RESEARCH ARTICLE

Gemcitabine And Cisplatin Followed by Chemo-Radiation for Advanced Nasopharyngeal Carcinoma

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Abstract

Concurrent chemo-radiation (CRT) has been established as the standard of care for non-metastatic loco-regionally advanced nasopharyngeal carcinoma (NPC) but recently the addition of induction chemotherapy in the already established regimen has presented an attractive multidisciplinary approach. This retrospective study was carried out to evaluate the efficacy of induction chemotherapy (IC) followed by CRT for the management of loco-regionally advanced NPC. Between July 2005 and September 2010, 99 patients were treated with cisplatin based IC followed by CRT. Induction chemotherapy included a 2 drug combination; intravenous gemcitabine 1000 mg/m^2 on day 1 and 8 and cisplatin 75 mg/m^2 on day 1 only. Radiotherapy (RT) was given as a phase treatment to a total dose of 70 Gy in 35 fractions. Concurrent cisplatin (75 mg/m^2) was administered to all patients on days 1, 22 and 43. All patients were evaluated for tumor response and adverse effects after IC and 6 weeks after the completion of the treatment protocol. Statistical analysis was performed using SPSS version 17 and Kaplan Meier estimates were applied to project survival. Median follow-up duration was 20 months. The 5-year overall survival (OS), loco regional control (LRC) and relapse free survival (RFS) rates were 71%, 73% and 50% respectively. Acute grade 4 toxicity related to induction chemotherapy and concurrent chemo-radiation was 4% and 2% respectively, with only 3 toxicity-related hospital admissions. We conclude that induction gemcitabine and cisplatin followed by chemo-radiation is a safe and effective regimen in management of nasopharyngeal carcinoma, meriting further investigation in randomized clinical trials.

Keywords: Nasopharyngeal cancer - concurrent chemo radiotherapy - induction chemotherapy

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Introduction

Mapping the geographic distribution, NPC is a rare tumor in the west and endemic in regions like Southern China with an incidence stretching from 2 to 25 per 100,000 respectively (Sankaranarayanan et al., 2010). The estimated incidence reported by GLOBCAN for Pakistan is over seven hundred new cases annually (Ferlay, 2008).

NPC also holds a unique and distinguished position amongst other head and neck tumors with respect to the epidemiology, histological variation, remote anatomic location with close proximity to the critical structures and therapeutic protocol. Being highly radiosensitive, radiotherapy remains the mainstay treatment protocol for the management of early stage I and IIA disease, achieving a 5-year overall survival of 90% and 84% respectively, however the results for loco regionally advanced patients with radiotherapy alone remains poor (Sham et al., 1990; Qin et al., 1998; Lee et al., 2005). After the publication of the Inter group 0099 trial in 1998, concurrent chemo radiotherapy became the gold standard in the management of loco regionally advanced NPC and numerous prospective trials since then have ascertained the therapeutic efficacy of this treatment protocol (Al-Sarraf et al., 1998). Lately there is been a renewed interest in the use of induction chemotherapy as in previous studies it had an added benefit in disease control but failed to show any significant improvement in overall survival. Currently several phase II studies have demonstrated good tolerability and improved overall survival with the use of induction chemotherapy (Oh et al., 2003; Al-Amro et al., 2005). A novel nucleoside antimetabolite gemcitabine has widely being used in the treatment of various solid tumors including breast, bladder, non-small cell lung cancer, ovarian, pancreatic and metastatic nasopharyngeal carcinoma (Ngan, 2002; Wang et al., 2008). Our study presents the results of a retrospective analysis of non metastatic loco regionally advanced nasopharyngeal carcinoma patients treated with induction chemotherapy (gemcitabine and cisplatin) followed by cisplatin based concurrent chemo radiotherapy.

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Materials and Methods

Eligibility criteria

Between July 2005 and September 2010, one hundred and fourteen patients were selected from head and neck database, treated radically for nasopharyngeal carcinoma. Fifteen patients were excluded from the study as they lacked the inclusion criteria. The details of patients excluded; eleven patients were lost to follow up or defaulted after IC, 2 patients had progressive disease after IC and were not suitable for CRT, one patient defaulted on day 24 of radiotherapy and one patient was treated with radiotherapy alone after IC due to medical conditions. Ninety nine non-metastatic nasopharyngeal carcinoma patients qualified the inclusion criteria and were treated with 2 drug IC regimen followed by cisplatin based CRT at Shaukat Khanum Memorial Cancer Hospital and Research Center. Patients were staged according to the AJCC 6th edition (American Joint Commission on Cancer). The pretreatment staging evaluation included clinical examination of head and neck, fiberoptic nasopharyngoscopy, MRI face and neck, bone scan, complete blood, biochemical, renal and liver profile. PET scan was reserved for patients suspected for distant metastasis. All patients were advocated on nutritional support via percutaneous gastrostomy tube.

