RESEARCH ARTICLE

Comparison of Three Different Induction Regimens for Nasopharyngeal Cancer

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Abstract

Background: The standard treatment of local advanced nasopharyngeal cancer is chemoradiotherapy. There is a lack of data concerning induction therapy. In this study we retrospectively examined patients treated with induction therapy and chemoradiotherapy. Materials and Methods: Locally advanced nasopharyngeal cancer patients treated between 1996 and 2013 in our clinic were included in the study. Three different induction regimens were administered to our patients in different time periods. The regimen dosages were: CF regimen, cisplatin 50mg/m^2 1-2 days, fluorouracil 500mg/m^2 1-5 days; DC, docetaxel 75mg/m^2 1 day, cisplatin 75mg/m^2 1 day; and DCF, docetaxel 75mg/m^2 1 day, cisplatin 75mg/m^2 1 day, 5-Fu 750mg/m^2 1-5 days. Most of the patients were stage III (36.4%) and stage IV (51.7%). Results: Median follow-up time was 50 months (2-201 months). Three-year progression-free survival (PFS) was 79.3%, and 5-year PFS 72.4% in all patients. Three-year overall survival (OS) was 87.4% and 5-year OS 76% in all patients. In terms of induction therapies, 3-year OS was 96.5% in the DCF group, 86.6% in the DC group and 76.3% in the CF group (p=0.03). Conclusions: There was no significant differences in response rate and PFS between the three regimens. OS in the DCF group was significantly higher than in the other groups. However, this study was retrospective and limited toxicity data were available; the findings therefore need to be interpreted with care.

Keywords: Local advanced nasopharyngeal cancer - induction therapy - comparison of regimens

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Introduction

Nasopharyngeal cancer, with a very different course, histopathology, epidemiology and etiology, also needs to be considered separately from other head and neck cancer in terms of staging.

Early stage (stage 1) disease is treated with radiotherapy (RT). RT is preferred because the anatomical location is an obstacle to surgery and the tumor is radiosensitive. Due to the risk of distant organ metastasis, combined modality treatment is administered in intermediate stage disease. In the treatment of advanced state disease (stages III and IV), according to meta-analyses of randomized studies, the addition to RT therapy of any chemotherapy (CT) regimen (concurrent, induction or adjuvant) reduces the risk of mortality by 18% and increases 5-year survival by 4-6% (Langendijk et al., 2004; Baujat et al., 2006). Chemoradiotherapy (CRT) is the standard treatment for local, advanced, non-metastatic nasopharyngeal cancer. However, the results of studies of induction therapy are inconsistent in terms of survival. The purpose of this study was to evaluate data for local, advanced nasopharyngeal cancer patients administered induction therapy in our clinic and the results of the different treatment regimens applied.

Materials and Methods

Nasopharyngeal cancer patients treated at the Hacettepe University Faculty of Medicine, Turkey, in 1996-2013 and whose file and follow-up details were available were evaluated retrospectively. Metastatic cases at time of diagnosis or cases with local recurrence who received initial treatment at external centers were excluded. Demographic data were first collected for 154 cases (age, sex, comorbidity, performance status,stage). Date of diagnosis regarding course of disease, cranial involvement, operation (biopsy, neck dissection, pathological diagnosis and histology (WHO classification) were recorded.

Treatment of our patient group was arranged in the form of CRT following three courses of induction CT (consecutive regime), and these patients were classified on the basis of the induction regimens they received;

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(CF (cisplatin 50mg/m^2 1-2 days, fluorouracil 500mg/m^2 1-5 days), DC (docetaxel 75mg/m^2 1 day, cisplatin 75 mg /m^2 1 day) and DCF (docetaxel 75mg/m^2 1 day, cisplatin 75mg/m^2 1 day, 5-fu 750mg/m^2 1-5 days). Patients' initial stages were recorded. Stage II-IV patients were included in the study. During staging, patients underwent physical examination, ENT examination, full blood count, biochemistry, abdominal ultrasound, bone scintigraphy when necessary and MRI, and some patients also underwent audiometric examination. Staging was performed on the basis of the American Joint Committee on Cancer (AJCC) tumor, lymph node and metastasis system (TNM) (7th ed. 2010).

