks cisplatin, which is likely because of all the patients have been planned with IMRT plan trying to save the parotid glands [7,9]. Ototoxicity was observed in 14.6% of the patients comparing to 28.6% in the 3 weeks arm and similar to that of the weekly arm (7.8%) as in Noronha et al. [9]. This side effect was exclusively detected in patients with oral cavity and oropharynx tumors raising the possibility of the additive effect of scattering radiation together with known cisplatin toxicity. The cochlea was not systematically delineated and the radiation dose was not calculated in our study. All patients was subjected to pre-treatment audiogram as a base line investigation.

Osteoradionecrosis was detected in 2 patients (4,2%) which is nearly the same incidence in weekly cisplatin with 3,6% in Iqbal et al. [21]. The incidence of trismus was 14,6% occurring predominantly in the adjuvant sittings representing 85.7% of the affected patients. Only one patient in the definitive treatment group suffered from trismus. Impairment of taste sensation was detected in 16.7% of the patients which is lower than that in both arms of Noronha et al. study (23 und 28%).82 patients suffered from stenosis, both were hypo pharyngeal cancer patients whom subjected to multiple surgical interventions before the adjuvant CCRT. Both patients have received radiation dose of 66 Gy with one of them manifested the side effect within 4 months after the treatment and the second one in 2 years after radiation which progress to absolute dysphagia. That might indicate that multiple primary operations of hypo pharynx carcinoma could increase the risk of radiation induced stenosis. The 2 and 3 year overall survival were for all patients 85.4% and 79.2% subsequently. Which is slightly higher than that in the most similar studies regardless the cisplatin dose and schedule of implementation.Albeit in the subgroups we found that the 2 and 3 year OS and DFS were in the definitive sittings similar to that in the other studies with definitive treatment intention [6,23,24].

Table 4: Comparison of OS and DFS with other studies.

	Present Study	Rades et al. 2016		Iqbal et al.	Sautois et al.	Noronha et al.		Fayette et al.	
Cisplatin Regimen	Fx3q	q1w	q3w	1q	q1w	q1w	q3w	q1w	q3w
2 years OS	85.40%	NM		NM	71.50%	60%	64.70%	NM	
3 years OS	79.20%	45%	60%	60%	NM	NM	NM	59.60%	71.30%
2 years DFS	70.80%	NM		NM	67%	50.70%	61.30%	NM	
3 years DFS	68.80%	58%	78%	71%	NM	NM		52.30%	62.90%

Abbreviations: Fx: fractionated cisplatin day1-5 in Week 1 and 5; q1w: once weekly cisplatin; q3w: every 3 weeks cisplatin; NM: not mentioned

Whereas in the adjuvant sub group were the 2 and 3 year OS and DFS still higher than that in the comparable studies as detailed in **(Table 4).**

It is important to mention that this treatment protocol have required a prolonged previously intended hospitalization time which need a supporting health system. And in spite of the effort done to select a homogenous group of patients and excluding the factors that may affect the results, still the study a retrospective and mono centric making it subjected to selection or information bias which may influence the end results.

Conclusion

This study showed that a fractioned cisplatin program (20 mg/m^2) over 5 days in the first and fifth radiotherapy weeks achieve higher compliance and tolerability in comparison to the standard highly cisplatin regimen (100 mg/m^2 every 3 weeks) and similar toxicity profile to the weekly cisplatin schedule (30-50 mg/m^2 once weekly). In comparison to other cisplatin regimen in the previously conducted studies were the OS and DFS in our study similar in patients treated with definitive intent and higher in those treated adjuvant. Further prospective randomized multicenter studies are required to determine the most effective and least toxic cisplatin regimen in the head and cancer patients treated with concomitant chemo radiation.

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