Induction chemotherapy

Induction chemotherapy was administered on outpatient basis. Two drug combination included; intravenous gemcitabine 1000 mg/m^2 on day 1 and day 8, cisplatin 75 mg/m^2 on day 1 only for each cycle respectively (Figure 1). A three week interval was observed between the 2 cycles. Due to low toxicity and good tumor control, almost twenty five percent of the patients received more than two cycles of IC (Table 2). After 2 weeks from the last cycle of IC, a response assessment was clinically devised. Toxicity assessment of IC was assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE 3.0). A dose modification or delay was carried out in severe toxicity.

Radiotherapy

All patients received a single dose daily fraction of 2.0 Gy reaching to a total dose of 70 Gy in 30 fractions for five days a week. Patients underwent simulation using fluoroscopic simulator and radiotherapy was administered on linear accelerator using two opposing lateral portals and an anterior posterior low neck portal to cover all neck node levels upto a total dose of 50.0 Gy. The spinal cord was shielded after 44.0 Gy using spinal cord block.

Concurrent Chemotherapy

Patients received cisplatin 75 mg/m^2, every 3 weeks during the course of external beam radiotherapy. Complete blood count, renal and liver profile were checked before the administration of the chemotherapy.

Follow up

Response to IC was assessed clinically and with MRI scan. Fiberoptic nasoendoscopy was used to evaluate the nasopharynx. Following completion of concurrent chemo radiation patients were evaluated for tumor response at 6 weeks by clinical examination, fiberoptic nasopharyngoscopy and MRI face and neck. Patients were followed up at 4-6 monthly intervals for the first 2 years six monthly in third year and annually thereafter.

Statistics

Statistical Package for Social Sciences (SPSS), version 17 was used for statistical analysis. Loco regional control, metastatic free control and overall survival were calculated by Kaplan Meier method. Primary end point was LRC and

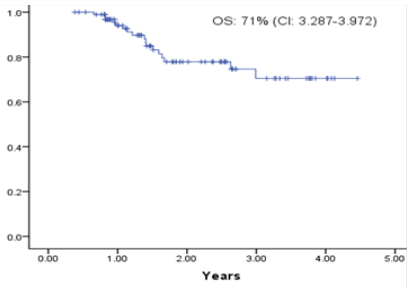

Figure 2. Expected 5 year Overall Survival (OS)

Table 2. Treatment Gegimen

Type of treatment		No (%)
Induction chemotherapy	2 cycles	75 (76)
	3 cycles	21 (21)
	4 cycles	02 (2)
	5 cycles	01 (1)
Concurrent chemotherapy	1 cycle	02 (3)
	2 cycles	02 (3)
	3 cycles	93 (94)
Radiation duration (days)	<50	30 (30)
	>50	69 (70)
	Total dose	70 Gy
Number of fractionation		35