Disease staging was performed again following induction regimen and CRT, and responses to therapy were recorded. Patients were classified on the basis of their degree of response, and patients developing local recurrence or metastasis during follow-up were identified.

Patients surviving or dying during treatment were recorded, and progression-free survival (PFS) and overall survival (OS) durations were calculated. Groupings based on patients' induction therapies were considered during these analyses. We sought to obtain data concerning which induction regimen was most effective on the basis of survival analyses.

Statistical analysis

Complete remission (CR) is defined as disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10mm. Partial response (PR) is defined as measurable tumor mass decreasing by 30 % after treatment, no new areas of tumor developing and no area of tumor showing progression. Progression is defined as ≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded or the appearance of new lesions including those detected by FDG-PET .Stable disease is defined as measurable tumor meeting the criteria for neither PR nor PD(RECIST guideline, version 1.1) (Eisenhauer et al., 2009).

Data obtained following the monitoring process were analyzed in a computer environment using SPSS 18.0. Survivals were calculated using Kaplan Meier analysis. OS was measured from the first day of diagnosis until death or the last day of clinical visit. PFS was defined as time from when the patient was free from clinically detectable cancer until recurrent cancer was diagnosed.

Results

Demographic data

One hundred fifty-four nasopharyngeal cancer patients were included in the study, 76% (n=117) male and 24% (n=37) female. Median age at diagnosis was 47 (20-73) years. Patients' demographic data are given in Table 1.

Tumor characteristics

Histopathological examination revealed non-keratinizing tumor in 44.8% of patients and undifferentiated tumor in 27.3%. Histological examination revealed WHO grade I tumor in 1.3%, WHO grade II in 48.1% and WHO grade III in 34.4%. EBV DNA levels were investigated during diagnosis in 50 patients, and were positive in 58% of these.

In terms of stage of disease at time of diagnosis, stage II was present in 11.9% (n=18), stage III disease in 36.4% (n=55) and stage IV disease in 51.7% (n=78).

Induction therapy

Of the 154 patients receiving induction therapy, 24.7% (n=38) received CF, 35.1% (n=54) DC and 40.3% (n=62) DCF. The dominant pathology in the CF group was undifferentiated carcinoma (44.7%) and non-keratinizing carcinoma in the DC and DCF groups (57.4%-45.2%) (p=0.004).

In terms of stage of disease at start of treatment, stage II disease was determined in 13.2% (n=5) of the CF group, stage III in 15.8% (n=6) and stage IV in 71.1% (n=27). In the DC group, stage II disease was determined in 7.5% (n=4), stage III in 45.3% (n=24) and stage IV in 47.2% (n=25). In the DCF group, stage II disease was determined in 15% (n=9), stage III in 41.7% (n=25) and stage IV in 43.3% (n=26) (p=0.2).

Staging was performed again following induction therapy, and response levels were evaluated. Complete response was determined in 9.5% (n=12) of patients, partial response in 71.4% (n=90), stable disease in 17.5% (n=22) and progressive disease in 1.6% (n=2). Response assessment revealed complete response in 5.7% (n=2) of patients in the CF group, partial response in 82.9% (n=29) and stable disease in 11.4% (n=4). In the DC group the figures were complete response in 11.4% (n=5), partial response in 59.1% (n=26) and stable disease in 25% (n=11), and in the DCF group complete response in 10.6% (n=5), partial response in 74.5% (n=35) and stable disease in 14.9% (n=7). Progression was only recorded in the DC group, in 4.5% (n=2) of patients (p=0.2) (Figure 1).