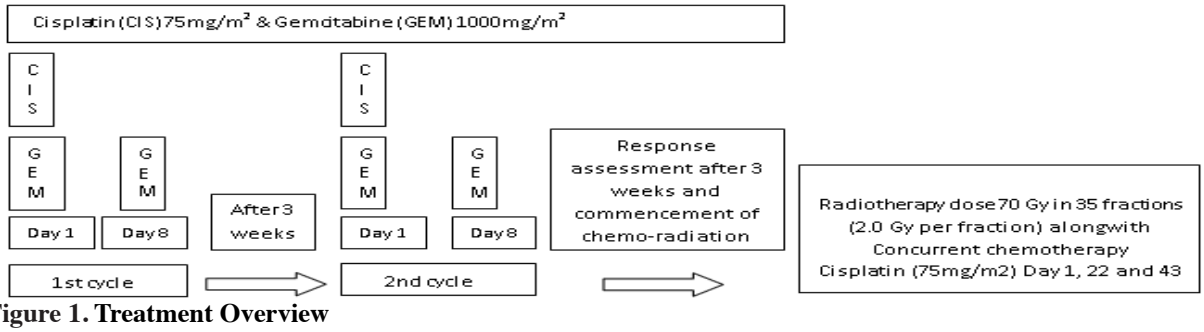

Figure 1. Treatment Overview

Table 1. Patient Characteristics

Characteristics		n (%)
Age	< 50	61 (62)
	> 50	38 (38)
	Median	44
	Range	18-76
Gender	Male	73 (74)
	Female	26 (26)
Histology	Type I	08 (8)
	Type III	56 (57)
	Unknown	35 (34)
Stage	IIB	03 (3)
	III	28 (28)
	IVA	47 (48)
	IVB	21 (21)
T stage	T1-2	22 (22)
	T3	17 (17)
	T4	60 (61)
N stage	N0	11 (11)
	N1	15 (15)
	N2	52 (53)
	N3	21 (21)
Intracranial extension	Yes	11 (11)
	No	88 (89)
PEG tube	Yes	81 (82)
	No	18 (18)

Table 3. Evaluation of Treatment Response

Number of patients n (%)			
Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease(PD)
After Induction Chemotherapy			
15 (15)	84 (85)	-	-
6 weeks after Concurrent Chemo radiotherapy			
93 (94)	-	02 (2)	04 (4)

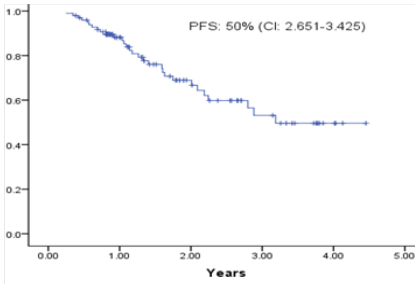

Figure 3. Expected 5 year Relapse Free Survival (RFS)

secondary end point was OS. LRC and OS were calculated from the start of the treatment till the date of event. OS was defined as the time elapsed from the date of start of treatment to the date of death. Relapse free survival was measured from the date of start of treatment to the date of the first observation of recurrent disease. Metastatic free survival (MFS) was measured from the date of start of treatment to the date of presentation of metastatic disease.

Results

Patient characteristics

Table 1 enlists the pretreatment demographics of the patients with median age of 44 years (range 18-76) and female to male ratio of 1:3 respectively. Ninety six patients (97%) had loco regionally advance stage III/IV disease at presentation. Among T4, eleven percent of patients had intracranial extension at presentation. Over eighty percent of the patients had percutaneous gastrostomy tube for nutritional support.

Response

Response to induction chemotherapy and concurrent chemo-radiation is shown in Table 3. Fourteen of the fifteen patients showing complete response (CR) after IC had stage IV disease. Amongst the complete responders, only two patients developed distant metastatic disease and the rest of thirteen patients are maintaining routine follow up. MRI of the face and neck after 6 weeks of treatment completion showed ninety-three (94%) with complete response, two patients (2%) with stable disease whereas four patients (4%) had progressive disease respectively (Table 3). Three patients who did not have a complete response to the treatment protocol had stage IVB disease. Two patients that failed locally (Table 5) had T4 disease whereas 1 patient that failed locally had T2 disease but had a tumor with a maximum dimension of 5 cm. Regional failures (Table 5) also include six patients who had persistent disease after completion of the treatment. An interesting finding is the N stage of the patients that failed regionally; only 3 patients had N3 disease while only 1 patient had N1 disease, which was salvaged with neck dissection followed by palliative chemotherapy. Distant failures (Table 5) were pretty evenly distributed according to the stage with 6, 3 and 7 patients having stage III, IVA and IVB disease respectively with majority of the patients in this group having undifferentiated nasopharyngeal carcinoma. Amongst eleven patients with intracranial extension, 2 patients failed regionally, 1 patient had distant failure while other eight patients maintain routine follow up with no evidence of any recurrence. Status at the last follow up: 68, 14 and 17 patients alive, alive with disease and dead respectively.

Toxicity

Patient compliance with the treatment protocol was good despite the fact that they received a long and cumbersome treatment protocol with induction chemotherapy followed by chemo radiotherapy. Discussing the demographics of the patients more then ninety percent of the patients came from distant areas of Pakistan with temporary stay in the close vicinity of the hospital but still the treatment was well tolerated by the patients. No death was reported during and after the completion of treatment, related to the toxicity of the regimen. Table 4 separately explains the acute toxicities related to induction chemotherapy and concurrent chemo radiotherapy. Radiotherapy related toxicity was not formally recorded. Regarding hospital admission only 3 patients were admitted during the course of induction chemotherapy, 2 with febrile neutropenia and stayed in the hospital for four days and one with diarrhea and remain admitted for only two days. There were no toxicity related hospital admissions during the course of concurrent chemo-radiotherapy.