Radiotherapy

Of the patients receiving CRT, 57% received concurrent cisplatin 35 mg/m^2, 38.5% concurrent cisplatin 75 mg/m^2 and 4.4% concurrent carboplatin therapy. Repeat staging and response analysis was subsequently performed. Forty-eight percent (n=59) of patients were determined as stage 0, 17.1% (n=21) as stage I, 8.9% (n=22) as stage II, 9.8% (n=12) as stage III and 16.3% (n=20) as stage IV. In terms of response assessment, complete response was observed in 72.1% (n=103) of patients, partial response in 8.4% (n=12), stable disease in 12.6% (n=18), progression in 5.6% (n=8) and metastasis in 0.7% (n=1). One patient (0.7%) died (Table 1).

Complete response was achieved in 69.4% (n=25) of patients in the DCF group, in 74.5% (n=38) of the DC group and in 71.4% (n=40) of the CF group. Progression was observed in 11.1% (n=4) of patients in the CF group and in 7.1% (n=4) of the DCF group. One patient died in the CF group and metastasis developed in one patient in the DC group (p=0.1).

Table 1 shows the initial Disease course

Median follow-up time was 50 months (2-201 months),

Table 1. Nasopharyngeal Cancer Patients' Demographic Data and Response to Therapy

	%	n
Gender		
Male	76%	117
Female	24%	37
Histology		
WHO grade I	1.3%	2
WHO grade II	48.1%	74
WHO grade III	34.4%	53
Cranial nerve involvement		
Yes	12.2%	18
No	87.8%	129
Stage		
II	11.9%	18
III	36.4%	55
IV	51.7%	78
Stages after induction		
0	21.9%	23
I	8.6%	9
II	21%	22
III	30.5%	32
IV	18.1%	19
Response assessment after induction		
Complete (CR)	9.5%	12
Partial (PR)	71.5%	90
Stable	17.5%	22
Progressive	1.6%	2
Staging after CRT		
0	48%	59
I	17.1%	21
II	8.9%	11
III	9.8%	12
IV	16.3%	20
Response assessment after CRT		
Complete (CR)	72.1%	103
Partial (PR)	8.4%	12
Stable	12.6%	18
Progressive	5.6%	8
Metastasis	0.7%	1

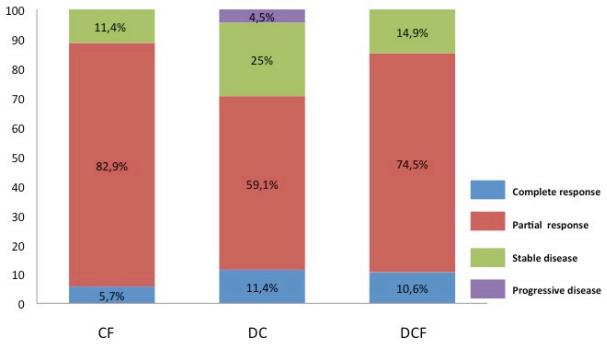

Figure 1. Groups' Response to Treatment Levels Following Induction Theraphy

Table 2. Comparison of Progression-free Survival and Overall Survival Values in Induction Therapy Groups

	3-year PFS	5-year PFS	3-year OS
CF	73.6%	62.7%	76.3%
DC	81.1%	76.9%	86.6%
DCF	79.8%	79.8%	96.5%