Prognostic factors

The 5 year estimated relapse free survival and overall

Table 4. Summary of Acute Adverse Effects During Treatment

Adverse Effects	Toxicity grade during Induction Chemotherapyn (%)					Toxicity grade during Concurrent Chemo Radiotherapy n (%)				
	0	1	2	3	4	0	1	2	3	4
Anemia	88 (89)	8 (8)	3 (3)	-	-	91 (92)	4 (4)	1 (1)	3 (3)	-
Neutropenia	34 (34)	24 (24)	16 (16)	21 (21)	4 (4)	91 (92)	4 (4)	1 (1)	3 (3)	-
Thrombocytopenia	88 (89)	10 (10)	1 (1)	-	-	71 (71)	18 (18)	5 (5)	3 (3)	2 (2)
Fever	96 (97)	2 (2)	1 (1)	-	-	98 (99)	1 (1)	-	-	-
Diarrhea	96 (97)	-	3 (3)	-	-	99 (100)	-	-	-	-
Vomiting	87 (88)	5 (5)	5 (5)	2 (2)	-	92 (93)	3 (3)	4 (4)	-	-
Raised ALT	67 (68)	23 (23)	6 (6)	3 (3)	-	89 (90)	9 (9)	1 (1)	-	-
Raised AST	77 (78)	19 (19)	-	3 (3)	-	91 (92)	7 (7)	1 (1)	-	-
Raised bilirubin	99 (100)	-	-	-	-	95 (96)	4 (4)	-	-	-
Raised creatinine	89 (90)	9 (9)	-	1 (1)	-	98 (99)	1 (1)	-	-	-

Table 5. Patterns of Failure

Patterns of failure	n (%)
Local	3 (10)
Regional	11 (35)
Loco regional	2 (7)
Distant	15 (48)

Table 6. FiveYear Estimates of Time to Event End Points

Stage	RFS*	OS**
IIB	100	100
III	55	78
IVA	53	65
IVB	37	67

*Relapse free survival; **Overall survival

survival of study group were 50% (95%Confidence interval CI 3.287-3.972) and 71% (95%Confidence interval CI 2.651-3.425) respectively (Figure 2, 3). The local control (LC), regional control (RC), loco-regional control (LRC) and distant control (DC) of our study was 92%, 83%, 73% and 68% respectively. Table 6 explains the relapse free survival (RFS) and overall survival (OS) according to the stage. The value of various prognostic factors; age, gender, stage, radiation duration on predicting LC, MFS, RFS, and OS were calculated. Both age (Table 1) and duration of radiation (Table 2) were subdivided into two groups. Only sex and radiation duration had prognostic significance on the overall survival. An interesting finding from the analysis shows that female had a significantly better RC, DC, PFS and OS.

Discussion

For over a decade chemotherapy in concurrent settings has been inducted as part of the treatment protocol for loco regionally advanced NPC. Traditionally Nasopharyngeal carcinoma was treated with radiotherapy alone. The current standard of care for loco regional advanced (stages III, IVA and IVB) non metastatic Nasopharyngeal carcinoma is CRT as chemotherapy in concurrent setting both augments the therapeutic implication of radiotherapy and decreases the incidence of micro metastasis. The current practice of adding concurrent chemotherapy (cisplatin) to radiotherapy is based on intergroup 0099 study published in 1998 however the study was criticized firstly due to unexplained inferior results in the radiotherapy arm, secondly it lacked data on the late toxicity effects of the regimen and thirdly the application of its results to patients in endemic regions was questioned due to its less aggressive histological subtypes (Al-Sarraf M et al., 1998). Concurrent chemo radiotherapy protocol has been compared and argued in several meta-analysis based on published trials both in endemic areas and non-endemic regions. In one meta-analysis, radiotherapy combined with chemotherapy in concurrent setting could increase the 5 year survival rate by 4-6% and reduce the risk for death by 18% in patients with locally advanced NPC (Baujat et al., 2006). In another meta-analysis of several phase III trials conducted among endemic regions confirmed that concurrent chemoradiotherapy was more beneficial than radiotherapy alone in the management of advanced nasopharyngeal carcinoma although the relative benefit of this treatment protocol is slightly less when compared with the results of prospective trials in non-endemic regions (Li et al., 2010). Langendijk et al., published a review analysis of several prospective trials comparing the combined treatment protocol versus the radiotherapy alone and showed a significant value (p=0.02) when chemotherapy was added to the treatment protocol although only chemotherapy in concurrent setting proved to show improvement in overall survival whereas adjuvant chemotherapy had no survival advantage and induction chemotherapy only showed loco regional disease control with no impact on overall survival (Langendijk et al., 2004). Although concurrent chemotherapy has been added to the definitive treatment protocol, the use of particular chemotherapeutic agent and its dose has yet to be established. With a slight modification in the dosage, cisplatin is employed both in weekly (40 mg/m^2 for 6–8 weeks) and 3 weekly (100 mg/m^2 on days 1, 22 and 43) regimen with acceptable tolerability, toxicity and efficacy (Chan et al., 2002). In our study 75 mg/m^2 cisplatin was administered 3 weekly with good compliance with the patients and low incidence of toxicity. Despite of dose reduction of cisplatin from the set standards, our study group showed promising response of 94% (Table 3). Carboplatin as concurrent chemotherapeutic agent in the management of advanced NPC has been compared with cisplatin with better tolerability however with no added advantage on overall survival (Chitapanarux I et al., 2007). Chemotherapy has been employed in the adjuvant setting both after radiotherapy alone and

chemo radiotherapy but it not only failed to show any survival benefit rather showed poor patient compliance and increase in the toxicity. Induction chemotherapy is preferred over adjuvant chemotherapy for a variety of reasons including reducing the size of the bulky disease before radiotherapy ultimately leading to better loco regional control, secondly reducing the incidence of distant metastasis by arresting their proliferation in the micro metastatic stage; thirdly the drug delivery to an untreated tumor is better in its native vascular bed. Although a variety of chemotherapeutic agents have been employed in the past but the debate to optimize the drugs and the protocol is far from over. Combination of cisplatin with 5-FU has been widely used and investigated in induction chemotherapy settings, with high response rates but comparing with other chemotherapeutic drugs it has severe adverse effects especially mucositis (Al-Kourainy et al., 1987; Al-Sarraf et al., 1988; Bernal et al., 1989). In our study group all the patients responded to the induction chemotherapy with as high as 15% complete responders. Another advantage of gemcitabine cisplatin combination, it is administered in the outpatient facility in short period of time unlike 5-FU that requires 120 hours of continuous infusion and hospital admission. Few studies have used gemcitabine plus cisplatin combination as IC in the treatment of advance nasopharyngeal carcinoma patients. Yau et al., in their study of 37 patients staged IV (A-B) used gemcitabine (1250 mg/m^2 on days 1, 8) and cisplatin (80 mg/m^2) based IC followed by accelerated RT with 100 mg/m^2 of cisplatin in concurrent setting (Yau TK et al., 2006). The OS and DFS of the study group at 3 years was 76% and 63% respectively. With a median follow up of 30 months Xiayun et al. (2012) also used gemcitabine and cisplatin both as IC and in adjuvant settings after intensity modulated radiation therapy (IMRT) (Xiayun et al., 2012). With 89% of the patients having stage III-IV, the 3 year OS of the group was 87.7%. An interesting study was conducted by Yau et al, comparing two different IC regimens followed by accelerated radiotherapy with cisplatin in concurrent settings (Yau et al., 2006). Cisplatin plus 5 FU was compared with cisplatin plus gemcitabine. Although there was no statistical significance in patients treated with either IC regimen but cisplatin plus gemcitabine showed better loco-regional failure-free survival. 5 year estimated relapse free survival and overall survival of our study group were 50% and 71% respectively which is comparable with already published literature using gemcitabine and cisplatin as IC regimen. The low toxicity incidence and quick administration of the drug reduces the cost of the treatment, patient compliance is high and response rates are as good as other chemotherapeutic agents. Recently new induction chemotherapeutic agents like Paclitaxel and Docetaxol have been added, with good response rate, but patients receiving Docetaxol show higher incidence of grade III and IV neutropenia with statistically significant difference when compared with 5-FU regimen (Nabell et al., 2003). In our study there were only 3 toxicity related short hospital admission, of which two patients had febrile neutropenia and one patient was admitted for 3 days with diarrhea. Most of the patients in our study group had bulky nodal disease therefore more then 2 cycles of gemcitabine and cisplatin combination were administered with good response and acceptable toxicity.

The use of chemo-radiation in advance NPC patients is widely accepted and followed. The optimization of induction chemotherapy remains to be defined. The high response rates, acceptable toxicity profile, convenient administration time and cost effectiveness, gemcitabine cisplatin IC stays short of randomized controlled trial.

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