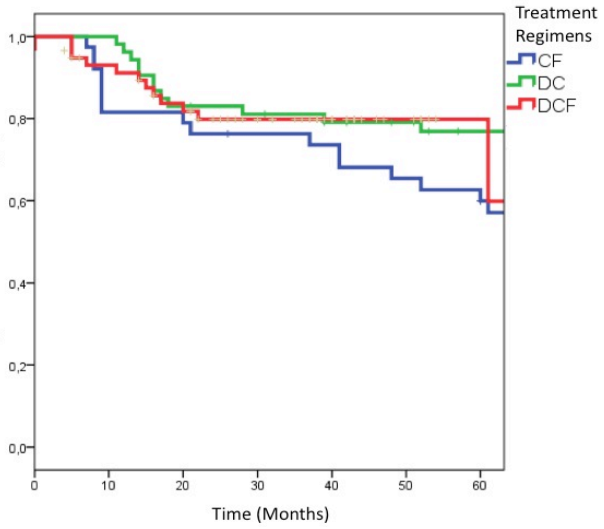

Figure 2. Comparison of Progression-free survival Values by Induction Theraphy

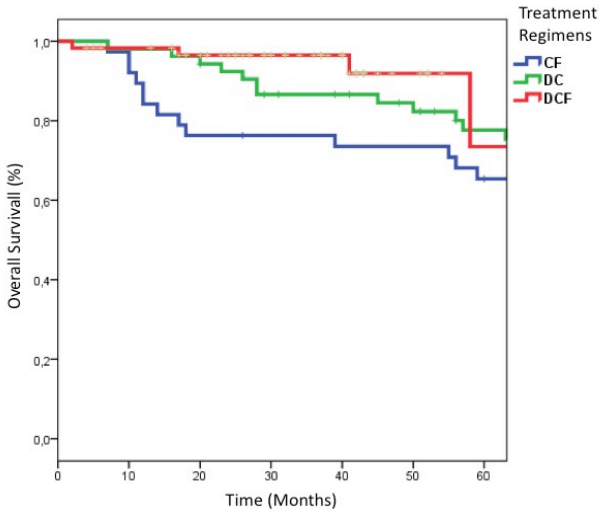

Figure 3. Comparison of Overall Survival Rates by Induction Theraphy

74 months (7-201 ay) in the CF group, 82 months (7-130 months) in the DC group and 35 months (2-76 months) in the DCF group.

Distant organ metastasis developed in 17.5% of patients (n=27) and local recurrence in 13.6% (n=21). In terms of induction therapy received, distant organ metastasis was observed in 23.7% (n=9) of patients receiving CF, 16.7% (n=9) of patients receiving DC and 14.5% (n=9) of patients receiving DCF (p=0.4).

Local recurrence was seen in 18.4% (n=7) of patients in the CF group, 13% (n=7) of the DC group and 11.3% (n=7) of the DCF group (p=0.5).

Survival analysis

Progression-Free Survival: In terms of PFS in nasopharyngeal cancer cases receiving induction therapy, 3-year PFS was 79.3% and 5-year PFS 72.4%. There was no significant difference between the induction therapy groups (p=0.3) (Table 2) (Figure 2).

Lengths of local recurrence-free survival (LRFS) and

distant metastasis-free survival (DMFS) were compared with induction therapies received and no significant difference was determined (p=0.08 and p=0.06).

Overall survival: Patients' 3-year OS rates were 87.4%, and 5-year OS 76%. No significant difference was determined in terms of induction therapies (p= 0.03) (Table 2) (Figure 3).

Discussion

Retrospective evaluation of data from 154 nasopharyngeal cancer patients attending our clinic revealed that the preferred induction regimens were CF, DC and DCF. No statistically significant difference was determined when responses for treatment groups were compared, and no difference was determined between the groups after chemotherapy. Survival analysis revealed no significant difference in PFS (p=0.3), LFFS and DMSF (p=0.08-p=0.06) rates in terms of induction therapies, although a significant difference in favor of DCF therapy was determined at comparison of 3-year OS values (p=0.03).

The standard treatment for local advanced nasopharyngeal cancer is chemoradiotherapy (Phua et al., 2013). Due to the risk of distant organ metastasis, combined modality therapies are administered. According to meta-analyses of randomized studies, the addition of any CT regimen (concurrent, induction or adjuvant) to RT therapy in the treatment of advanced stage disease (stage III and IV) reduces the risk of death by 18% and increases 5-year survival by 4-6% (Langendijk et al., 2004; Baujat et al., 2006).

The administration of CRT after induction CT in local advanced nasopharyngeal cancer is being investigated as a possible treatment option that will improve results. According to the literature, 16 single arm phase II studies and 3 randomized studies have been published on the subject of induction CT (Chua et al., 1998; Wee Rischin et al., 2002; Rischin et al., 2002; Oh et al, 2003; Chan et al., 2004; Wee et al., 2005; Al-Amro et al, 2005; Lee et al., 2005; Chua et al, 2005; Yau et al, 2006; Lee et al., 2008; Airoldi et al., 2009; Woo Kyun Bae et al., 2010; Kong et al., 2010; Bossi et al, 2011; Airoldi et al, 2011; Lee et al., 2012; Liang et al., 2013). Comparing induction CT and adjuvant therapy after CRT, induction therapy has been found more advantageous in terms of patient compliance (Lee et al., 2012).

In our study, the application of CRT following induction CT resulted in 5-year PFS and OS levels of 72% and 76%. Distant organ metastasis was observed in 23.7% (n=9) of patients receiving CF, 16.7% (n=9) of patients receiving DC and 14.5% (n=9) of those receiving DCF during mean 50-month monitoring (p=0.49). In terms of local recurrence levels, recurrence was observed in 18.4% (n=7) of the CF group, 13% (n=7) of the DC group and 11.3% (n=7) of the DCF group (p=0.5). An induction study from Turkey by Ekenel et al. (Ekenel M et al, 2011) used cisplatin and docetaxel in combination as the induction regimen, and relapse was observed in 9 (15.5%) out of 58 patients during the 29-month follow-up. Three-year GS and PFS levels in that study were 94.9% and 84.7%, better than our results (87.4% and 79.3%). The PFS and OS values in our study were low, but in terms of disease stages, T4, N3 and stage IV disease were greater in our study group. Another induction study demonstrated that gemcitabine and cisplatin followed by chemo-radiation is a safe and effective regimen in treatment of locally advanced nasopharyngeal carcinoma .The 5-year OS, loco regional control (LRC) and PFS rates were 71%, 73% and 50% (Jamshed et al., 2014).

Studies comparing induction regimens with RT have shown an increase in response rates and PFS values, but no contribution to OS (Chua et al, 1998; Ma et al., 2001). One randomized phase II study, by the Hellenic Cooperative Oncology Group, compared CRT after induction therapy (cisplatin, epirubicin and paclitaxel) and CRT alone (Fountzilas et al., 2012). Three-year PFS values after 55-month follow-up were 64.5% compared to 63.5% (p=0.7). Three-year OS values were 66.6% and 71.8% (p=0.6). Another phase II study, by Hui EP et al., compared the application of CRT with cisplatin after an induction regimen of docetaxel-cisplatin with CRT with cisplatin alone. They reported good toleration (Hui EP et al., 2009).

Another randomized phase II study from 2002, by Hareyama et al., compared RT after induction therapy and RT alone. No 5-year OS (60% vs. 48%) or 5-year PFS (55% vs. 43%) contribution was determined following a median 49-month follow-up (Hareyama et al., 2002).

A significant contribution to survival was determined with DCF between induction regimes in our study. However, since there was no group receiving CRT alone, no comparison was possible.

Until phase III studies are complete, the application of CRT following induction therapy remains experimental. Nonetheless, some researchers prefer induction therapy in conditions in which full-dose RT cannot be given (optic nerve, brain stem, temporal lobe) due to the close association between size of primary tumor (T4 tumor), spread of nodal disease (wide or supraclavicular) and critical organs.

The main limitation of this study is that it is retrospective. No toxicity data could therefore be obtained. Another significant limitation is the lengthy inclusion process. Treatment groups were treated with CF in the earlier years before 2000 and generally with DCF and DC in later years. Thus there are any randomization of the treatment groups.Also significant differences occurred during this process in terms of both pathological assessment and radiotherapy techniques and equipment. The majority of patients receiving CF were hospitalized during treatment, while treatment in the DCF patient group was administered on an outpatient basis using an intravenous port.

In our clinic, we prefer CRT after DCF as induction therapy in patients with local advanced nasopharyngeal cancer. This regimen made a significant contribution to OS compared to the other regimens (CF and DC). Clearer evidence is needed on the subject of application of induction therapy, and we await the results of continuing phase III studies.

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